ORIGINAL RESEARCH

Habitual Fish Consumption, n-3 Fatty Acids, and Nuclear Magnetic Resonance Lipoprotein Subfractions in Women

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Background—Supplementation with omega-3 (n-3) fatty acid or dietary fish may protect against atherosclerosis, but the potential mechanisms are unclear. Prior studies found modest triglyceride-lowering effects and slight increases in LDL (low-density lipoprotein) cholesterol. Limited evidence has examined n-3 effects on more detailed lipoprotein biomarkers.

Methods and Results—We conducted a study of 26 034 healthy women who reported information on fish and n-3 intake from a 131-item food-frequency questionnaire. We measured plasma lipids, apolipoproteins, and nuclear magnetic resonance spectroscopy lipoproteins and examined their associations with dietary intake of fish, total n-3, and the n-3 subtypes (eicosapentaenoic, docosahexaenoic, and α-linolenic acids). Top- versus bottom-quintile intake of fish and n-3 were significantly associated with lower triglyceride and large VLDL (very-low-density lipoprotein) particles. Fish intake, but not total n-3, was positively associated with total cholesterol, LDL cholesterol, apolipoprotein B, and larger LDL size, but only α-linolenic acid was associated with lower LDL cholesterol. Total n-3, docosahexaenoic acid, and α-linolenic acid intake were also positively associated with larger HDL (high-density lipoprotein) size and large HDL particles. High eicosapentaenoic acid intake was significantly associated with only a decreased level of VLDL particle concentration and VLDL triglyceride content. The n-3 fatty acids had some similarities but also differed in their associations with prospective cardiovascular disease risk patterns.

Conclusions—Higher consumption of fish and n-3 fatty acids were associated with multiple measures of lipoproteins that were mostly consistent with cardiovascular prevention, with differences noted for high intake of eicosapentaenoic acid versus docosahexaenoic acid and α-linolenic acid that were apparent with more detailed lipoprotein phenotyping. These hypothesis-generating findings warrant further study in clinical trials.

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Key Words: fish • n-3 • nuclear magnetic resonance lipoprotein subfractions

Moderate consumption of fatty fish, a major source of omega-3 (n-3) fatty acids, is recommended by numerous dietary guidelines as a preventive strategy against atherosclerotic cardiovascular disease (CVD).[1–3] Although some randomized trials and subsequent meta-analyses have questioned the value of n-3 fatty acid supplementation in CVD risk reduction,[4] 2 recent clinical trials—VITAL (Vitamin D and Omega-3 Trial) and REDUCE IT (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention)—found cardiovascular benefits with n-3 supplementation.[5,6] Experimental studies have found pleiotropic effects of n-3 fatty acids. In addition to anti-arrhythmic effects,[7] beneficial influences on a number of cardiometabolic risk factors have been demonstrated, including blood pressure,[8] thrombosis, inflammation,[9] vascular reactivity, and lipid levels.[10,11]

Reported n-3 fatty acid effects on lipids are mixed.[12] When administered in supplemental doses, n-3 fatty acids, particularly marine-derived, produce a meaningful decrease in triglycerides,[13] a modest increase in HDL (high-density lipoprotein) cholesterol (HDL-C),[14] and an increase in LDL (low-density lipoprotein) cholesterol (LDL-C).[15,16] Typically, a

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Clinical Perspective

What Is New?

- It is unclear if differences exist in the lipid and lipoprotein profiles associated with dietary intake of fish, omega-3 (n-3) fatty acids, and each of the main n-3 subtypes (eicosapentaenoic, docosahexaenoic, and α-linolenic acids).
- Although intake of fish and n-3 fatty acids was significantly associated mostly with a lipoprotein profile consistent with cardiovascular benefit, there were notable differences for high intake of eicosapentaenoic acid (lower VLDL [very-low-density lipoprotein] particles and VLDL triglyceride) versus docosahexaenoic and α-linolenic acids (larger LDL [low-density lipoprotein] and HDL [high-density lipoprotein] size) versus α-linolenic acids (lower LDL cholesterol and apolipoprotein B_{100}) that were apparent with detailed lipoprotein phenotyping using nuclear magnetic resonance spectroscopy.

What Are the Clinical Implications?

- Among apparently healthy women, the n-3 fatty acids differed in their lipoprotein profiles, with greater differences noted with detailed lipoprotein profiling compared with traditional lipids.
- These findings may provide insight into potential mechanisms for cardiovascular disease benefit for n-3 fatty acids.

decrease in triglycerides and an increase in HDL-C would be expected to reduce CVD risk, but an increase in LDL-C would typically be expected to increase CVD risk, producing an overall indeterminate effect. Habitual fish consumption or dietary n-3 fatty acids, which contain lower amounts of n-3 fatty acids compared with supplemental doses, have less substantial effects on traditional lipids.[17]

The association of habitual dietary n-3 fatty acids with lipoprotein particle fractions is poorly characterized.[18,19] Studies examining the association of n-3 fatty acids with lipoprotein particle subfractions have been limited to small nutritional studies of 4 g/day[16,20] or 5.9 g/day[21] of supplemental doses of n-3 fatty acids. It is increasingly appreciated that lipoprotein particles, and not their major lipid components, serve as both direct mediators of atherosclerosis and principal targets of lipid-modifying therapies proven to reduce the risk of CVD.[22,23] Therefore, we investigated whether more detailed measures of LDL-C, HDL-C, and triglyceride-rich remnant subfractions and other lipoprotein measures could provide insight into the CVD risk associations with dietary intake of fish, total n-3, and the main n-3 subtypes: eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and α-linolenic acid (ALA). Using data from the WHS (Women's Health Study), a large cohort of female health professionals, we quantified the association between habitual fish intake and intake of n-3 fatty acids and their subtypes with detailed lipoprotein subfraction profiles. We then examined these associations in relation to recently reported associations of these subfraction profiles with prospectively ascertained incident CVD events in the same population of participants[24] to generate hypotheses regarding potential mechanisms of benefit for fish and n-3 intake.

Methods

Study Population

Study participants were drawn from the WHS, a completed, randomized, double-blind, placebo-controlled trial of low-dose aspirin and vitamin E in the primary prevention of CVD and cancer in US female healthcare professionals.[25] The randomized intervention ended in 2004 with no significant reduction in the primary end points of the trial; therefore, the 2 intervention groups were combined for this analysis. All participants provided written informed consent, and the institutional review board of the Brigham and Women's Hospital (Boston, MA) approved the study protocol. At enrollment (1992–1996), study participants completed questionnaires on demographics, anthropometrics, medical history, and lifestyle behaviors. A blood sample at enrollment was requested, but not required, from the 39 876 women who were randomized; 28 345 women provided one. On an a priori basis, of the women who provided baseline blood samples, we excluded those who had prevalent diabetes mellitus (n=767), reported total energy intake of <600 or >3500 kcal/d (n=889), were missing >50% of the 131 items assessed on the food-frequency questionnaire (FFQ; n=15), or were missing information on any lipid or lipoprotein variable (n=640). A total sample of 26 034 women were analyzed for the current study.

Dietary Assessment

A semiquantitative baseline FFQ, which was previously validated,[8,26–29] captured information on 131 commonly consumed food items (including fish oil supplements). For each item, a portion size was specified, and each woman was asked how often, on average, during the past year she had consumed that amount. Nine responses were possible, ranging from "never or less than once a month" to "6 times a day." A detailed description of the FFQ and the procedures used for calculating nutrient intake, as well as data on reproducibility and validity, were published previously.[30] Nutrient scores were computed by multiplying the frequency of consumption of each unit of food from the FFQ by the

nutrient content of that specific portion size of the food according to food composition tables from the US Department of Agriculture.[31]

Fish consumption was obtained through 4 items from the FFQ: participants were asked to report their average consumption of canned tuna fish (portion size: 85–113 g); other dark-flesh fish such as mackerel, salmon, sardines, bluefish, and swordfish (portion size: 85–142 g); light-flesh fish (portion size: 85–142 g); and shrimp, lobster, or scallops (or all 3) as a main dish. Possible responses included never, <1 time/month, 1 to 3 times/month, 1 time/week, 2 to 4 times/week, 1 time/day, 2 to 3 times/day, 4 to 5 times/day, and ≥6 times/day. We converted individual responses into servings per day by using the midpoint for each category. We summed the frequency of consumption of canned tuna; dark fish; other fish; and shrimp, lobster, and scallops as a main dish to obtain a fish variable and created quintiles of fish consumption.

Dietary n-3 fatty acids were also derived from the FFQ. We calculated the marine-derived intake of EPA and DHA by assigning grams per serving as follows: 1.51 g for dark-flesh fish; 0.42 g for canned tuna fish; 0.48 g for light-flesh fish; and 0.32 g for shrimp, lobster, or scallops. These n-3 fatty acids values were derived by weighting the mean values of n-3 fatty acids for the most commonly caught types of fish in US catches in 1984 (according to the US Department of Commerce), as described elsewhere.[32] Intake of ALA fatty acids, obtained primarily from plant sources, and other n-3 fatty acids was also estimated and used to calculate total n-3 fatty acid intake. The total marine n-3, EPA, DHA, and ALA fatty acid intakes were individually adjusted for energy intake using the residual method.[33] For each adjusted n-3 fatty acid intake, we created quintiles of the exposure variables.

Laboratory Measurements

EDTA blood samples were obtained at the time of enrollment into the WHS and stored in vapor-phase liquid nitrogen (−170°C). In a laboratory (N. Rifai, Children's Hospital, Boston, MA) certified by the National Heart, Lung, and Blood Institute/Centers for Disease Control and Prevention Lipid Standardization Program, baseline samples were thawed and analyzed for standard lipids and apolipoproteins.[24] Standard lipids were measured directly with reagents from Roche Diagnostics. Apolipoproteins B_{100} (apo B_{100}) and A-I were measured with immunoturbidometric assays (DiaSorin).

Samples for lipoprotein particle analysis by proton nuclear magnetic resonance (NMR) spectroscopy were shipped to LipoScience (now LabCorp), as reported previously (Lipoprofile® version 3).[24] Particle concentrations of lipoproteins of different sizes were calculated from the measured amplitudes of their spectroscopically distinct lipid methyl group signals. Weighted-average lipoprotein particle sizes (diameter, Ø nm) were derived from the sum of the diameter of each subclass multiplied by its relative mass percentage based on the amplitude of its methyl NMR signal.[34] The particle diameter ranges are reported in Table S1.

Ascertainment of Other Clinical Factors

Demographic data were collected at baseline. Self-reported baseline weight and height were used to compute the body mass index (weight in kilograms divided by height in meters squared). Self-reported walking, stair climbing, and participation in 8 groups of recreational activities were obtained to estimate the energy expended on physical activity.[35] In addition, information on prevalence of hypertension, hypercholesterolemia, parental history of diabetes mellitus, menopausal status, postmenopausal hormone therapy, smoking, and alcohol consumption was obtained at baseline.[36]

Statistical Analyses

Statistical analyses were conducted using SAS (v9.1; SAS Institute). All tests for significance were performed at α=0.05, 2-tailed. Log transformations were used for triglycerides and for all NMR-derived lipoprotein variables before calculating inferential statistics. The small LDL particle concentration variable presented a clearly bimodal distribution; therefore, we dichotomized and represented it with 2 different values to describe the mean scores, dividing the women into 2 groups according to their small LDL particle concentration (small A: <164 nmol/L; small B: ≥164 nmol/L).

We divided women according to quintiles of the exposure variables. We explored the median of the baseline demographic and anthropometric values across the quintiles of the exposure variables and used a Wilcoxon rank sum test (continuous variables) or a χ^2 test (categorical variables) to compare the baseline values of the different groups.

To examine the relationship of intake of habitual fish, n-3, and specific subtypes of n-3 (EPA, DHA and ALA fatty acids) in relation to lipids and lipoprotein profiles, we computed the geometric mean (with 95% CI) for log-transformed variables and the raw mean±SD for natural-scale variables across quintiles of exposure variables. We then used multivariable linear regression models to calculate the least squares means (with 95% CI) and β coefficients (with SE) for all lipids and lipoprotein variables across quintiles of the nutritional exposure variables after adjusting for demographic, clinical, and dietary factors. We tested for trend across quintiles of the exposure variables using category medians modeled as a continuous variable. We used isocaloric multivariable nutrient-density models with energy-adjusted exposure variables in which the n-3 fats replaced the percentage of energy from carbohydrates, as reported previously.[37]

For fish intake, multivariable models were adjusted for age and total energy (reported as model 1), and then additionally adjusted for lifestyle factors, including smoking, alcohol use, body mass index, exercise, menopausal status, use of hormone therapy, hypertension, antihypertensive treatment, hypercholesterolemia, treatment for high cholesterol, parental history of coronary heart disease, energy-adjusted glycemic index, multivitamin use, aspirin use, red meat consumption, and fruit and vegetable consumption (reported as model 2).

For n-3 intake, multivariable models were adjusted as described but were adjusted for energy-adjusted saturated fats, energy-adjusted monounsaturated fats, energy-adjusted transfat, energy-adjusted n-6, and energy-adjusted proteins. When EPA, DHA, and ALA were modeled, they were additionally adjusted.

To facilitate the visualization of differences between quintiles, we expressed the percentage of difference in the expected value of the outcome due to differences among quintile 2 (Q2) through Q5 compared with Q1 using equation (1) for the log-transformed output variables and equation (2) for the natural-scale outcome variables:

$$\text{Difference}\,(\%) = (e^{\beta i} - 1) \cdot 100 \quad (1)$$

$$\text{Difference}\,(\%) = \frac{\beta_i}{\mu_1} \cdot 100 \quad (2)$$

where i=2, 3, 4, and 5 corresponds to the β coefficients of Q2 through Q5 and μ corresponds to the quintile mean.

Finally, to understand the nature and extent of the effect of lipid and lipoprotein differences associated with fish and n-3 intake on clinical CVD events, we used previously published results of the same cohort in which the contribution of the lipoprotein and lipid profiles to risk for prospectively ascertained CVD events was reported using Cox regression model hazard ratio (HR) values.[24] By using the HR, we identified NMR-derived variables that were associated with a lower risk for CVD, including larger HDL and LDL particle sizes, elevated levels of HDL-C, and elevated large HDL particle concentration; conversely, variables that were associated with a higher risk for CVD, including increased levels of the small LDL particle concentration, increased levels of all subclasses of VLDL (very-low-density lipoprotein) particle concentrations, total cholesterol (TC), LDL-C and triglyceride concentration.

To easily visualize the global impact on CVD events of all variables at the same time, we plotted the percentage of the difference in the expected value of outcome related to differences between the highest (Q5) and lowest (Q1) intake groups. The lipid and lipoprotein variables were sorted in descending order of their previously mentioned HRs on a colored red to green heat map according to their contribution toward CVD incident risk.

The data supporting the findings of this study are available to researchers on request from the WHS data usage review committee.

Results

Among the 26 034 apparently healthy women at baseline, habitual fish and energy-adjusted fatty acid intake ranged from 0 to 5.1 servings/day for fish, 0.27 to 5.05 g/day for total n-3, 0 to 1.72 g/day for DHA, 0.01 to 1.35 g/day for EPA, and 0.26 to 4.78 g/day for ALA. The baseline characteristics according to quintiles of total fish intake and n-3 intake adjusted by total calorie intake are shown in Tables S2 and S3. Women consuming greater amounts of fish and n-3 were older, had higher body mass index, and were more likely to be active and postmenopausal (and treated with hormone therapy) and to have hypertension but were less likely to be current smokers. Intake of fish and n-3 was also positively associated with intake of fruits, nuts, vegetables, dietary magnesium, and cereal fiber and inversely associated with saturated and transfat intake.

Table 1 depicts the raw and multivariable adjusted means for LDL-related variables (lipids, apolipoproteins, and NMR subfractions) with fish and total n-3 intake. Greater fish intake quintile (Q5 versus Q1) was positively associated with higher mean levels for TC, LDL-C, and apo B_{100} levels (P_{trend} ranges from <0.0001 to 0.03), but these associations were not significant for n-3 intake. When the more detailed NMR LDL measurements were analyzed, we found that only the large LDL particle concentration was higher for greater fish and n-3 intake (up to 10±4%, P_{trend}<0.01) but not the small LDL subfraction. We consistently found a positive association between fish (and n-3 intake) with larger LDL mean particle size (P_{trend} ranges from <0.001 to 0.03).

Table 2 depicts the raw and the adjusted means for VLDL and remnant particle-related variables with fish and n-3 intake. Notably, the associations of the triglycerides and the NMR subfractions with intake of fish and total n-3 were in the same direction—women consuming higher amounts of both exposure variables had up to 4% lower levels of total triglycerides (P_{trend}=0.05 and <0.01, respectively) and NMR VLDL-triglyceride content (P_{trend}<0.0001) when Q1 and Q5 were compared. Women consuming greater amounts of fish (or n-3) also had smaller VLDL size (P_{trend}=0.07 and <0.01, respectively) and lower concentration of total VLDL particles (P_{trend}=0.01 and <0.001, respectively). In particular, this group also had up to a 15% lower concentration of large VLDL particles (P_{trend}<0.0001), lower medium VLDL particles (P_{trend}≤0.01), and no significant differences in the small VLDL particles (P_{trend}≥0.1) in the multivariable models.

Table 1. Raw Mean±SD and Adjusted Geometric Mean (95% CI) of LDL-Related Variables According to Fish and n-3 Intake

	Fish				n-3			
	Q1	Q3	Q5	P_{Trend}	Q1	Q3	Q5	P_{Trend}
n	5839	5465	5617		5248	4991	5123	
Intake, median [min, max]*	0.07 [0, 0.07]	0.21 [0.2, 0.21]	0.5 [0.43, 0.64]		0.95 [0.86, 1.02]	1.35 [1.31, 1.39]	1.89 [1.77, 2.1]	
LDL-C, mg/dL								
Raw mean	123±34	124±33	125±35		123±34	124±33	125±35	
Adjusted mean†	123 (122–124)	124 (123–124)	125 (124–126)	0.01	125 (124–126)	124 (123–125)	124 (123–125)	0.61
Adjusted mean‡	123 (122–124)	124 (123–124)	124 (123–125)	0.03	124 (123–125)	123 (122–124)	123 (122–124)	0.08
TC, mg/dL								
Raw mean	210±41	212±41	213±42		210±42	211±41	213±42	
Adjusted mean†	210 (209–211)	212 (211–213)	213 (212–214)	<0.0001	212 (210–213)	211 (210–212)	212 (211–213)	0.43
Adjusted mean‡	210 (210–211)	212 (211–212)	212 (211–212)	0.01	212 (211–213)	211 (210–212)	211 (210–212)	0.36
Apo B_{100}, mg/dL								
Raw mean	103±27	103±27	104±28		103±28	104±28	104±28	
Adjusted mean†	103 (102–103)	103 (102–104)	104 (104–105)	<0.001	104 (103–105)	104 (103–104)	103 (103–104)	0.73
Adjusted mean‡	102 (102–103)	103 (102–104)	104 (103–104.2)	0.005	103 (103–104)	103 (103–104)	103 (102–103.4)	0.36
LDL size (Ø nm)								
Geometric mean	21.05 (21.03–21.06)	21.08 (21.06–21.1)	21.08 (21.06–21.09)		21.06 (21.04–21.08)	21.07 (21.05–21.09)	21.07 (21.05–21.09)	
Adjusted mean†	21.04 (21.02–21.06)	21.08 (21.06–21.09)	21.09 (21.07–21.1)	<0.001	21.02 (21–21.04)	21.08 (21.06–21.09)	21.1 (21.08–21.12)	<0.0001
Adjusted mean‡	21.06 (21.04–21.08)	21.06 (21.05–21.08)	21.09 (21.07–21.11)	0.03	21.03 (21.01–21.05)	21.08 (21.06–21.09)	21.1 (21.08–21.12)	<0.001
LDL particles								
Total, nm/L								
Geometric mean	1188 (1178–1198)	1188 (1179–1198)	1208 (1198–1219)		1188 (1177–1198)	1196 (1185–1207)	1209 (1198–1220)	
Adjusted mean†	1189 (1179–1199)	1189 (1179–1199)	1206 (1196–1216)	0.005	1204 (1192–1216)	1195 (1185–1206)	1195 (1183–1207)	0.49
Adjusted mean‡	1182 (1173–1191)	1192 (1183–1202)	1195 (1186–1205)	0.02	1196 (1185–1207)	1190 (1180–1199)	1186 (1174–1197)	0.35
IDL, nm/L								
Geometric mean	146 (143–149)	146 (143–149)	146 (144–149)		151 (149–154)	144 (142–147)	141 (139–144)	
Adjusted mean†	146 (143–148)	146 (144–149)	147 (144–149)	0.78	147 (144–151)	144 (142–147)	145 (142–148)	0.90
Adjusted mean‡	147 (145–150)	145 (143–148)	145 (142–148)	0.22	147 (143–150)	144 (141–147)	144 (141–148)	0.75
Large, nm/L								
Geometric mean	466 (457–475)	483 (473–492)	492 (482–501)		460 (450–469)	483 (473–493)	499 (489–509)	
Adjusted mean†	462 (453–471)	483 (474–492)	495 (486–505)	<0.0001	455 (445–466)	485 (475–495)	498 (486–510)	0.001
Adjusted mean‡	469 (460–479)	479 (469–489)	498 (488–508)	0.006	458 (447–470)	485 (475–496)	496 (484–509)	0.006
Small A, nm/L								

Continued

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Table 1. Continued

	Fish				n-3			
	Q1	Q3	Q5	P_{trend}	Q1	Q3	Q5	P_{trend}
Geometric mean	62 (60.8–63.3)	64.4 (63.2–65.6)	64 (62.7–65.3)		60.4 (59.1–61.7)	63.9 (62.6–65.3)	65.4 (64–66.7)	
Adjusted mean†	62 (60.8–63.2)	64.3 (63.1–65.6)	64.1 (62.9–65.3)	0.03	62.2 (60.8–63.6)	64 (62.7–65.3)	63.5 (62.1–65)	0.24
Adjusted mean‡	62 (60.8–63.3)	63.8 (62.6–65.1)	63.8 (62.5–65.1)	0.09	61.5 (60–63)	64 (62.7–65.4)	63.6 (62–65.2)	0.13
Small B, nm/L								
Geometric mean	661 (650–671)	654 (643–666)	663 (653–674)		658 (647–669)	657 (646–668)	669 (657–680)	
Adjusted mean†	661.8 (651.7–672)	654 (643–666)	661 (651–672)	0.59	669 (657–682)	657 (646–668)	657 (644–670)	0.34
Adjusted mean‡	658 (647–668)	658 (647–670)	653 (642–663)	0.92	668 (656–681)	657 (646–668)	650 (637–663)	0.13

Data are shown as geometric mean (95% CI) for log-transformed variables and raw mean±SD for natural-scale variables across quintiles of exposure variable intake, except as noted. Apo indicates apolipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; n-3, omega-3; Q, quintile; TC, total cholesterol.

*Fish intake shown as servings per day, n-3 intake shown as grams per day.

†Model 1: the adjusted means are estimated from linear regression models adjusted for age (continuous) and total energy (quintiles; plus energy-adjusted saturated fats [quintiles], energy-adjusted monounsaturated fats [quintiles], energy-adjusted transfat [quintiles], energy-adjusted total n-6 [quintiles], and energy-adjusted proteins [quintiles] for n-3 intake models).

‡Model 2: adjusted as in model 1 but including smoking (current, past, never), alcohol use (rarely/never, 1–3 drinks/mo, 1–6 drinks/wk, and 1 drink/d), body mass index (continuous), exercise (quintiles of metabolic equivalent task hours per week), menopausal status (premenopausal, uncertain, postmenopausal), use of hormone therapy (current, past/never), hypertension (systolic blood pressure of at least 140 mm Hg, diastolic blood pressure of at least 90 mm Hg), antihypertensive treatment (yes or no), hypercholesterolemia (total cholesterol of at least 240 mg/dL), treatment for high cholesterol (yes or no), parental history of coronary heart disease (yes or no), energy-adjusted glycemic index (quintiles), multivitamin use (current, past, and never), aspirin use (current >1 time/wk), and red meat consumption and fruit and vegetable consumption (both quintiles).

Associations of fish and n-3 intake with the HDL-related variables are reported in Table 3. Greater fish and n-3 intake was positively associated with a larger HDL size (P_{trend}=0.05 and <0.001, respectively). The increased HDL size was consistent with a statistically significant redistribution between large and medium HDL subfractions for the same amount of HDL-C.

The associations of intake of the n-3 subtypes (EPA, DHA, and ALA) in relation to the lipid and lipoprotein profiles are described in Tables S4 through S12. To summarize, intake of the different n-3 subtypes had different patterns of association. After adjusting for potential confounders, the highest EPA intake was significantly associated with only a decreased level of VLDL particle concentration (P_{trend}=0.03) and VLDL-triglycerides (P_{trend}=0.03; Tables S4, S7, and S10). In contrast, greater intake of DHA and ALA was associated with several significant differences in lipids and lipoproteins, such as LDL and HDL size and particle concentration. The most pronounced differences in LDL and HDL sizes were associated with DHA intake, which also had a higher concentration of large LDL particles (Table S5) and large HDL particles (Table S11). Although higher intake of all n-3 subtypes showed an association with decreased levels of large VLDL particles, only the ALA intake was significant (Table S9) and associated with a significant decrease in LDL-C.

The effect size of the energy-adjusted exposure variables was determined by the modeling of the β coefficients and the P_{linear} trend reflecting the same results extracted from the adjusted means analysis (see Table S13 for the correspondence between absolute and per-1% and per-5% differences). To easily visualize the association between the exposure variables and the lipid and lipoprotein profiles, we defined a model based on a variable computing the percentages of difference between Q2 through Q5 and Q1 of the exposure variables. Figure 1 depicts these results for LDL-, VLDL-, and HDL-related variables according to fish and total n-3 intake adjusted by anthropometric, clinical, and dietary factors. Generally, greater effects were seen for n-3 intake than fish intake, although they were mostly consistent in direction. The adjusted percentages according to the different n-3 subtype intakes are shown in Figure 2, with differences in particular noted for EPA compared with DHA or ALA (the latter 2 being more similar in lipoprotein associations).

Finally, we evaluated the associations between the different dietary variables in the lipid and lipoprotein profiles in relation to prospective CVD events in this population. Figure 3 is a heat map that shows the percentage of the difference in the expected value of outcome due to differences between the highest (Q5) and

Table 2. Raw Mean±SD and Adjusted Geometric Mean (95% CI) of VLDL-Related Variables According to Fish and n-3 Intake

	Fish				n-3			
	Q1	Q3	Q5	P_{Trend}	Q1	Q3	Q5	P_{Trend}
n	5839	5465	5617		5248	4991	5123	
Intake, median [min, max]*	0.07 [0, 0.07]	0.21 [0.2, 0.21]	0.5 [0.43, 0.64]		0.95 [0.86, 1.02]	1.35 [1.31, 1.39]	1.89 [1.77, 2.1]	
TG, mg/dL								
Geometric mean	123 (121–125)	120 (119–122)	122 (120–123)		123 (121–125)	123 (121–125)	121 (119–123)	
Adjusted mean	123 (122–125)	120 (119–122)	121 (119–123)	0.14	125 (123–127)	123 (121–124)	119 (117–121)	0.007
Adjusted mean	122 (121–124)	121 (120–123)	119 (118–121)	0.05	124 (122–126)	122 (120–124)	118 (116–120)	0.001
VLDL size (Ø nm)								
Geometric mean	51.11 (50.93–51.29)	50.96 (50.78–51.15)	51.09 (50.91–51.28)		51.51 (51.31–51.72)	51 (50.81–51.19)	50.65 (50.46–50.84)	
Adjusted mean	51.15 (50.97–51.34)	50.97 (50.78–51.15)	51.04 (50.85–51.22)	0.84	51.28 (51.06–51.5)	51.01 (50.82–51.21)	50.85 (50.62–51.07)	0.01
Adjusted mean	51.25 (51.06–51.43)	51.01 (50.82–51.19)	50.89 (50.7–51.08)	0.07	51.27 (51.04–51.5)	51.01 (50.81–51.21)	50.75 (50.52–50.98)	0.007
VLDL particles								
Total, nm/L								
Geometric mean	56.9 (56.3–57.6)	55.6 (54.9–56.2)	54.9 (54.2–55.6)		55.4 (54.7–56)	56.9 (56.2–57.6)	56.3 (55.6–57.1)	
Adjusted mean	57.1 (56.4–57.8)	55.5 (54.9–56.2)	54.7 (54–55.4)	<0.0001	57.6 (56.8–58.5)	56.7 (56–57.4)	54.5 (53.7–55.3)	<0.0001
Adjusted mean	56.2 (55.5–56.9)	55.7 (55.1–56.4)	54.9 (54.2–55.6)	0.01	57 (56.2–57.9)	56.5 (55.8–57.3)	54.6 (53.8–55.5)	<0.001
Large, nm/L								
Geometric mean	2.59 (2.53–2.66)	2.4 (2.33–2.47)	2.41 (2.34–2.48)		2.71 (2.63–2.78)	2.52 (2.44–2.59)	2.29 (2.22–2.36)	
Adjusted mean	2.63 (2.56–2.7)	2.4 (2.34–2.47)	2.37 (2.3–2.43)	<0.0001	2.71 (2.62–2.8)	2.51 (2.44–2.58)	2.31 (2.23–2.38)	<0.0001
Adjusted mean	2.62 (2.55–2.7)	2.41 (2.35–2.48)	2.32 (2.26–2.39)	<0.0001	2.69 (2.6–2.78)	2.48 (2.41–2.56)	2.28 (2.2–2.36)	<0.0001
Medium, nm/L								
Geometric mean	13.3 (13.0–13.6)	12.9 (12.6–13.2)	12.8 (12.5–13.1)		13.1 (12.8–13.4)	13.3 (13.0–13.6)	12.8 (12.5–13.1)	
Adjusted mean	13.4 (13.2–13.7)	12.9 (12.6–13.2)	12.7 (12.4–12.9)	<0.0001	13.6 (13.3–14)	13.2 (12.9–13.5)	12.4 (12.1–12.8)	<0.0001
Adjusted mean	13.2 (12.9–13.5)	12.9 (12.6–13.2)	12.6 (12.3–12.9)	0.01	13.4 (13–13.8)	13.1 (12.7–13.4)	12.4 (12.1–12.8)	0.003
Small, nm/L								
Geometric mean	36.4 (35.9–36.9)	35.6 (35.1–36.2)	35 (34.5–35.6)		34.9 (34.4–35.5)	36.4 (35.9–37)	36.6 (36.0–37.2)	
Adjusted mean	36.4 (35.9–36.9)	35.6 (35.1–36.1)	35 (34.5–35.5)	<0.0001	36.5 (35.8–37.1)	36.3 (35.8–36.9)	35.3 (34.7–36)	0.04
Adjusted mean	35.8 (35.3–36.3)	35.8 (35.2–36.3)	35.3 (34.8–35.9)	0.13	36.2 (35.5–36.9)	36.3 (35.7–36.9)	35.5 (34.8–36.2)	0.21
VLDL-TG, mg/dL								
Geometric mean	76 (75.1–77)	73.7 (72.7–74.7)	73.2 (72.3–74.2)		75.4 (74.4–76.5)	75.6 (74.5–76.6)	73.4 (72.4–74.4)	
Adjusted mean	76.4 (75.5–77.4)	73.7 (72.7–74.7)	72.8 (71.8–73.7)	<0.0001	77.5 (76.3–78.7)	75.4 (74.4–76.4)	71.9 (70.7–73)	<0.0001
Adjusted mean	75.6 (74.6–76.6)	74 (73–74.9)	72.5 (71.5–73.5)	<0.0001	76.6 (75.4–77.9)	75.1 (74–76.1)	71.7 (70.6–72.9)	<0.0001

Data are shown as geometric mean (95% CI) for log-transformed variables and raw mean±SD for natural-scale variables across quintiles of exposure variable intake, except as noted. Adjustments for models 1 and 2 are shown in Table 1. n-3 indicates omega-3; Q, quintile; TG, triglycerides; VLDL, very-low-density lipoprotein.

*Fish intake shown as servings per day, n-3 intake shown as grams per day.

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Table 3. Raw Mean±SD and Adjusted Geometric Mean (95% CI) of HDL-Related Variables According to Fish and n-3 Intake

	Fish				n-3			
	Q1	Q3	Q5	P_{Trend}	Q1	Q3	Q5	P_{Trend}
n	5839	5465	5617		5248	4991	5123	
Intake, median [min, max]*	0.07 [0, 0.07]	0.21 [0.2, 0.21]	0.5 [0.43, 0.64]		0.95 [0.86, 1.02]	1.35 [1.31, 1.39]	1.89 [1.77, 2.1]	
HDL-C, mg/dL								
Raw mean	53.3±14.7	54.7±15.5	54.2±15		53.1±14.4	54±14.8	54.8±15.3	
Adjusted mean	53 (52.7–53.4)	54.7 (54.3–55.1)	54.5 (54.1–54.9)	<0.0001	53.2 (52.8–53.7)	54.1 (53.6–54.5)	54.5 (54.1–55)	0.0078
Adjusted mean	53.8 (53.5–54.2)	54.4 (54–54.8)	54.3 (54–54.7)	0.12	53.6 (53.2–54.1)	54.1 (53.7–54.5)	54.4 (53.9–54.9)	0.13
Apo A-I, mg/dL								
Raw mean	150±26	152±26	152±26		150±25	152±25	153±26	
Adjusted mean	150 (149–150)	152 (152–153)	152 (152–153)	<0.0001	150 (149–151)	152 (151–152)	152 (151–153)	0.001
Adjusted mean	151 (151–152)	152 (151–152)	152 (151–152)	0.37	151 (150–152)	152 (151–152)	152 (151–153)	0.15
HDL size (Ø nm)								
Geometric mean	9.18 (9.17–9.19)	9.22 (9.21–9.23)	9.2 (9.19–9.21)		9.18 (9.17–9.2)	9.2 (9.19–9.21)	9.21 (9.19–9.22)	
Adjusted mean	9.17 (9.16–9.19)	9.22 (9.21–9.23)	9.21 (9.2–9.22)	<0.001	9.17 (9.15–9.18)	9.2 (9.19–9.22)	9.22 (9.2–9.23)	<0.0001
Adjusted mean	9.19 (9.18–9.21)	9.21 (9.2–9.22)	9.21 (9.2–9.23)	0.05	9.17 (9.16–9.19)	9.21 (9.19–9.22)	9.23 (9.21–9.24)	<0.001
HDL particles								
Total, μm/L								
Geometric mean	36.7 (36.5–36.8)	37.1 (36.9–37.3)	36.9 (36.7–37.1)		36.8 (36.6–37)	37 (36.8–37.2)	37 (36.8–37.2)	
Adjusted mean	36.6 (36.4–36.8)	37.1 (36.9–37.3)	37 (36.8–37.2)	0.002	37 (36.8–37.2)	37 (36.8–37.2)	36.8 (36.6–37)	0.17
Adjusted mean	36.9 (36.8–37.1)	37 (36.8–37.2)	36.8 (36.6–37)	0.13	37.1 (36.9–37.3)	37 (36.8–37.2)	36.7 (36.5–36.9)	0.002
Large, μm/L								
Geometric mean	5.36 (5.29–5.44)	5.64 (5.56–5.73)	5.5 (5.42–5.59)		5.33 (5.25–5.42)	5.49 (5.40–5.58)	5.61 (5.53–5.7)	
Adjusted mean	5.32 (5.24–5.4)	5.64 (5.56–5.73)	5.56 (5.47–5.64)	<0.001	5.31 (5.22–5.41)	5.51 (5.42–5.6)	5.58 (5.48–5.69)	0.002
Adjusted mean	5.46 (5.38–5.54)	5.58 (5.51–5.67)	5.56 (5.48–5.64)	0.22	5.37 (5.28–5.47)	5.54 (5.46–5.62)	5.61 (5.51–5.71)	0.01
Medium, μm/L								
Geometric mean	11.2 (11.1–11.4)	11.4 (11.2–11.5)	11.3 (11.2–11.5)		11.6 (11.4–11.7)	11.3 (11.1–11.4)	11.1 (11.0–11.3)	
Adjusted mean	11.2 (11.1–11.4)	11.4 (11.2–11.5)	11.3 (11.2–11.5)	0.26	11.5 (11.4–11.7)	11.3 (11.1–11.4)	11.1 (10.9–11.3)	0.0035
Adjusted mean	11.4 (11.3–11.6)	11.3 (11.2–11.5)	11.2 (11–11.4)	0.07	11.6 (11.4–11.8)	11.3 (11.1–11.4)	11.1 (10.9–11.3)	0.0020
Small, μm/L								
Geometric mean	17.7 (17.6–17.8)	17.6 (17.5–17.8)	17.7 (17.5–17.8)		17.4 (17.3–17.6)	17.8 (17.6–18)	17.9 (17.7–18)	
Adjusted mean	17.7 (17.6–17.9)	17.6 (17.5–17.8)	17.7 (17.5–17.8)	0.54	17.7 (17.5–17.9)	17.8 (17.6–17.9)	17.6 (17.5–17.8)	0.68
Adjusted mean	17.6 (17.5–17.8)	17.6 (17.5–17.8)	17.6 (17.4–17.7)	0.52	17.7 (17.5–17.9)	17.7 (17.6–17.9)	17.5 (17.3–17.7)	0.22

Geometric mean (95% CI) for log-transformed variables and raw mean±SD for natural-scale variables across quintiles of exposure variable intake, except as noted. Adjustments for models 1 and 2 are shown in Table 1. Apo indicates apolipoprotein; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; n-3, omega-3; Q, quintile.
*Fish intake shown as servings per day, n-3 intake shown as grams per day.

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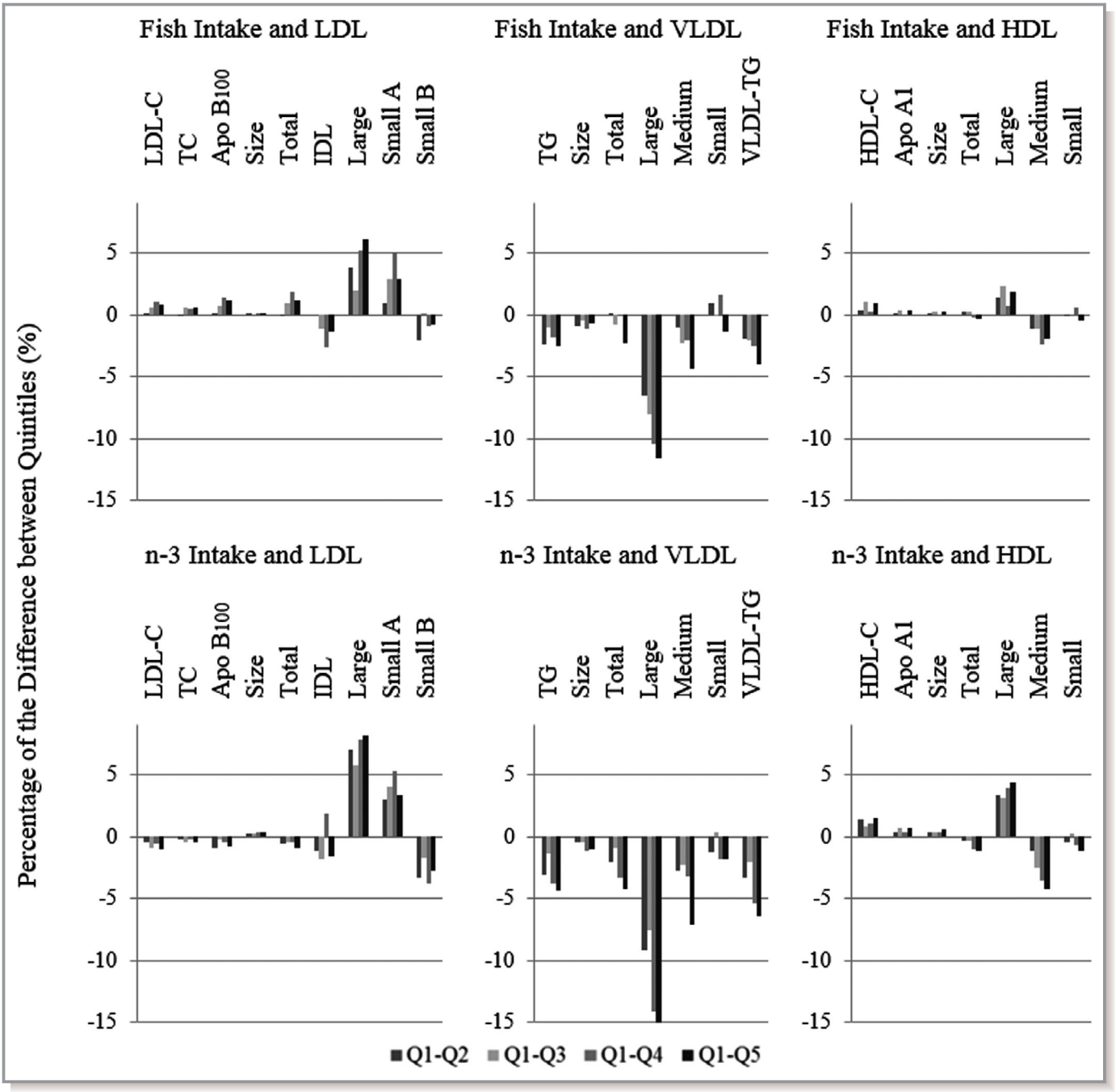


Figure 1. Percentage difference in outcome between quintiles (Qs; Q2–Q5) compared with Q1 of fish and n-3 intake after adjusting for all demographic, clinical, and dietary factors. Individual distribution: fish: Q1, n=5839; Q2, n=5035; Q3, n=5465; Q4, n=4078; Q5, n=5617; n-3: Q1, n=5248; Q2, n=5406; Q3, n=4991; Q4, n=5266; Q5, n=5123. Apo indicates apolipoprotein; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; n-3, omega-3; TC, total cholesterol; TG, triglycerides; VLDL, very-low-density lipoprotein.

lowest (Q1) intake groups of all exposure variables in terms of risk of CVD events. Figure 4 summarizes the significant associations (P_{trend}<0.05) between the exposure variables and lipid and lipoprotein subfractions.

The n-3 fatty acids had some similarities but also differed in their associations with lipid and lipoprotein CVD risk patterns. The higher intake of fish and total n-3 was associated with a decrease of large VLDL particle concentration, but ALA was the only n-3 that had a significant association with lower levels of LDL-C. In contrast, higher DHA and ALA intake was associated with an increased size of LDL and HDL particles, factors known to be associated with a

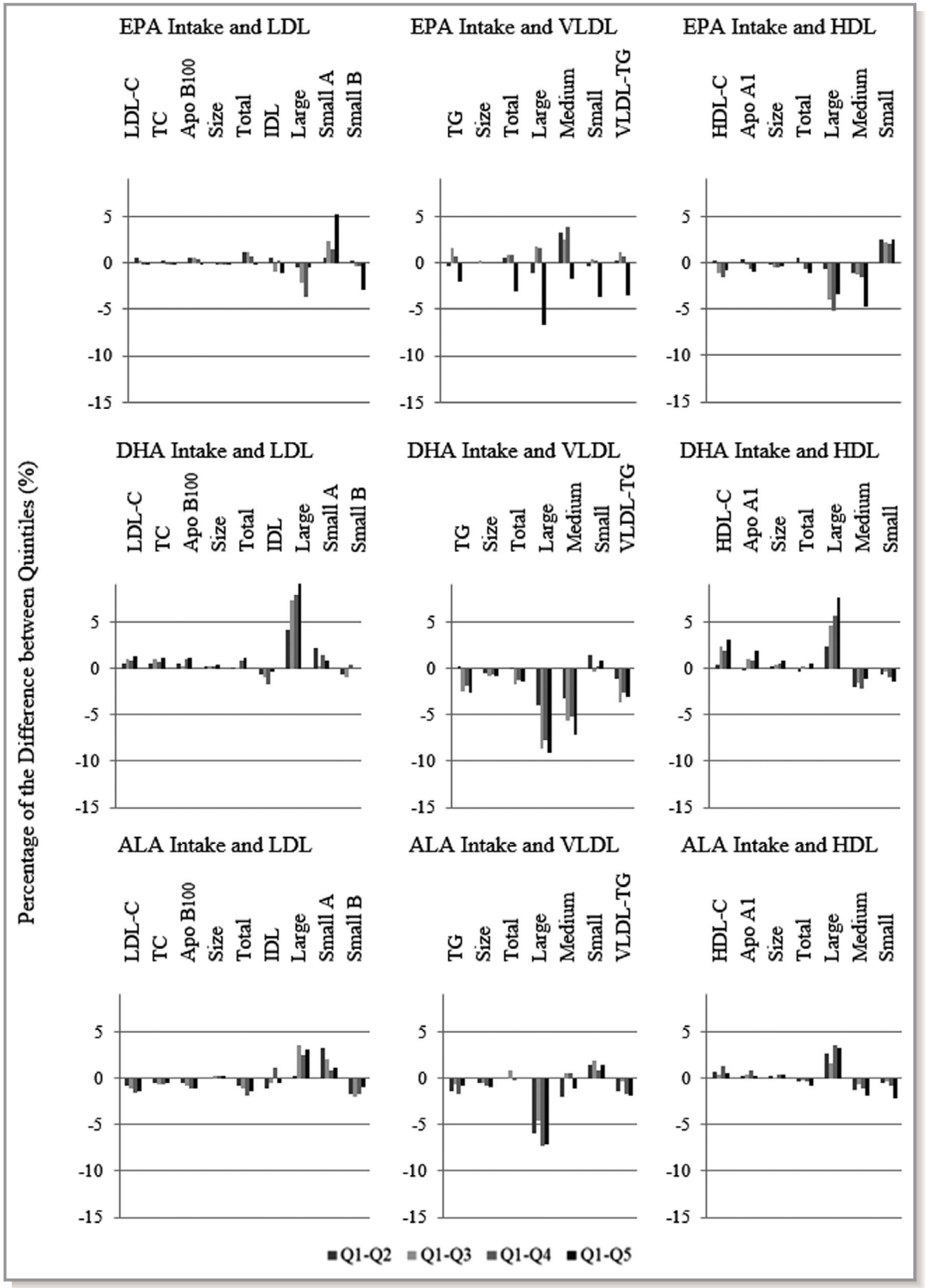


Figure 2. Adjusted percentage difference in lipids and lipoproteins between quintiles (Qs; Q2–Q5) compared with Q1 of n-3 subtype intakes. ALA indicates α-linolenic acid; Apo, apolipoprotein; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; n-3, omega-3; TC, total cholesterol; TG, triglycerides; VLDL, very-low-density lipoprotein.

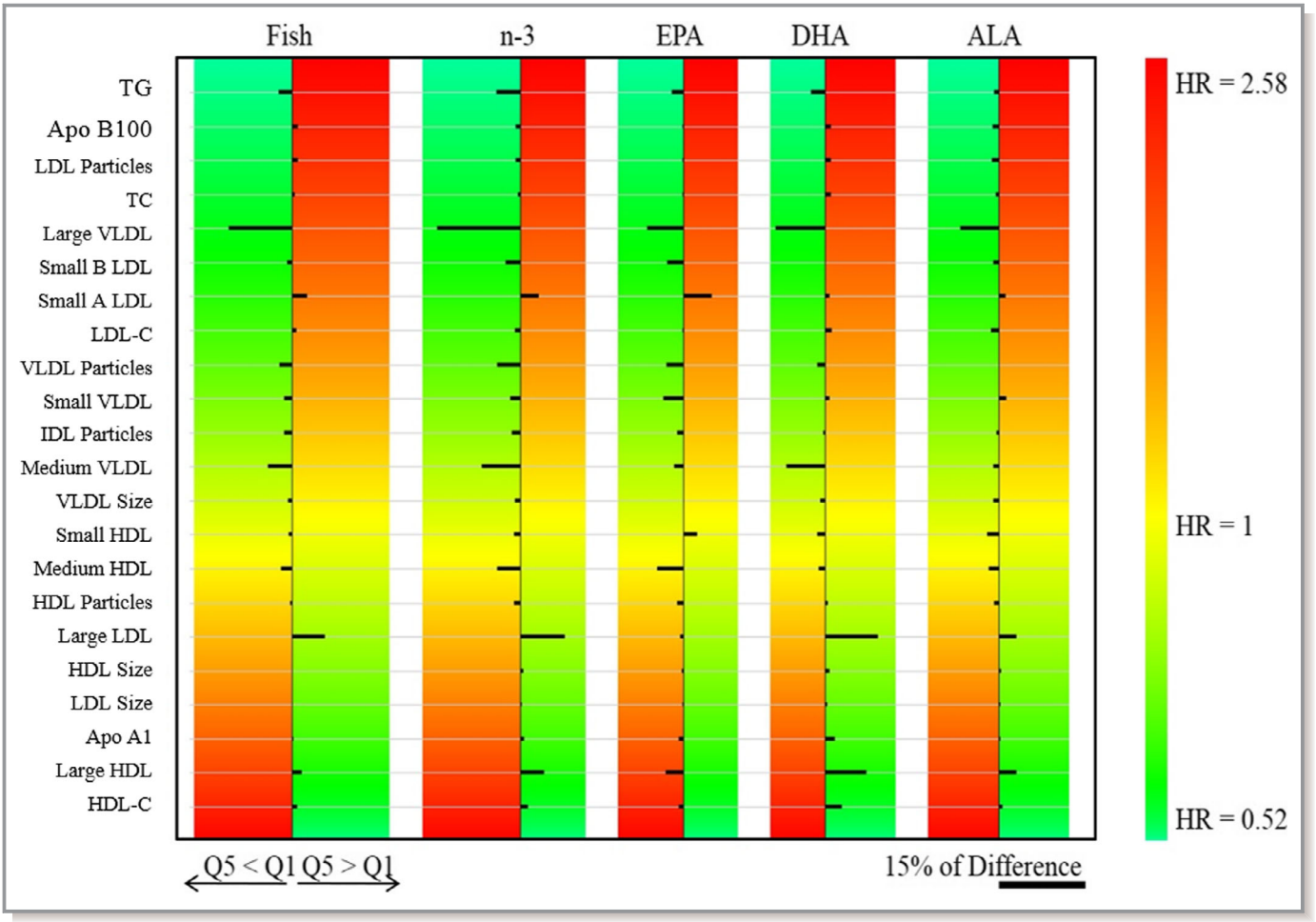


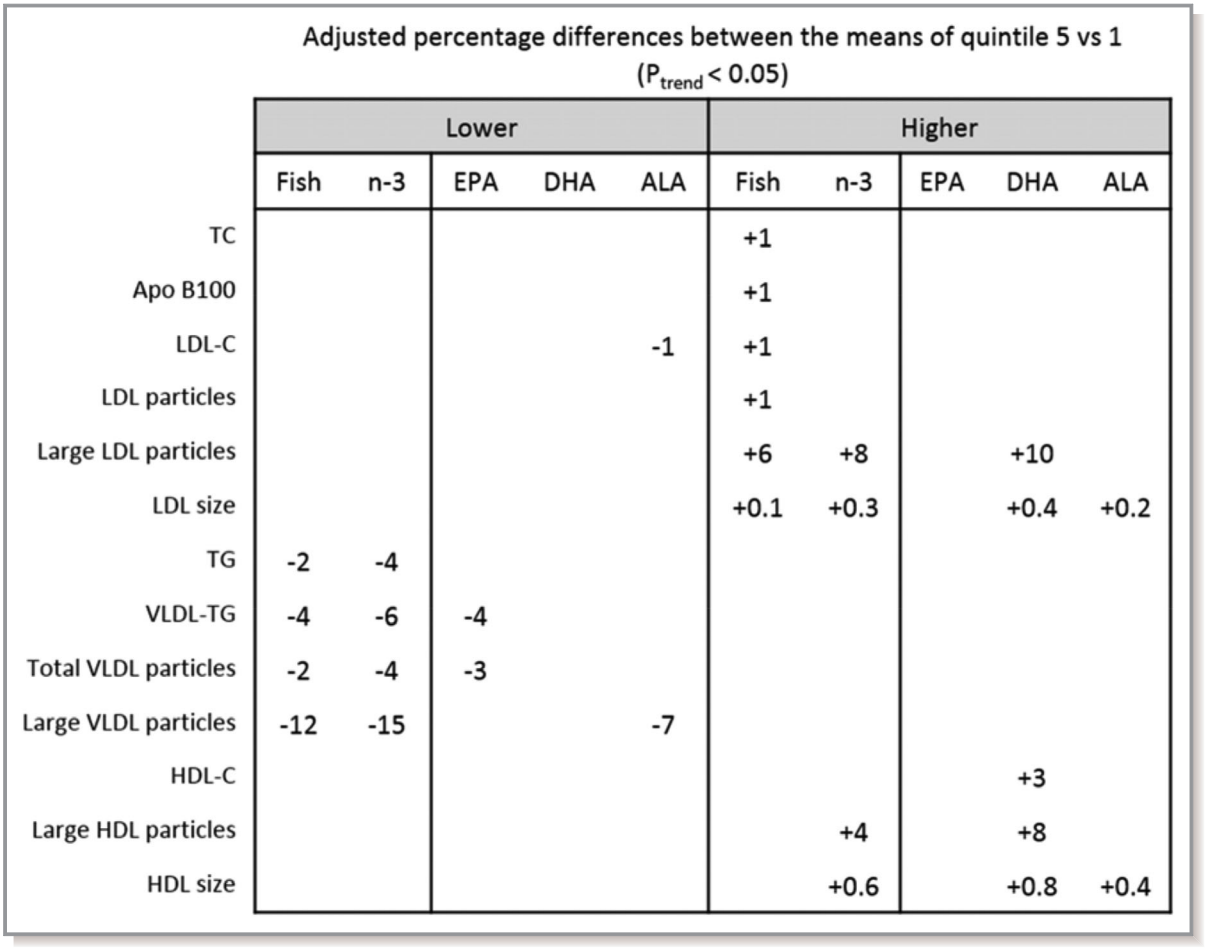
Figure 3. Heat map of percentage differences between adjusted means of greater and lower intake groups of the exposure variables (Q5–Q1) according to intake of fish, total n-3, and n-3 subtypes. Outcome variables are sorted according to previously reported hazard ratios (HRs) adjusted for nonlipid risk factors. Green is associated with lower risk of cardiovascular disease (CVD), and red is associated with higher risk of CVD. The right-lower scale bar illustrates the magnitude (length) of a 15% difference between Q5 and Q1, in which smaller bars represent <15% difference and larger bars represent >15% difference. When the consumption of higher amounts of exposure variables decreases the outcome variable, Q5<Q1; when the consumption of higher amounts of exposure variables increases the outcome variable, Q5>Q1 (fish: Q1, n=5839; Q5, n=5617; n-3: Q1, n=5248; Q5, n=5123; EPA: Q1, n=5370; Q5, n=4947; DHA: Q1, n=6351; Q5, n=4797; ALA: Q1, n=5286; Q5, n=5097). ALA indicates α-linolenic acid; Apo, apolipoprotein; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; n-3, omega-3; Q, quintile; TC, total cholesterol; VLDL, very-low-density lipoprotein.

lower risk for CVD. EPA was associated with lower VLDL particles, a finding that would be expected to result in lower risk for CVD.

Discussion

In this large cohort of 26 034 female healthcare professionals, we found that habitual fish consumption and total dietary-derived n-3 fatty acids had generally similar and predominantly cardioprotective patterns of associations with lipid, apolipoprotein, and lipoprotein particle measurements. Notable exceptions include the observation that only higher consumption of fish (but not n-3) was associated with higher levels of LDL-C and apo B_{100}; conversely, only dietary n-3 fatty acids showed a significant increase in HDL size and in large HDL particles. The different intake of n-3 subtypes had different patterns of association. DHA and ALA (but not EPA) were associated with larger HDL and LDL size, whereas only ALA was associated with lower LDL-C. In contrast, high EPA intake was significantly associated with only a decreased level of VLDL particle concentration and VLDL-triglycerides. Finally, associations became evident from analysis of detailed lipoprotein particle measurements and were not as readily detected with standard lipid measurements.

Both higher habitual fish and total n-3 fatty acid intake were significantly associated with lower levels of triglycerides



Adjusted percentage differences between the means of quintile 5 vs 1 ($P_{trend} < 0.05$)

	Lower					Higher				
	Fish	n-3	EPA	DHA	ALA	Fish	n-3	EPA	DHA	ALA
TC						+1				
Apo B100						+1				
LDL-C					-1	+1				
LDL particles						+1				
Large LDL particles						+6	+8		+10	
LDL size						+0.1	+0.3		+0.4	+0.2
TG	-2	-4								
VLDL-TG	-4	-6	-4							
Total VLDL particles	-2	-4	-3							
Large VLDL particles	-12	-15			-7					
HDL-C									+3	
Large HDL particles							+4		+8	
HDL size							+0.6		+0.8	+0.4

Figure 4. Percentage differences between the means of the greater and lower intake groups of the exposure variables (Q5–Q1) after adjusting for all demographic, clinical, and dietary factors that showed a significant association ($P_{Trend}<0.05$) among fish, total n-3, and the different n-3 subtypes of fatty acid intake and lipid and lipoprotein subfractions. Blank spaces indicate no significant association (fish: Q1, n=5839; Q5, n=5617; n-3: Q1, n=5248; Q5, n=5123; EPA: Q1, n=5370; Q5, n=4947; 6 DHA: Q1, n=6351; Q5, n=4797; ALA: Q1, n=5286; Q5, n=5097). ALA indicates α-linolenic acid; Apo, apolipoprotein; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; TC, total cholesterol; LDL, low density lipoprotein; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; VLDL, very-low-density lipoprotein; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol. For the adjusted means please see Table S14.

and a tendency toward increased levels of HDL-C, but their associations with LDL-C were discordant. Specifically, higher fish intake was associated with a significant but small increase in LDL-C, whereas total dietary n-3 fatty acid intake was associated with a trend toward reduced levels of LDL-C that was mostly accounted for by the plant-derived ALA. Both higher habitual fish and total n-3 fatty acid intake were associated with increased LDL size, which was accounted for by a shift toward larger LDL particles. Whereas increased fish consumption was associated with higher levels of LDL particle concentration and apo B_{100}, increased intake of dietary n-3 fatty acids was not associated with higher levels of either measure. This finding suggests that another factor (possibly cooking oil) may underlie the association of fish consumption with increased LDL particles and apo B_{100}.

The VLDL fractions showed similar associations with both higher habitual fish consumption and higher total n-3 fatty acid intake in the form of a reduction in all VLDL subfractions, which was most pronounced for the large subfraction. As such, total VLDL particle concentration and average VLDL particle size were also reduced. With regard to HDL particles, only n-3 fatty acids were associated with larger HDL size and a significant increase in concentration of large HDL particles.

We know of only 1 study that examined the detailed associations of dietary intake of n-3 fatty acids with detailed lipoprotein particle phenotypes.[38] Consistent with our findings, that study found that higher intake of dietary n-3 fatty acids was associated with lower concentrations of large VLDL particles, smaller average VLDL size, and higher concentration of large HDL. In contrast, a direct association with large LDL

particle concentration was found only in men and not in women in that study. Two Finnish cohorts used serum markers of n-3 fatty acids as a surrogate for habitual fish consumption. One cohort used the ratio of DHA to total fatty acid,[39] and the other cohort used circulating n-3 fatty acids.[40] These were both found to be negatively correlated with VLDL particle size and positively correlated with HDL particle size. One of these cohorts also found that a 6-year change in serum n-3 was positively correlated with a 6-year change in HDL and LDL particle size but was negatively correlated with change in VLDL particle size.[40] Our findings are additionally supported by 2 small randomized placebo-controlled feeding studies that found an increase in HDL particle size with fatty fish consumed 3 times weekly for 12 weeks[41] or 4 times weekly for 8 weeks.[42]

Mechanistically, n-3 fatty acids reduce VLDL production by inhibiting the hepatic synthesis of fatty acids and reducing packaging of VLDL and increase the clearance of VLDL by enhancing lipoprotein lipase activity,[43] thus explaining the lower levels of all VLDL subclasses and triglycerides. The role of n-3 fatty acids on LDL metabolism is unclear, particularly regarding clearance, although the increase in VLDL metabolism with n-3 fatty acids may imply a high turnover toward larger LDL particles, as shown in our study. Improvement in reverse cholesterol transport with n-3 fatty acid supplementation[44] provides a biological rationale for the associated increase toward large HDL size with higher intake of fish or dietary n-3 fatty acids. The differential association we found between fish consumption versus dietary n-3 fatty acids on LDL particle concentration or apo B_{100} deserves further mention. This likely relates to their differential association with LDL-C, similar to findings from other studies showing that fatty fish consumption increases LDL-C,[16] but n-3 polyunsaturated fatty acids (PUFA) supplementation reduces the apo B_{100} concentration without reducing LDL-C levels and subsequently increases LDL particle size.[45] Accounting for other sources of fat, as in our n-3 fatty analysis, was not possible when we examined fish consumption. This may partly explain the differential association in relation to LDL particle concentration apo B_{100}.

To our knowledge, no prior study has examined dietary doses of various n-3 fatty acids types with lipoprotein particles. With the exception of a few notable differences, the associations we found for n-3 fatty acids were generally similar to those observed for dietary-derived EPA or DHA, the major types of fish-derived n-3 fatty acids, and those observed for ALA, the plant-derived n-3 fatty acid. Unlike EPA, both DHA and ALA were associated with a redistribution of HDL particles toward larger ones. In addition, ALA was the only n-3 associated with lower levels of LDL-C and lower apo B_{100}, suggesting that a reduction in total LDL particle number may partly account for its differential association on LDL-C (by comparison, fish intake was associated with increased levels of LDL-C, as shown by other studies[14,45,46]). The biological activity of ALA is mostly linked to its conversion to EPA and DHA, with the direct effects of ALA-rich oils being largely unknown. Diets high in ALA have been shown to reduce hepatic cholesterol synthesis, which may account for the unique inverse association we found between ALA and LDL-C.[47] It is also plausible that residual confounding arising from the plant-based source of ALA partly accounts for its LDL-lowering effect.

In this study, we report for the first time that higher habitual fish consumption and higher levels of dietary-derived n-3 fatty acid intake were both associated with greater differences in lipoprotein subfractions than traditional lipids. This finding suggests that dietary-derived n-3 fatty acids may influence CVD risk through lipid and lipoprotein metabolism, perhaps more than previously appreciated. Lipoprotein particle numbers, particularly LDL and HDL, have been shown to perform better than their respective major lipid components (ie, LDL-C and HDL-C) in assessing CVD risk.[22–24] In this regard, the direction of association we observed for the lipoprotein subfractions was consistent with a generally beneficial profile for future CVD risk, as observed in studies evaluating lipoproteins and CVD risk.[23,24,48–51] In a prior analysis of the same WHS population, we found that larger average sizes of LDL and HDL were associated with lower risk of future CVD.[24] Similar results were observed in analyses of other more recent studies.[48,49] Furthermore, recent studies have shown that other components of VLDL particles, such as VLDL cholesterol and remnant cholesterol, perform better than triglycerides in assessing CVD risk.[52] This also suggests that the larger magnitude of association that we found for VLDL particles compared with triglycerides may relate to dietary-derived n-3 fatty acid intake affecting CVD risk, occurring more through lipoproteins than through traditional lipids. Nonetheless, additional studies will be needed to confirm our findings and to directly examine the relative impact of lipids versus lipoproteins in mediating the attributable CVD risk of dietary n-3 fatty acids.

The current study has potential limitations. First, dietary assessment was ascertained in only 1 baseline FFQ; as such, we could not account for dietary changes over time. Second, given that participants were asked to self-report their average dietary pattern over the year before the questionnaires were administered, and it is possible that estimated dietary intake may not reflect dietary intake at the time of the blood draw; however, we expect such misclassification to be nondifferential and thus bias the observed results toward the null hypothesis. Third, the study design limits our ability to infer causality for dietary fish or n-3 intake and the lipid phenotypes that we examined because we cannot exclude the possibility of residual confounding or reverse causation, although we adjusted for

many potential confounders. Moreover, the n-3 fatty acid intake came from food sources and/or supplements that represent different sources of n-3 fatty acid. Fourth, our study was restricted to middle-aged women who were healthcare professionals. As such, the generalizability of our findings to other populations may be limited, particularly for those with prevalent diabetes mellitus, who would likely have high TG as findings of other studies may not be directly applicable to this population of relatively healthy women. Multiple comparisons were performed, increasing the chance of a type I error. However, many *P* values were highly statistically significant, and the findings are supported by prior biological and epidemiologic studies. Nonetheless, given the multiplicity of hypotheses tested, these results should be viewed as hypothesis-generating and require further validation in additional cohorts. Our study had notable strengths including the large sample size, comprehensive assessment of dietary factors and other cardiometabolic risk markers, and detailed assessment of lipids and lipoprotein particle measurements. A unique attribute of our study is the use of energy-adjusted dietary measures, which provide the most robust parameterization of nutrients for assessing CVD risk, underscored by the reciprocal composition of macronutrients that comprise total caloric intake.

In sum, our study adds insights to the literature by showing that fish consumption and isocaloric dietary-derived n-3 fatty acids relate to a profile of lipoprotein particles consistent mostly with cardiovascular benefit, with differences noted for high intake of EPA (lower VLDL particles and VLDL triglycerides) compared with DHA and ALA (larger LDL and HDL size) and with ALA (lower LDL-C and apo B_{100}) that were apparent with detailed lipoprotein phenotyping. These hypothesis-generating findings warrant further study in randomized controlled trials.

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Mora received research grant support from Atherotech Diagnostics and NHLBI; served as consultant to Quest Diagnostics, for work outside the current study; and is coinventor on a patent on the use of an nuclear magnetic resonance (NMR)–measured biomarker (GlycA) for predicting risk of colorectal cancer. Amigó and Correig are stock owners of Biosfer Teslab and have a patent for an NMR method for lipoprotein characterization. The remaining authors have no disclosures to report.

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SUPPLEMENTAL MATERIAL

Online Supporting Material

Supplemental Figures and Tables:

Table s1- Particle Diameter ranges.

Table s2- Baseline characteristics of 26034 apparently healthy women according to quintiles (Q) of fish and energy adjusted marine n-3 intake.

Table s3- Baseline characteristics of 26034 apparently healthy women according to quintiles (Q) of energy adjusted ALA, EPA and DHA fatty acid intake.

Table s4- Raw means (or geometrical means) and adjusted means of LDL related variables according to quintiles of energy adjusted EPA intake.

Table s5- Raw means (or geometrical means) and adjusted means of LDL related variables according to quintiles of energy adjusted DHA intake.

Table s6- Raw means (or geometrical means) and adjusted means of LDL related variables according to quintiles of energy adjusted ALA intake.

Table s7- Raw means (or geometrical means) and adjusted means of VLDL related variables according to quintiles of energy adjusted EPA intake.

Table s8- Raw means (or geometrical means) and adjusted means of VLDL related variables according to quintiles of energy adjusted DHA intake.

Table s9- Raw means (or geometrical means) and adjusted means of VLDL related variables according to quintiles of energy adjusted ALA intake.

Table s10- Raw means (or geometrical means) and adjusted means of HDL related variables according to quintiles of energy adjusted EPA intake.

Table s11- Raw means (or geometrical means) and adjusted means of HDL related variables according to quintiles of energy adjusted DHA intake.

Table s12- Raw means (or geometrical means) and adjusted means of HDL related variables according to quintiles of energy adjusted ALA intake.

Table s13- Correspondence between absolute values and per 1% and per 5% differences.

Table s14- Adjusted means for the lower exposure quintiles (Q1) that showed a significant association (Ptrend<0.05).

Table s1- Particle diameter ranges.

	Diameter range (nm)	% CV
LDL Particles		
Total	18-23	2.1
Large	21.2-23	6.3
Small	18-21.2	4.7
IDL Particles	23-27	13.1
HDL Particles		
Total	7.3-13	1.5
Large	8.8-13	5.9
Medium	8.2-8.8	<30
Small	7.3-8.2	3.7
VLDL Particles		
Total	≥27	3.1
Large	> 60	5.1
Medium	35-60	4.1
Small	27-35	7.1

Table s2- Baseline characteristics of 26,034 apparently healthy women according to quintiles of fish and energy adjusted marine n-3 intake.

	Total fish intake (median [min, max] serv/day)				**Total marine n-3 (median [min, max] g/day)**			
Characteristic	Q:1	Q:3	Q:5	*P*	Q:1	Q:3	Q:5	*P*
	0.07 [0, 0.07]	0.21 [0.2, 0.21]	0.5 [0.43, 0.64]		0.95 [0.86, 1.02]	1.35 [1.31, 1.39]	1.89 [1.77, 2.1]	
N	5839	5465	5617		5248	4991	5123	
Age (y)	52.5 [48.6, 59.0]	52.8 [49.0, 58.8]	53.2 [49.2, 59.0]	0.0025	52.1 [48.5, 57.7]	52.7 [48.9, 58.7]	54 [49.6, 60]	<0.0001
White (%)	96.0	95.8	94.0	<0.0001	95.2	96.0	95.1	<0.0001
BMI (kg/m^2)	24.7 [22.3, 28.2]	24.6 [22.3, 27.8]	25.0 [22.6, 28.3]	<0.0001	24.3 [22.1, 27.9]	24.9 [22.5, 28.2]	25.0 [22.6, 28.3]	<0.0001
Exercise (MET-h/wk)	6.87 [1.97, 17.51]	9.11 [3.03, 20.74]	11.3 [4.02, 23.55]	<0.0001	7.70 [2.30, 19.5]	9.20 [3.10, 20.94]	9.90 [3.01, 21.50]	<0.0001
Fruits and vegetables (serving/d)	4.44 [2.96, 6.30]	5.45 [3.93, 7.34]	6.96 [5.08, 9.32]	<0.0001	4.66 [3.14, 6.64]	5.58 [4.01, 7.63]	6.06 [4.29, 8.32]	<0.0001
Nuts (serving/d)	0 [0 0.13]	0.07 [0, 0.13]	0.07 [0, 0.13]	<0.0001	0 [0, 0.13]	0.07 [0, 0.13]	0.07 [0, 0.13]	<0.0001
Red meat (serving/d)	0.55 [0.27, 0.91]	0.63 [0.34, 0.98]	0.56 [0.33, 0.98]	<0.0001	0.63 [0.34, 1.06]	0.63 [0.34, 0.99]	0.50 [0.28, 0.85]	<0.0001
Energy intake (kcal/d)	1471 [1177, 1826]	1686 [1377, 2035]	1896 [1557, 2284]	<0.0001	1639 [1324, 2008]	1707 [1368, 2105]	1649 [1322, 2017]	<0.0001
Dietary magnesium (mg) [1]	314 [273, 366]	327 [289, 372]	352 [314, 399]	<0.0001	323 [279, 374]	329 [291, 377]	334 [294, 386]	<0.0001
***trans* Fatty acids (g/d) [1]**	2.27 [1.65, 3.09]	2.10 [1.58, 2.82]	1.81 [1.33, 2.47]	<0.0001	2.02 [1.48, 2.7]	2.1 [1.56, 2.83]	2.08 [1.47, 2.86]	<0.0001
Saturated fatty acids (g/d) [1]	20.3 [17.1, 23.7]	19.5 [16.7, 22.5]	18.0 [15.2, 20.9]	<0.0001	19.6 [16.3, 23.1]	19.4 [16.5, 22.4]	19.0 [16.3, 21.9]	<0.0001
Cereal fiber (g/d) [1]	4.27 [3.57, 5.12]	4.33 [3.70, 5.11]	4.57 [3.91, 5.41]	<0.0001	4.11 [3.44, 4.91]	4.4 [3.74, 5.16]	4.62 [3.92, 5.45]	<0.0001
Parental history of diabetes (%)	24.5	23.9	26.3	0.01	24.3	24.6	26.0	0.13
Glycated hemoglobin (%)	4.99 [4.84, 5.18]	4.99 [4.83, 5.17]	5.00 [4.83, 5.18]	0.13	4.99 [4.83, 5.17]	4.99 [4.83, 5.18]	5.00 [4.83, 5.17]	0.33
Current smoking (%)	12.5	11.6	10.2	<0.0001	14.2	10.4	11.5	<0.0001
Daily alcohol use (%)	7.1	11.9	12.0	<0.0001	11.8	10.5	9.78	<0.0001
Postmenopausal (%)	53.6	53.8	54.7	0.0019	51.5	53.7	57.5	<0.0001
Hormone Therapy use (%)	43.0	44.5	44.5	0.03	42.2	44.3	45.8	<0.001
Hypertension (%)	23.2	23.6	25.8	0.01	23.2	23.1	26.0	0.0015

Values shown are medians (25th 75th percentile) or percentages. MET-h indicates metabolic equivalent task hours. P values were derived from Wilcoxon rank sum test (continuous variables) or chi-squared test (categorical variables).[1]Energy adjusted.

Table s3- Baseline characteristics of 26034 women according to quintiles (Q) of energy adjusted EPA, DHA and ALA fatty acid intake.

	Eicosapentaenoic acid (EPA)				Docosahexaenoic acid (DHA)				α-Linolenic acid (ALA)			
Characteristic	Q:1	Q:3	Q:5	*P*	Q:1	Q:3	Q:5	*P*	Q:1	Q:3	Q:5	*P*
N	5370	3226	4947		6351	4860	4797		5286	5225	5079	
Age (y)	52.6 [48.6 59.0]	52.7 [48.8 58.3]	53.6 [49.4 59.2]	<.0001	52.5 [48.6 58.9]	52.8 [48.8 58.6]	53.4 [49.5 59.1]	<.0001	52.2 [48.6 58.0]	52.7 [48.9 58.7]	53.8 [49.4 60.1]	<.0001
White (%)	96.7	96.5	92.1	<.0001	96.7	96.1	92.2	<.0001	93.7	96.0	96.8	<.0001
BMI (kg/m^2)	24.9 [22.3 28.3]	25.1 [22.6 28.3]	24.5 [22.3 27.5]	<.0001	24.8 [22.3 28.3]	24.8 [22.5 28.3]	24.8 [22.5 28.2]	0.57	24.3 [22.1 27.8]	24.9 [22.6 28.3]	25.0 [22.5 28.4]	<.0001
Exercise (MET-h/wk)	7.14 [2.11 17.50]	8.83 [2.92 20.20]	11.8 [4.25 24.39]	<.0001	7.00 [2.12 17.87]	8.70 [2.87 20.20]	11.8 [4.15 24.4]	<.0001	8.69 [2.63 20.94]	9.00 [3.01 20.61]	8.68 [2.64 20.20]	0.01
Fruits & veg. (serving/d)	4.92 [3.44 6.82]	5.36 [3.77 7.30]	6.04 [4.28 8.23]	<.0001	4.89[3.33 6.87]	5.45 [3.89 7.50]	6.15 [4.34 8.43]	<.0001	4.87 [3.25 6.86]	5.65 [4.00 7.73]	5.81 [4.10 7.98]	<.0001
Nuts (serving/d)	0 [0 0.13]	0 [0 0.13]	0.07 [0 0.13]	<.0001	0 [0 0.13]	0.07 [0 0.13]	0.07 [0 0.13]	<.0001	0 [0 0.13]	0.07 [0 0.13]	0.07 [0 0.13]	<.0001
Red meat (serving/d)	0.64 [0.34 1.06]	0.56 [0.34 0.91]	0.43 [0.27 0.77]	<.0001	0.70 [0.34 1.07]	0.63 [0.35 0.99]	0.42 [0.27 0.71]	<.0001	0.56 [0.29 0.98]	0.63 [0.34 0.99]	0.56 [0.33 0.91]	<.0001
Energy intake (kcal/d)	1604 [1325 1988]	1545 [1281 1954]	1577 [1288 1947]	<.0001	1655 [1330 2050]	1681 [1362 2074]	1592 [1280 1961]	<.0001	1644 [1329 2004]	1713 [1368 2093]	1656 [1334 2026]	<.0001
Diet. magnesium (mg) [1]	314 [274 364]	331 [294 378]	351 [312 400]	<.0001	312 [272 362]	327 [291 373]	357 [316 406]	<.0001	332 [285 384]	331 [291 379]	323 [286 370]	<.0001
***trans* FA (g/d) [1]**	2.31 [1.67 3.12]	2.08 [1.56 2.76]	1.75 [1.29 2.35]	<.0001	2.34 [1.71 3.15]	2.10 [1.59 2.82]	1.72 [1.27 2.33]	<.0001	1.86 [1.37 2.55]	2.11 [1.58 2.79]	2.28 [1.62 3.08]	<.0001
Saturated FA (g/d) [1]	20.4 [17.2 23.7]	19.3 [16.5 22.1]	17.9 [15.1 20.9]	<.0001	20.5 [17.3 23.8]	19.5 [16.7 22.3]	17.7 [14.9 20.7]	<.0001	18.9 [15.6 22.3]	19.3 [16.6 22.3]	19.6 [16.9 22.5]	<.0001
Cereal fibre (g/d) [1]	4.27 [3.59 5.13]	4.38 [3.75 5.12]	4.58 [3.89 5.44]	<.0001	4.24 [3.57 5.09]	4.33 [3.70 5.10]	4.61 [3.92 5.49]	<.0001	4.15 [3.47 4.99]	4.39 [3.73 5.16]	4.55 [3.86 5.38]	<.0001
Par. Hist. diabetes (%)	24.4	26.0	24.8	0.17	24.4	24.2	25.8	0.32	24.4	24.7	25.6	0.38

GH (%)	5.00 [4.84 5.18]	4.99 [4.83 5.16]	4.98 [4.82 5.17]	0.03	5.00 [4.84 5.17]	4.99 [4.84 5.17]	4.99 [4.83 5.17]	0.25	4.99 [4.83 5.17]	4.98 [4.83 5.17]	5.01 [4.84 5.18]	0.03
Current smoking (%)	12.4	13.2	10.1	<.0001	12.9	11.9	10.3	<.0001	13.8	10.4	12.1	<.0001
Daily alcohol use (%)	7.32	10.3	13.7	<.0001	8.36	10.3	11.5	<.0001	13.5	9.90	9.18	<.0001
Postmenopausal (%)	53.7	52.6	55.8	<.0001	53.5	54.3	55.4	<.0001	51.6	54.1	57.6	<.0001
HT use (%)	42.4	45.2	46.8	<.0001	42.4	43.6	46.0	<.001	41.7	44.4	45.5	0.0018
Hypertension (%)	22.9	24.0	24.4	0.22	23.3	23.7	25.8	0.02	23.6	23.6	25.4	0.14

Values shown are medians (25^{th} 75^{th} percentile) or percentages. MET-h indicates metabolic equivalent task hours. veg.: vegetables. Diet. Magnesium: Dietary magnesium. FA: Fatty Acids. Par. Hist. Diabetes: Parental History of Diabetes. GH: Glycated Haemoglobin. P values were derived from Wilcoxon rank sum test (continuous variables) or chi-squared test (categorical variables). [1]Energy adjusted

Table s4- LDL related variables. Strategy based on modelling energy adjusted variables.

		Quintile of energy adjusted EPA intake (gm)			
		Q1 0.01 [0.01 0.01]	Q3 0.04 [0.04 0.05]	Q5 0.12 [0.11 0.16]	P_{Trend}
LDL-C	Raw mean	123 ± 34	125 ± 34	124 ± 35	
(mg/dL)	Adj. mean[1]	123 [122 124]	125 [124 126]	124 [123 125]	0.29
	Adj. mean[2]	123 [122 125]	124 [123 125]	123 [122 125]	0.50
TC	Raw mean	210 ± 41	213 ± 42	213 ± 42	
(mg/dL)	Adj. mean[1]	210 [208 211]	213 [212 214]	213 [212 214]	0.002
	Adj. mean[2]	211 [210 212]	211 [210 212]	211 [209 212]	0.39
ApoB100	Raw mean	103 ± 28	104 ± 28	103 ± 28	
(mg/dL)	Adj. mean[1]	103 [102 103]	105 [104 105]	103 [103 104]	0.68
	Adj. mean[2]	103 [102 104]	103 [102 104]	103 [101 103.7]	0.52
LDL Size	Geom. mean	21.04 [21.02 21.06]	21.05 [21.03 21.07]	21.12 [21.11 21.14]	
(Ø nm)	Adj. mean[1]	21.04 [21.02 21.06]	21.05 [21.03 21.07]	21.12 [21.1 21.13]	<.0001
	Adj. mean[2]	21.1 [21.08 21.13]	21.06 [21.03 21.08]	21.07 [21.04 21.1]	0.52
LDL Particles					
Total	Geom. mean	1189 [1179 1200]	1211 [1198 1225]	1190 [1180 1201]	
(nm/L)	Adj. mean[1]	1189 [1178 1199]	1214 [1200 1227]	1191 [1180 1202]	0.41
	Adj. mean[2]	1184 [1169 1199]	1197 [1183 1210]	1182 [1165 1199]	0.30
IDL	Geom. mean	146 [143 148]	145 [141 148]	147 [145 150]	
(nm/L)	Adj. mean[1]	146 [143 148]	145 [142 149]	146 [143 149]	0.96
	Adj. mean[2]	146 [142 151]	145 [141 149]	144 [139 149]	0.68
Large	Geom. mean	463 [454 473]	481 [469 494]	515 [505 525]	
(nm/L)	Adj. mean[1]	462 [453 471]	482 [470 494]	512 [501 523]	<.0001
	Adj. mean[2]	491 [475 507]	480 [467 494]	488 [470 506]	0.89
Small A	Geom. mean	62.2 [61.3 63.2]	64 [62.6 65.5]	65.8 [64.4 67.2]	
(nm/L)	Adj. mean[1]	62.3 [61.3 63.2]	64 [62.6 65.4]	66 [64.5 67.4]	<.001
	Adj. mean[2]	62.4 [60.7 64.2]	63.9 [62.3 65.6]	65.7 [63.2 68.2]	0.16
Small B	Geom. mean	661 [650 671]	662 [648 676]	647 [635 658]	
(nm/L)	Adj. mean[1]	662 [651 673]	663 [649 676]	644 [632 656]	0.02
	Adj. mean[2]	657 [640 673]	654 [640 669]	637 [619 656]	0.27

Raw means ± sd and geometric (Geom.) means [CI]. [1] Model 1: The adjusted means (Adj.) are estimated from linear regression models adjusted for age (continuous), total energy (quintiles), energy adjusted saturated fats (quintiles), energy adjusted monounsaturated fats (quintiles), energy adjusted *trans*-fat (quintiles), energy adjusted total n-6 (quintiles) and energy adjusted proteins (quintiles). *ls-means.

[2] Model 2: Adjusted as in model 1 but including smoking (current, past, never), alcohol use (rarely/never, 1–3 drinks/month, 1–6 drinks/week, and 1 drinks/day), BMI (continuous), exercise (quintiles of metabolic equivalent task hours per week), menopausal status (premenopausal, uncertain, postmenopausal), use of HT (current, past/never), hypertension (systolic blood pressure of at least 140 mmHg, diastolic blood pressure of at least 90 mmHg), antihypertensive treatment (yes or no), hypercholesterolemia (total cholesterol of at least 240 mg/dL), treatment for high cholesterol (yes or no), parental history of CHD (yes or no), energy adjusted glycemic index (quintiles), multivitamin use (current, past and never), aspirin use (Current use > 1x/week), read meat consumption, fruits and vegetables consumption (both quintiles) and energy adjusted ALA and DHA fatty acids (both in quintiles).

Table s5- LDL related variables. Strategy based on modelling energy adjusted variables.

		Quintile of energy adjusted DHA intake (gm)			
		Q2	Q3	Q5	P_{Trend}
		0.09 [0.08 0.1]	0.12 [0.11 0.13]	0.28 [0.24 0.35]	
LDL-C	Raw mean	124 ± 33	125 ± 35	125 ± 35	
(mg/dL)	Adj. mean[1]	124 [123 125]	125 [124 126]	125 [124 126]	0.005
	Adj. mean[2]	123 [122 124]	124 [123 125]	124 [123 126]	0.23
TC	Raw mean	212 ± 41	212 ± 42	214 ± 42	
(mg/dL)	Adj. mean[1]	212 [210 213]	213 [211 214]	214 [213 215]	<.0001
	Adj. mean[2]	211 [210 212]	212 [211 213]	212 [211 214]	0.11
ApoB100	Raw mean	104 ± 28	104 ± 28	104 ± 28	
(mg/dL)	Adj. mean[1]	104 [103 104]	104 [103 104]	104 [103 105]	0.01
	Adj. mean[2]	103 [102 104]	103 [102 103]	104 [102 104.8]	0.27
LDL Size	Geom. mean	21.06 [21.04 21.08]	21.08 [21.06 21.1]	21.11 [21.09 21.13]	
(Ø nm)	Adj. mean[1]	21.06 [21.04 21.08]	21.08 [21.06 21.1]	21.11 [21.09 21.13]	<.0001
	Adj. mean[2]	21.07 [21.04 21.09]	21.09 [21.07 21.11]	21.12 [21.08 21.15]	0.0075
LDL Particles					
Total	Geom. mean	1198 [1187 1210]	1201 [1190 1212]	1203 [1192 1214]	
(nm/L)	Adj. mean[1]	1197 [1186 1208]	1201 [1190 1211]	1204 [1192 1216]	0.09
	Adj. mean[2]	1186 [1173 1199]	1187 [1176 1198]	1198 [1180 1217]	0.38
IDL	Geom. mean	147 [144 150]	146 [144 149]	147 [144 150]	
(nm/L)	Adj. mean[1]	147 [144 150]	147 [144 150]	146 [143 149]	0.85
	Adj. mean[2]	146 [142 150]	145 [142 149]	146 [141 152]	0.83
Large	Geom. mean	476 [466 487]	489 [479 499]	507 [496 518]	
(nm/L)	Adj. mean[1]	477 [467 487]	490 [480 500]	508 [497 519]	<.0001
	Adj. mean[2]	479 [465 492]	493 [482 505]	504 [485 524]	0.02
Small A	Geom. mean	63.7 [62.5 64.9]	63.3 [61.9 64.7]	65.3 [63.9 66.7]	
(nm/L)	Adj. mean[1]	63.5 [62.3 64.8]	63.2 [61.9 64.6]	65.4 [63.9 66.9]	0.005
	Adj. mean[2]	64.2 [62.6 66]	62.9 [61.4 64.5]	63.3 [60.9 65.9]	0.72
Small B	Geom. mean	655 [644 667]	651 [640 663]	658 [647 670]	
(nm/L)	Adj. mean[1]	657 [645 668]	651 [641 663]	655 [643 667]	0.23
	Adj. mean[2]	650 [636 664]	648 [636 660]	654 [635 674]	0.96

Raw means ± sd and geometric (Geom.) means [CI]. [1] Model 1: The adjusted means (Adj.) are estimated from linear regression models adjusted for age (continuous), total energy (quintiles), energy adjusted saturated fats (quintiles), energy adjusted monounsaturated fats (quintiles), energy adjusted *trans* fat (quintiles), energy adjusted total n-6 (quintiles) and energy adjusted proteins (quintiles).

[2] Model 2: Adjusted as in model 1 but including smoking (current, past, never), alcohol use (rarely/never, 1–3 drinks/month, 1–6 drinks/week, and 1 drinks/day), BMI (continuous), exercise (quintiles of metabolic equivalent task hours per week), menopausal status (premenopausal, uncertain, postmenopausal), use of HT (current, past/never), hypertension (systolic blood pressure of at least 140 mmHg, diastolic blood pressure of at least 90 mmHg), antihypertensive treatment (yes or no), hypercholesterolemia (total cholesterol of at least 240 mg/dL), treatment for high cholesterol (yes or no), parental history of CHD (yes or no), energy adjusted glycemic index (quintiles), multivitamin use (current, past and never), aspirin use (Current use > 1x/week), read meat consumption, fruits and vegetables consumption (both quintiles) and energy adjusted ALA and EPA fatty acids (both in quintiles).

Table s6- LDL related variables. Strategy based on modelling energy adjusted variables.

		Quintile of energy adjusted ALA intake (gm)			
		Q1	Q3	Q5	P_{Trend}
		0.79 [0.71 0.84]	1.12 [1.08 1.16]	1.61 [1.5 1.79]	
LDL-C	Raw mean	123 ± 34	124 ± 35	125 ± 34	
(mg/dL)	Adj. mean[1]	125 [124 126]	124 [123 125]	124 [122 125]	0.10
	Adj. mean[2]	125 [124 126]	123 [123 124]	123 [122 124]	0.03
TC	Raw mean	211 ± 42	212 ± 42	213 ± 42	
(mg/dL)	Adj. mean[1]	213 [211 214]	212 [211 213]	211 [210 213]	0.38
	Adj. mean[2]	212 [211 213]	211 [210 212]	211 [210 212]	0.25
ApoB100	Raw mean	103 ± 28	104 ± 28	104 ± 28	
(mg/dL)	Adj. mean[1]	104 [103 105]	104 [103 104]	103 [102 104]	0.19
	Adj. mean[2]	104 [103 105]	103 [102 104]	103 [102 103.4]	0.09
LDL Size	Geom. mean	21.08 [21.06 21.1]	21.07 [21.06 21.09]	21.05 [21.04 21.07]	
(Ø nm)	Adj. mean[1]	21.04 [21.02 21.07]	21.08 [21.06 21.1]	21.08 [21.06 21.11]	0.03
	Adj. mean[2]	21.05 [21.03 21.07]	21.08 [21.07 21.1]	21.1 [21.07 21.12]	0.002
LDL Particles					
Total	Geom. mean	1189 [1178 1199]	1200 [1189 1211]	1212 [1202 1223]	
(nm/L)	Adj. mean[1]	1208 [1196 1221]	1199 [1188 1209]	1195 [1181 1208]	0.23
	Adj. mean[2]	1203 [1191 1215]	1189 [1180 1199]	1186 [1173 1199]	0.12
IDL	Geom. mean	152 [149 155]	146 [144 149]	141 [138 144]	
(nm/L)	Adj. mean[1]	147 [144 151]	146 [144 149]	146 [142 149]	0.80
	Adj. mean[2]	146 [143 150]	145 [143 148]	145 [142 149]	0.95
Large	Geom. mean	474 [464 484]	490 [480 500]	493 [483 503]	
(nm/L)	Adj. mean[1]	472 [460 484]	492 [482 503]	489 [477 502]	0.09
	Adj. mean[2]	476 [463 489]	493 [482 503]	491 [477 505]	0.15
Small A	Geom. mean	60.7 [59.4 62.1]	64.1 [62.9 65.4]	65.8 [64.4 67.1]	
(nm/L)	Adj. mean[1]	63.1 [61.6 64.7]	64 [62.7 65.3]	63.4 [61.7 65.1]	0.84
	Adj. mean[2]	62.5 [60.8 64.2]	63.8 [62.4 65.1]	63.2 [61.5 65.1]	0.98
Small B	Geom. mean	654 [643 665]	652 [641 663]	669 [658 681]	
(nm/L)	Adj. mean[1]	663 [650 677]	652 [641 663]	659 [645 673]	0.78
	Adj. mean[2]	661 [648 675]	648 [637 659]	655 [641 669]	0.80

Raw means ± sd and geometric (Geom.) means [CI]. [1] Model 1: The adjusted means (Adj.) are estimated from linear regression models adjusted for age (continuous), total energy (quintiles), energy adjusted saturated fats (quintiles), energy adjusted monounsaturated fats (quintiles), energy adjusted *trans* fat (quintiles), energy adjusted total n-6 (quintiles) and energy adjusted proteins (quintiles).

[2] Model 2: Adjusted as in model 1 but including smoking (current, past, never), alcohol use (rarely/never, 1–3 drinks/month, 1–6 drinks/week, and 1 drinks/day), BMI (continuous), exercise (quintiles of metabolic equivalent task hours per week), menopausal status (premenopausal, uncertain, postmenopausal), use of HT (current, past/never), hypertension (systolic blood pressure of at least 140 mmHg, diastolic blood pressure of at least 90 mmHg), antihypertensive treatment (yes or no), hypercholesterolemia (total cholesterol of at least 240 mg/dL), treatment for high cholesterol (yes or no), parental history of CHD (yes or no), energy adjusted glycemic index (quintiles), multivitamin use (current, past and never), aspirin use (Current use > 1x/week), read meat consumption, fruits and vegetables consumption (both quintiles) and energy adjusted EPA and DHA fatty acids (both in quintiles).

Table s7- VLDL related variables. Strategy based on modelling energy adjusted variables.

		Quintile of energy adjusted EPA intake (gm)			
		Q1	Q3	Q5	P_{Trend}
		0.01 [0.01 0.01]	0.04 [0.04 0.05]	0.12 [0.11 0.16]	
TG	Geom. mean	124 [122 125]	124 [122 127]	117 [115 119]	
(mg/dL)	Adj. mean[1]	124 [122 126]	125 [122 127]	117 [115 119]	<.0001
	Adj. mean[2]	121 [118 124]	123 [120 125]	118 [115 121]	0.19
VLDL Size	Geom. mean	51.11 [50.92 51.31]	51.05 [50.81 51.3]	50.87 [50.68 51.07]	
(Ø nm)	Adj. mean[1]	51.12 [50.93 51.31]	51.1 [50.86 51.35]	50.87 [50.67 51.07]	0.07
	Adj. mean[2]	50.93 [50.62 51.24]	51.06 [50.79 51.32]	50.91 [50.58 51.25]	0.87
VLDL Particles					
Total	Geom. mean	57.3 [56.7 58]	56.7 [55.8 57.7]	53.1 [52.4 53.8]	
(nm/L)	Adj. mean[1]	57.3 [56.6 58]	56.6 [55.8 57.5]	53.4 [52.7 54.1]	<.0001
	Adj. mean[2]	55.9 [54.8 57.1]	56.4 [55.4 57.4]	54.1 [53 55.4]	0.03
Large	Geom. mean	2.62 [2.54 2.69]	2.53 [2.45 2.63]	2.21 [2.14 2.28]	
(nm/L)	Adj. mean[1]	2.61 [2.54 2.69]	2.56 [2.47 2.66]	2.23 [2.16 2.29]	<.0001
	Adj. mean[2]	2.46 [2.35 2.58]	2.51 [2.41 2.6]	2.3 [2.19 2.41]	0.07
Medium	Geom. mean	13.4 [13.1 13.7]	13.2 [12.9 13.6]	12.2 [11.9 12.5]	
(nm/L)	Adj. mean[1]	13.5 [13.2 13.8]	13.2 [12.9 13.6]	12.1 [11.8 12.4]	<.0001
	Adj. mean[2]	12.7 [12.3 13.2]	13.1 [12.6 13.5]	12.5 [12 13.1]	0.26
Small	Geom. mean	36.8 [36.2 37.3]	36.4 [35.7 37.1]	34.2 [33.6 34.8]	
(nm/L)	Adj. mean[1]	36.5 [36 37.1]	36.3 [35.6 36.9]	34.6 [34 35.1]	<.0001
	Adj. mean[2]	36.1 [35.2 37]	36.2 [35.5 37]	34.8 [33.8 35.7]	0.07
VLDL-TG	Geom. mean	76.5 [75.5 77.6]	75.6 [74.3 76.9]	70.3 [69.3 71.3]	
(mg/dL)	Adj. mean[1]	76.6 [75.6 77.6]	75.7 [74.4 77]	70.6 [69.6 71.6]	<.0001
	Adj. mean[2]	74.2 [72.7 75.9]	75 [73.7 76.4]	71.6 [70 73.3]	0.02

Raw means ± sd and geometric (Geom.) means [CI]. [1] Model 1: The adjusted means (Adj.) are estimated from linear regression models adjusted for age (continuous), total energy (quintiles), energy adjusted saturated fats (quintiles), energy adjusted monounsaturated fats (quintiles), energy adjusted *trans*-fat (quintiles), energy adjusted total n-6 (quintiles) and energy adjusted proteins (quintiles).

[2] Model 2: Adjusted as in model 1 but including smoking (current, past, never), alcohol use (rarely/never, 1–3 drinks/month, 1–6 drinks/week, and 1 drinks/day), BMI (continuous), exercise (quintiles of metabolic equivalent task hours per week), menopausal status (premenopausal, uncertain, postmenopausal), use of HT (current, past/never), hypertension (systolic blood pressure of at least 140 mmHg, diastolic blood pressure of at least 90 mmHg), antihypertensive treatment (yes or no), hypercholesterolemia (total cholesterol of at least 240 mg/dL), treatment for high cholesterol (yes or no), parental history of CHD (yes or no), energy adjusted glycemic index (quintiles), multivitamin use (current, past and never), aspirin use (Current use > 1x/week), read meat consumption, fruits and vegetables consumption (both quintiles) and energy adjusted ALA and DHA fatty acids (both in quintiles).

Table s8- VLDL related variables. Strategy based on modelling energy adjusted variables.

		Quintile of energy adjusted DHA intake (gm)			
		Q1	Q3	Q5	P_{Trend}
		0.05 [0.03 0.06]	0.12 [0.11 0.13]	0.28 [0.24 0.35]	
TG	Geom. mean	123 [121 125]	121 [119 123]	119 [117 121]	
(mg/dL)	Adj. mean[1]	123 [122 125]	121 [119 123]	118 [117 120]	<.0001
	Adj. mean[2]	122 [119 125]	119 [117 121]	119 [116 122]	0.35
VLDL Size	Geom. mean	51.18 [51 51.36]	50.77 [50.58 50.97]	50.92 [50.72 51.12]	
(Ø nm)	Adj. mean[1]	51.17 [50.99 51.36]	50.78 [50.59 50.98]	50.91 [50.7 51.12]	0.30
	Adj. mean[2]	51.22 [50.92 51.53]	50.77 [50.56 50.99]	50.83 [50.47 51.19]	0.39
VLDL Particles					
Total	Geom. mean	57.2 [56.5 57.8]	56.3 [55.6 57.1]	53.9 [53.1 54.6]	
(nm/L)	Adj. mean[1]	57.2 [56.5 57.9]	56.2 [55.5 56.9]	54 [53.2 54.7]	<.0001
	Adj. mean[2]	56.3 [55.2 57.4]	55.3 [54.5 56.1]	55.4 [54.1 56.8]	0.61
Large	Geom. mean	2.63 [2.57 2.7]	2.43 [2.36 2.5]	2.27 [2.2 2.34]	
(nm/L)	Adj. mean[1]	2.63 [2.56 2.7]	2.43 [2.36 2.5]	2.28 [2.21 2.35]	<.0001
	Adj. mean[2]	2.58 [2.47 2.7]	2.36 [2.29 2.44]	2.35 [2.23 2.48]	0.12
Medium	Geom. mean	13.4 [13.2 13.7]	13.2 [12.9 13.5]	12.3 [12 12.7]	
(nm/L)	Adj. mean[1]	13.6 [13.3 13.9]	13.2 [12.8 13.5]	12.2 [11.9 12.5]	<.0001
	Adj. mean[2]	13.5 [13 14]	12.7 [12.4 13.1]	12.5 [12 13.1]	0.10
Small	Geom. mean	36.5 [36 37]	36.1 [36.5 36.7]	34.6 [34.1 35.2]	
(nm/L)	Adj. mean[1]	36.4 [35.8 36.9]	36 [35.5 36.6]	34.9 [34.4 35.5]	<.001
	Adj. mean[2]	35.7 [34.8 36.6]	35.6 [35 36.2]	36 [34.9 37]	0.70
VLDL-TG	Geom. mean	76.5 [75.6 77.4]	74.2 [73.2 75.2]	71.4 [70.4 72.5]	
(mg/dL)	Adj. mean[1]	76.7 [75.7 77.7]	74.1 [73.1 75.1]	71.4 [70.3 72.5]	<.0001
	Adj. mean[2]	75.5 [73.9 77.1]	72.7 [71.6 73.8]	73.1 [71.3 75]	0.30

Raw means ± sd and geometric (Geom.) means [CI]. [1] Model 1: The adjusted means (Adj.) are estimated from linear regression models adjusted for age (continuous), total energy (quintiles), energy adjusted saturated fats (quintiles), energy adjusted monounsaturated fats (quintiles), energy adjusted *trans* fat (quintiles), energy adjusted total n-6 (quintiles) and energy adjusted proteins (quintiles).

[2] Model 2: Adjusted as in model 1 but including smoking (current, past, never), alcohol use (rarely/never, 1–3 drinks/month, 1–6 drinks/week, and 1 drinks/day), BMI (continuous), exercise (quintiles of metabolic equivalent task hours per week), menopausal status (premenopausal, uncertain, postmenopausal), use of HT (current, past/never), hypertension (systolic blood pressure of at least 140 mmHg, diastolic blood pressure of at least 90 mmHg), antihypertensive treatment (yes or no), hypercholesterolemia (total cholesterol of at least 240 mg/dL), treatment for high cholesterol (yes or no), parental history of CHD (yes or no), energy adjusted glycemic index (quintiles), multivitamin use (current, past and never), aspirin use (Current use > 1x/week), read meat consumption, fruits and vegetables consumption (both quintiles) and energy adjusted ALA and EPA fatty acids (both in quintiles).

Table s9- VLDL related variables. Strategy based on modelling energy adjusted variables.

		Quintile of energy adjusted ALA intake (gm)			
		Q1	Q3	Q5	P_{Trend}
		0.79 [0.71 0.84]	1.12 [1.08 1.16]	1.61 [1.5 1.79]	
TG	Geom. mean	122 [120 123]	122 [121 124]	122 [121 124]	
(mg/dL)	Adj. mean[1]	123 [121 125]	122 [120 124]	122 [119 124]	0.62
	Adj. mean[2]	122 [120 124]	121 [119 123]	121 [118 123]	0.64
VLDL Size	Geom. mean	51.53 [51.34 51.74]	51 [50.81 51.19]	50.61 [50.42 50.8]	
(Ø nm)	Adj. mean[1]	51.26 [51.03 51.5]	51.03 [50.83 51.22]	50.84 [50.59 51.09]	0.04
	Adj. mean[2]	51.25 [51 51.5]	50.98 [50.78 51.17]	50.72 [50.46 50.97]	0.01
VLDL Particles					
Total	Geom. mean	54.2 [53.5 54.9]	56.6 [55.9 57.3]	57.6 [56.9 58.3]	
(nm/L)	Adj. mean[1]	56.3 [55.4 57.2]	56.4 [55.7 57.1]	55.7 [54.8 56.6]	0.45
	Adj. mean[2]	55.7 [54.8 56.7]	56.2 [55.5 56.9]	55.8 [54.8 56.7]	0.94
Large	Geom. mean	2.63 [2.56 2.7]	2.5 [2.42 2.57]	2.36 [2.29 2.43]	
(nm/L)	Adj. mean[1]	2.59 [2.5 2.68]	2.49 [2.41 2.56]	2.43 [2.34 2.52]	0.06
	Adj. mean[2]	2.56 [2.47 2.66]	2.45 [2.38 2.52]	2.38 [2.29 2.47]	0.04
Medium	Geom. mean	12.9 [12.6 13.1]	13.3 [13 13.7]	13.1 [12.8 13.5]	
(nm/L)	Adj. mean[1]	13.2 [12.8 13.6]	13.3 [12.9 13.6]	13 [12.6 13.4]	0.65
	Adj. mean[2]	13 [12.6 13.4]	13.1 [12.8 13.4]	12.9 [12.5 13.3]	0.88
Small	Geom. mean	34.1 [33.5 34.7]	36.3 [35.7 36.8]	37.3 [36.8 37.9]	
(nm/L)	Adj. mean[1]	35.7 [35 36.4]	36.2 [35.6 36.7]	35.8 [35.1 36.5]	0.96
	Adj. mean[2]	35.4 [34.7 36.2]	36.1 [35.5 36.7]	35.9 [35.2 36.7]	0.61
VLDL-TG	Geom. mean	74.1 [73.1 75.1]	75.3 [74.3 76.3]	74.9 [73.9 76]	
(mg/dL)	Adj. mean[1]	75.6 [74.4 76.9]	75.1 [74.1 76.1]	73.8 [72.5 75.1]	0.11
	Adj. mean[2]	74.8 [73.5 76.1]	74.6 [73.5 75.6]	73.4 [72.1 74.7]	0.23

Raw means ± sd and geometric (Geom.) means [CI]. [1] Model 1: The adjusted means (Adj.) are estimated from linear regression models adjusted for age (continuous), total energy (quintiles), energy adjusted saturated fats (quintiles), energy adjusted monounsaturated fats (quintiles), energy adjusted *trans* fat (quintiles), energy adjusted total n-6 (quintiles) and energy adjusted proteins (quintiles).

[2] Model 2: Adjusted as in model 1 but including smoking (current, past, never), alcohol use (rarely/never, 1–3 drinks/month, 1–6 drinks/week, and 1 drinks/day), BMI (continuous), exercise (quintiles of metabolic equivalent task hours per week), menopausal status (premenopausal, uncertain, postmenopausal), use of HT (current, past/never), hypertension (systolic blood pressure of at least 140 mmHg, diastolic blood pressure of at least 90 mmHg), antihypertensive treatment (yes or no), hypercholesterolemia (total cholesterol of at least 240 mg/dL), treatment for high cholesterol (yes or no), parental history of CHD (yes or no), energy adjusted glycemic index (quintiles), multivitamin use (current, past and never), aspirin use (Current use > 1x/week), read meat consumption, fruits and vegetables consumption (both quintiles) and energy adjusted EPA and DHA fatty acids (both in quintiles).

Table s10- HDL related variables. Strategy based on modelling energy adjusted variables.

		Quintile of energy adjusted EPA intake (gm)			
		Q1	Q3	Q5	P_{Trend}
		0.01 [0.01 0.01]	0.04 [0.04 0.05]	0.12 [0.11 0.16]	
HDL-C	Raw mean	52.9 ± 14.5	53.8 ± 15	55.9 ± 15.7	
(mg/dL)	Adj. mean[1]	52.9 [52.5 53.3]	53.8 [53.3 54.3]	55.5 [55.1 55.9]	<.0001
	Adj. mean[2]	54.4 [53.8 55]	53.8 [53.3 54.4]	53.9 [53.3 54.6]	0.30
ApoA1	Raw mean	149 ± 25	152 ± 25	154 ± 26	
(mg/dL)	Adj. mean[1]	149 [149 150]	152 [151 152]	153 [152 154]	<.0001
	Adj. mean[2]	152 [151 153]	151 [150 152]	150 [149 151]	0.02
HDL Size	Geom. mean	9.17 [9.16 9.19]	9.18 [9.16 9.2]	9.25 [9.24 9.27]	
(Ø nm)	Adj. mean[1]	9.18 [9.16 9.19]	9.18 [9.16 9.2]	9.24 [9.23 9.26]	<.0001
	Adj. mean[2]	9.23 [9.21 9.25]	9.19 [9.17 9.2]	9.2 [9.18 9.22]	0.55
HDL Particles					
Total	Geom. mean	36.6 [36.4 36.8]	37.1 [36.9 37.4]	37.2 [37 37.4]	
(µm/L)	Adj. mean[1]	36.7 [36.5 36.9]	37.1 [36.9 37.3]	37 [36.8 37.2]	0.44
	Adj. mean[2]	37 [36.7 37.3]	37 [36.7 37.2]	36.5 [36.2 36.8]	0.004
Large	Geom. mean	5.32 [5.24 5.4]	5.42 [5.32 5.53]	5.86 [5.77 5.96]	
(µm/L)	Adj. mean[1]	5.35 [5.27 5.43]	5.41 [5.3 5.51]	5.76 [5.67 5.86]	<.0001
	Adj. mean[2]	5.66 [5.53 5.8]	5.44 [5.33 5.55]	5.47 [5.33 5.61]	0.16
Medium	Geom. mean	11.3 [11.1 11.4]	11.4 [11.2 11.6]	11.3 [11.1 11.5]	
(µm/L)	Adj. mean[1]	11.5 [11.3 11.6]	11.4 [11.2 11.6]	11.1 [10.9 11.3]	0.01
	Adj. mean[2]	11.5 [11.2 11.8]	11.3 [11.1 11.6]	10.9 [10.7 11.2]	0.01
Small	Geom. mean	17.6 [17.5 17.8]	17.8 [17.6 18]	17.5 [17.4 17.7]	
(µm/L)	Adj. mean[1]	17.5 [17.4 17.7]	17.8 [17.7 18]	17.7 [17.5 17.9]	0.70
	Adj. mean[2]	17.3 [17.1 17.6]	17.7 [17.5 17.9]	17.8 [17.5 18]	0.54

Raw means ± sd and geometric (Geom.) means [CI]. [1] Model 1: The adjusted means (Adj.) are estimated from linear regression models adjusted for age (continuous), total energy (quintiles), energy adjusted saturated fats (quintiles), energy adjusted monounsaturated fats (quintiles), energy adjusted *trans* fat (quintiles), energy adjusted total n-6 (quintiles) and energy adjusted proteins (quintiles).

[2] Model 2: Adjusted as in model 1 but including smoking (current, past, never), alcohol use (rarely/never, 1–3 drinks/month, 1–6 drinks/week, and 1 drinks/day), BMI (continuous), exercise (quintiles of metabolic equivalent task hours per week), menopausal status (premenopausal, uncertain, postmenopausal), use of HT (current, past/never), hypertension (systolic blood pressure of at least 140 mmHg, diastolic blood pressure of at least 90 mmHg), antihypertensive treatment (yes or no), hypercholesterolemia (total cholesterol of at least 240 mg/dL), treatment for high cholesterol (yes or no), parental history of CHD (yes or no), energy adjusted glycemic index (quintiles), multivitamin use (current, past and never), aspirin use (Current use > 1x/week), read meat consumption, fruits and vegetables consumption (both quintiles) and energy adjusted ALA and DHA fatty acids (both in quintiles

Table s11- HDL related variables. Strategy based on modelling energy adjusted variables.

		Quintile of energy adjusted DHA intake (gm)			
		Q1	Q3	Q5	P_{linear}
		0.05 [0.03 0.06]	0.12 [0.11 0.13]	0.28 [0.24 0.35]	
HDL-C	Raw mean	53 ± 14.6	54.2 ± 14.9	55.3 ± 15.3	
(mg/dL)	Adj. mean[1]	53.1 [52.7 53.5]	54.3 [53.8 54.7]	55.1 [54.7 55.6]	<.0001
	Adj. mean[2]	53.3 [52.7 54]	54.6 [54.2 55.1]	55 [54.3 55.7]	0.02
ApoA1	Raw mean	150 ± 25	152 ± 25	153 ± 26	
(mg/dL)	Adj. mean[1]	150 [149 150]	152 [151 152]	153 [152 154]	<.0001
	Adj. mean[2]	150 [149 151]	152 [151 153]	153 [152 154]	0.004
HDL Size	Geom. mean	9.17 [9.16 9.18]	9.19 [9.17 9.2]	9.23 [9.22 9.25]	
(Ø nm)	Adj. mean[1]	9.18 [9.16 9.19]	9.19 [9.18 9.2]	9.22 [9.21 9.24]	<.0001
	Adj. mean[2]	9.17 [9.15 9.19]	9.21 [9.19 9.22]	9.24 [9.21 9.26]	0.002
HDL Particles					
Total	Geom. mean	36.7 [36.6 36.9]	37 [36.8 37.2]	37.1 [36.9 37.3]	
(µm/L)	Adj. mean[1]	36.9 [36.7 37]	37 [36.8 37.2]	36.9 [36.7 37.1]	0.58
	Adj. mean[2]	36.9 [36.6 37.2]	37 [36.8 37.1]	37.1 [36.8 37.4]	0.29
Large	Geom. mean	5.32 [5.25 5.4]	5.48 [5.39 5.57]	5.72 [5.62 5.82]	
(µm/L)	Adj. mean[1]	5.36 [5.28 5.44]	5.48 [5.4 5.57]	5.65 [5.55 5.74]	<.0001
	Adj. mean[2]	5.33 [5.2 5.45]	5.57 [5.48 5.66]	5.74 [5.58 5.9]	0.002
Medium	Geom. mean	11.3 [11.2 11.5]	11.3 [11.1 11.5]	11.3 [11.1 11.5]	
(µm/L)	Adj. mean[1]	11.5 [11.4 11.7]	11.3 [11.1 11.5]	11.1 [10.9 11.2]	0.005
	Adj. mean[2]	11.4 [11.2 11.7]	11.3 [11.1 11.4]	11.3 [11 11.6]	0.94
Small	Geom. mean	17.7 [17.6 17.9]	17.8 [17.7 18]	17.6 [17.4 17.7]	
(µm/L)	Adj. mean[1]	17.6 [17.5 17.7]	17.8 [17.6 18]	17.7 [17.6 17.9]	0.53
	Adj. mean[2]	17.7 [17.5 18]	17.7 [17.5 17.9]	17.5 [17.2 17.8]	0.33

Raw means ± sd and geometric (Geom.) means [CI]. [1] Model 1: The adjusted means (Adj.) are estimated from linear regression models adjusted for age (continuous), total energy (quintiles), energy adjusted saturated fats (quintiles), energy adjusted monounsaturated fats (quintiles), energy adjusted *trans* fat (quintiles), energy adjusted total n-6 (quintiles) and energy adjusted proteins (quintiles).

2 Model 2: Adjusted as in model 1 but including smoking (current, past, never), alcohol use (rarely/never, 1–3 drinks/month, 1–6 drinks/week, and 1 drinks/day), BMI (continuous), exercise (quintiles of metabolic equivalent task hours per week), menopausal status (premenopausal, uncertain, postmenopausal), use of HT (current, past/never), hypertension (systolic blood pressure of at least 140 mmHg, diastolic blood pressure of at least 90 mmHg), antihypertensive treatment (yes or no), hypercholesterolemia (total cholesterol of at least 240 mg/dL), treatment for high cholesterol (yes or no), parental history of CHD (yes or no), energy adjusted glycemic index (quintiles), multivitamin use (current, past and never), aspirin use (Current use > 1x/week), read meat consumption, fruits and vegetables consumption (both quintiles) and energy adjusted ALA and EPA fatty acids (both in quintiles).

Table s12- HDL related variables. Strategy based on modelling energy adjusted variables.

		Quintile of energy adjusted ALA intake (gm)			
		Q1	Q3	Q5	P_{Trend}
		0.79 [0.71 0.84]	1.12 [1.08 1.16]	1.61 [1.5 1.79]	
HDL-C	Raw mean	53.5 ± 14.6	53.9 ± 15	54.3 ± 15.2	
(mg/dL)	Adj. mean[1]	53.7 [53.2 54.2]	54 [53.6 54.5]	53.9 [53.4 54.4]	0.83
	Adj. mean[2]	53.8 [53.3 54.3]	54 [53.6 54.4]	54.1 [53.6 54.7]	0.48
ApoA1	Raw mean	150 ± 25	151 ± 25	152 ± 26	
(mg/dL)	Adj. mean[1]	151 [150 151]	151 [151 152]	151 [150 152]	0.51
	Adj. mean[2]	151 [150 152]	151 [151 152]	151 [150 152]	0.50
HDL Size	Geom. mean	9.2 [9.19 9.21]	9.18 [9.17 9.2]	9.19 [9.18 9.21]	
(Ø nm)	Adj. mean[1]	9.18 [9.16 9.19]	9.19 [9.17 9.2]	9.21 [9.19 9.22]	0.08
	Adj. mean[2]	9.18 [9.17 9.2]	9.2 [9.18 9.21]	9.22 [9.2 9.24]	0.01
HDL Particles					
Total	Geom. mean	36.9 [36.7 37]	37 [36.8 37.2]	37 [36.8 37.1]	
(µm/L)	Adj. mean[1]	37 [36.8 37.3]	37 [36.8 37.2]	36.7 [36.5 37]	0.10
	Adj. mean[2]	37 [36.8 37.3]	37 [36.8 37.2]	36.7 [36.5 36.9]	0.09
Large	Geom. mean	5.4 [5.32 5.49]	5.44 [5.35 5.53]	5.55 [5.46 5.64]	
(µm/L)	Adj. mean[1]	5.37 [5.27 5.48]	5.46 [5.37 5.55]	5.52 [5.41 5.64]	0.19
	Adj. mean[2]	5.41 [5.31 5.51]	5.5 [5.42 5.58]	5.59 [5.48 5.7]	0.07
Medium	Geom. mean	11.6 [11.5 11.8]	11.3 [11.1 11.4]	11 [10.9 11.2]	
(µm/L)	Adj. mean[1]	11.5 [11.3 11.7]	11.3 [11.1 11.5]	11.2 [11 11.4]	0.09
	Adj. mean[2]	11.4 [11.2 11.6]	11.3 [11.2 11.5]	11.2 [11 11.4]	0.31
Small	Geom. mean	17.3 [17.2 17.5]	17.8 [17.7 18]	17.9 [17.8 18.1]	
(µm/L)	Adj. mean[1]	17.7 [17.5 17.9]	17.8 [17.7 18]	17.6 [17.4 17.8]	0.23
	Adj. mean[2]	17.8 [17.6 18]	17.7 [17.5 17.9]	17.4 [17.2 17.6]	0.03

Raw means ± sd and geometric (Geom.) means [CI]. [1] Model 1: The adjusted means (Adj.) are estimated from linear regression models adjusted for age (continuous), total energy (quintiles), energy adjusted saturated fats (quintiles), energy adjusted monounsaturated fats (quintiles), energy adjusted *trans*-fat (quintiles), energy adjusted total n-6 (quintiles) and energy adjusted proteins (quintiles).

[2] Model 2: Adjusted as in model 1 but including smoking (current, past, never), alcohol use (rarely/never, 1–3 drinks/month, 1–6 drinks/week, and 1 drinks/day), BMI (continuous), exercise (quintiles of metabolic equivalent task hours per week), menopausal status (premenopausal, uncertain, postmenopausal), use of HT (current, past/never), hypertension (systolic blood pressure of at least 140 mmHg, diastolic blood pressure of at least 90 mmHg), antihypertensive treatment (yes or no), hypercholesterolemia (total cholesterol of at least 240 mg/dL), treatment for high cholesterol (yes or no), parental history of CHD (yes or no), energy adjusted glycemic index (quintiles), multivitamin use (current, past and never), aspirin use (Current use > 1x/week), read meat consumption, fruits and vegetables consumption (both quintiles) and energy adjusted EPA and DHA fatty acids (both in quintiles).

Table s13- Correspondence between absolute values and per 1% and per 5% differences.

		Absolute values	1% differences	5 % differences
LDL-C	(mg/dL)	123	1.23	6.17
TC	(mg/dL)	210	2.10	10.51
ApoB100	(mg/dL)	103	1.03	5.16
LDL Size	(Ø nm)	21	0.21	1.05
LDL Particles				
Total	(nm/L)	1188	11.88	59.38
IDL	(nm/L)	151	1.51	7.56
Large	(nm/L)	460	4.60	22.98
Small A	(nm/L)	60	0.06	3.00
Small B	(nm/L)	658	6.58	32.90
TG	(mg/dL)	123	1.23	6.15
VLDL Size	(Ø nm)	52	0.52	2.58
VLDL Particles				
Total	(nm/L)	55	0.55	2.77
Large	(nm/L)	3	0.03	0.14
Medium	(nm/L)	13	0.13	0.65
Small	(nm/L)	35	0.35	1.75
VLDL-TG	(mg/dL)	75	0.75	3.77
HDL-C	(mg/dL)	53	0.53	2.66
ApoA1	(mg/dL)	150	1.50	7.49
HDL Size	(Ø nm)	9	0.09	0.46
HDL Particles				
Total	(µm/L)	37	0.37	1.84
Large	(µm/L)	5	0.05	0.27
Medium	(µm/L)	12	0.12	0.58
Small	(µm/L)	17	0.17	0.87

The absolute values are the raw mean values of the n-3 1st quintile intake.

Table s14- Adjusted means (95% CI) for the lower exposure quintiles (Q1) that showed a significant association (Ptrend<0.05).

	Fish	n-3	EPA	DHA	ALA
TC (mg/dL)	210 (210– 211)				
Apo B100 (mg/dL)	102 (102–103)				
LDL-C (mg/dL)	123 (122–124)				125 (124–126)
LDL particles (nm/L)	1189 (1173–1198)				
Large LDL particles (nm/L)	469 (460–479)	458 (447–470)		479 (465–492)	
LDL size (nm)	21.06 (21.04–21.08)	21.03 (21.01–21.05)		21.07 (21.04–21.09)	21.05 (21.03–21.07)
TG (mg/dL)	123 (122–124)	124 (123–125)			
VLDL-TG (mg/dL)	75.6 (74.6–76.6)	76.6 (75.4–77.9)	74.2 (72.7–75.9)		
Total VLDL particles (nm/L)	56.2 (55.5–56.9)	57 (56.2–57.9)	55.9 (54.8–57.1)		
Large VLDL particles (nm/L)	2.62 (2.55–2.7)	2.69 (2.6–2.78)			2.56 (2.47–2.66)
HDL-C (mg/dL)				53.3 (52.7–54)	
Large HDL particles (μm/L)		5.37 (5.28–5.47)		5.33 (5.2–5.45)	
HDL size (nm)		9.17 (9.16–9.19)		9.17 (9.15–9.19);	9.18 (9.17–9.2)

The means were adjusted for all demographic, clinical, and dietary factors. Blank spaces indicate no significant association (fish: Q1, n=5839; Q5, n=5617; n-3: Q1, n=5248; Q5, n=5123; EPA: Q1, n=5370; Q5, n=4947; 6 DHA: Q1, n=6351; Q5, n=4797; ALA: Q1, n=5286; Q5, n=5097). ALA indicates a-linolenic acid; Apo, apolipoprotein; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; TC, total cholesterol; LDL, low density lipoprotein; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; VLDL, very low-density lipoprotein; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol.