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# Intake of fish and long-chain omega-3 polyunsaturated fatty acids and incidence of metabolic syndrome among American young adults: a 25-year follow-up study

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## Abstract

**Purpose—**Studies suggest that long-chain ω-3 polyunsaturated fatty acid (LCω3PUFA) intake and its primary food source—fish—may have beneficial effects on the individual components of metabolic syndrome (MetS). We examined the longitudinal association between fish or LCω3PUFA intake and MetS incidence.

**Methods—**We prospectively followed 4356 American young adults, free from MetS and diabetes at baseline, for incident MetS and its components in relation to fish and LCω3PUFA intake. MetS was defined by the National Cholesterol Education Program/Adult Treatment Panel III criteria. Cox proportional hazards model was used for analyses, controlling for socio-demographic, behavioral, and dietary factors.

**Results—**During the 25-year follow-up, a total of 1069 incident cases of MetS were identified. LCω3PUFA intake was inversely associated with the incidence of MetS in a dose–response manner. The multivariable adjusted hazards ratio (HR) [95 % confidence interval (CI)] of incident

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MetS was 0.54 (95 % CI 0.44, 0.67; *P* for linear trend < 0.01) as compared the highest to the lowest quintile of LCω3PUFA intake. A threshold inverse association was found between non-fried fish consumption and the incidence of MetS. The multivariable adjusted HRs (95 % CIs) from the lowest to the highest quintile were 1.00, 0.70 (0.51, 0.95), 0.68 (0.52, 0.91), 0.67 (0.53, 0.86), and 0.71 (0.56, 0.89) (*P* for linear trend = 0.49). The observed inverse associations were independent of the status of baseline individual components of MetS.

**Conclusions—**Our findings suggest that intakes of LCω3PUFAs and non-fried fish in young adulthood are inversely associated with the incidence of MetS later in life.

### Keywords

Longitudinal studies; Omega-3 fatty acids; Fish consumption; Metabolic syndrome

## Introduction

The prevalence of metabolic syndrome (MetS) in the U.S. has persistently increased over the last two decades, and is estimated to affect approximately one-third of American adults [1]. Studies have reported that certain dietary factors are associated with the risk of developing MetS. Fish, the major dietary source of long-chain ω-3 polyunsaturated fatty acid (LCω3PUFA), is of great interest, because evidence suggests that fish oil supplementation may have beneficial effects on lipid profile and blood pressure (BP), which are associated with MetS [2, 3]. However, data directly relating fish or dietary LCω3PUFA intake to the risk of MetS are sparse. Several cross-sectional studies reported an inverse correlation between fish consumption and prevalence of MetS [4–6], whereas some other cross-sectional analyses found no association [7–9]. One prospective cohort study conducted in a Korean population reported an inverse association between fish intake and the incidence of MetS in male Koreans [10]. However, whether findings from that study can be generalized to other ethnic populations is uncertain. Therefore, we prospectively examined fish and dietary LCω3PUFA intake in relation to the incidence of MetS in a large cohort of African American and Caucasian young adults participating in the Coronary Artery Risk Development in Young Adults (CARDIA) study.

## Methods

### Study population

The CARDIA study is an ongoing, multicenter, community-based, prospective cohort study designed to investigate the influence of physiological, psychological and other lifestyle factors on the development of risk factors for cardiovascular disease among African American and Caucasian young adults. The detailed descriptions of the study design have been published [11]. In brief, 5114 men and women, aged 18–30 years, were initially enrolled from four US cities including Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California at baseline from 1985 to 1986. Gender, age, race, and status of education of the participants in this cohort were roughly balanced at baseline by design. To date, seven follow-up examinations have been completed. Follow-up examinations conducted in 1987–1988 (year 2), 1990–1991 (year 5), 1992–1993 (year 7),

1995–1996 (year 10), 2000–2001 (year 15), 2005–2006 (year 20), and 2010–2011 (year 25) had retention rates of 90.4, 85.1, 79.9, 77.2, 71.8, 69.3, and 68.4 % of the surviving cohort, respectively.

In the present study, exclusions were made in a sequential manner. Participants who were determined to have MetS ($n$ = 110) or diagnosed with diabetes ($n$ = 24) at baseline were excluded. Participants were also excluded if they had missing data on diet ($n$ = 4), body mass index (BMI, $n$ = 15), smoking status ($n$ = 34), alcohol consumption ($n$ = 18), physical activity ($n$ = 1), or any component of MetS ($n$ = 113) at baseline. Participants were further excluded if they had insufficient information for defining incident MetS at any follow-up exam ($n$ = 166) and excluded if they reported implausible total energy intake at diet measurements ($n$ = 43; <800 or >8000 kcal/day for men; <600 or >6000 kcal/day for women). To be conservative, pregnant women at any examination ($n$ = 230) were excluded. After these exclusions, a total of 4356 participants remained in the analyses. Written informed consent was obtained from all study participants. The study design, data collection, and analyses were approved by the institutional review boards of the participating centers.

## Ascertainment of fish consumption and LCω3PUFA intake

The details of diet assessment and validation of fish consumption and LCω3PUFA intake in CARDIA have been described previously [12]. In brief, dietary data including fish consumption were obtained at baseline and exam years 7 and 20, using an interviewer-administered CARDIA Diet History Questionnaire [13, 14]. Reported foods and beverages were grouped into food groups according to the Nutrient Data Software for Research (NDSR) food grouping scheme [15]. Daily intake of each food or beverage group was calculated as the sum number of servings consumed per day. Fish consumption was categorized into fried and non-fried fish, recognizing that the risk of cardiovascular disease may be influenced by the preparation method, especially frying [16]. Because of skewed and narrow distribution of fried fish consumption, we did not use fried fish data as an exposure of interest, but adjusted for fried fish intake when examining non-fried fish. Nutrient intake was calculated based on the updated nutrient database version 36 (Nutrition Data System for Research [NDS-R] 2005) from the Nutrition Coordinating Center (NCC) at the University of Minnesota, Minneapolis, MN. In the present study, LCω3PUFA intake was calculated based on both food and supplemental sources, and was defined as the sum of eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA). DPA was not used in the analyses as a separate exposure due to a relatively small amount and narrow distribution.

The CARDIA Diet History Questionnaire was evaluated for the reliability and comparative validity in 128 individuals. The correlation coefficients for logarithmically transformed nutrient values and energy-adjusted nutrient values from two dietary histories ranged from 0.50 to 0.80 for Caucasians and 0.30 to 0.70 for African Americans [14].

## Measurements of other covariates

Socio-demographic variables including age, gender, race and years of education at baseline were obtained by interview or self-administered questionnaire and verified during clinical

examinations. The major lifestyle variables and clinical measurements were reevaluated in the follow-up examinations. Concurrent smoking status was self-reported and classified as never, former, and current smokers. Cumulative average alcohol consumption was classified into four groups based on daily intake measured by validated questionnaire: 0 (never drink), 0.1–9.9, 10–19.9 and ≥20 g/day. Physical activity was assessed using the interviewer-administered, validated, CARDIA Physical Activity History Questionnaire [17]. The physical activity (PA) score was calculated in exercise units (EU) reflecting the frequency and duration of activity over the previous year. A score of 100 EU is approximately equivalent to participation in a vigorous activity for 2–3 h/week for 6 months of the year. Cumulative average PA was categorized into quintiles.

### Metabolic syndrome ascertainment

Waist circumference was measured at the maximum abdominal girth, and all anthropometric measures were taken in duplicate and averaged. BP was measured using a random-zero sphygmomanometer in the first six examinations (i.e. exam years 0, 2, 5, 7, 10 and 15) and the *OmROn* HEM907XL at exam years 20 and 25 by trained and certified technicians [18]. BP measurements were taken three times on the right arm with the participant seated at 1-min intervals after 5 min of rest. The average of the second and third measurements was used for the analyses. Systolic and diastolic BPs were recorded as phase I and V Korotkoff sounds through year 15 examination. To make the BPs across examinations more comparable, systolic and diastolic BPs at exam year 20 and 25 were calculated as follows: estimated systolic BP = 3.74 + 0.96 × observed *OmROn* systolic BP; estimated diastolic BP = 1.30 + 0.97 × observed *OmROn* diastolic BP based on a study in 900 participants [18].

Serum glucose was measured at year 0 using the hexokinase ultraviolet method by American Bio-Science Laboratories (Van Nuys, California), and at years 7, 10, 15, 20 and 25 using hexokinase coupled to glucose-6-phosphate dehydrogenase by Linco Research (St. Louis, Missouri). Plasma high-density lipoprotein cholesterol (HDL-C), and triglycerides were determined using an enzymatic assay by Northwest Lipids Research Laboratory (Seattle, Washington) at all exam years. The quality control for lipid profile measurement was expressed as intraassay technical error calculated as $\sqrt{d^2/2n \times 100}$, where d is the difference between measurements of duplicated samples and n is the number of paired specimens. In particular, the technical error was 3.9 % for HDL and 8.4 % for triglycerides [19].

MetS was defined using the National Cholesterol Education Program/Adult Treatment Panel III definition at all eight examinations. Participants with three or more of the following were determined to have MetS: fasting glucose level ≥6.1 mmol/L; systolic BP ≥ 130 or diastolic BP ≥ 85 mmHg; waist circumference >88 cm for women or >102 cm for men; triglyceride level ≥1.7 mmol/L; HDL cholesterol level <1.3 mmol/L in women or <1.04 mmol/L in men [20]. Participants who reported using antidiabetic or antihypertensive medications were regarded as having high glucose or high BP.

## Statistical analysis

Baseline characteristics of the study population by quintiles of LCω3PUFA intake were described with mean (standard deviation, SD) for normally distributed or approximately normally-distributed variables (e.g., non-fried fish consumption and BMI), medians (interquartile range, IQR) for variables with skewed distribution (e.g., alcohol intake and physical activity), and proportions for categorical variable (e.g., gender and race). The difference in these baseline characteristics by quintiles of LCω3PUFA intake were compared using analysis of variance, the Kruskal–Wallis test or the Chi-squared test, as appropriate.

The Cox proportional hazards regression model was used to examine intakes of LCω3PUFAs, DHA, EPA and non-fried fish in relation to incidence of MetS. To reduce measurement errors caused by within-person variation and to best represent the long-term dietary intakes, we used cumulative average nutrient intake from the measurements at baseline and exam years 7 and 20 in the analysis. For example, we related LCω3PUFA intake reported at baseline to the new cases identified at exam years 2 and 5; the average LCω3PUFA intake reported at baseline and year 7 to the new cases identified at exam years 7, 10 and 15; and the average LCω3PUFA intake reported at baseline, years 7 and 20 to the new cases identified at years 20 and 25. The linear assumption between the continuous covariates and the log (HR) was tested by using restricted cubic spline method [21]. If there was a linear association between a certain covariate and the log (HR), we treated the covariate as a continuous variable (e.g. age and education) in the model; if not, we categorized it based on either quintiles (e.g. physical activity) or the objective cut-off points (e.g. BMI).

Intakes of LCω3PUFA, DHA and EPA were divided into quintiles based on their distributions. Fish consumption was categorized into five groups based on the Health Professionals Follow-up Study and the Nurse's Health Study: <1 serving/month, 1–3 servings/month, 1 serving/week, 2–4 servings/week, and ≥5 servings/week [22]. We used a sequential covariates-adjusted strategy in the Cox model. Model 1 (initial model): adjustment for age, gender, race, and study center. Model 2 (final model): Model 1 with additional adjustment for education, smoking status, alcohol consumption, physical activity, BMI and family history of diabetes. In Model 2, fried fish consumption (yes vs. no) was also adjusted when non-fried fish was examined. *P* for trend was tested by using medians in each quintile or category exposure of interest. To examine whether gender or race is an effect modifier, the interaction of gender or race and the exposures of interest was detected by using a likelihood ratio test. We also examined whether statin (one of the lipid-lowering drugs) usage would modify the results.

In addition, we conducted the following sensitivity analyses based on the final model (Model 2). First, we considered dietary variables and additionally adjusted for a few potential dietary confounders including intakes of protein, saturated fatty acid, polyunsaturated fatty acid, and total energy (Model 3a). Second, to investigate whether the associations were confounded by dietary pattern extracted by principal component analysis, we additionally adjusted for total energy intake and two dietary patterns (quintiles): one reflects higher intake of vegetables, fruits, whole grains, nuts and seeds; and the other one reflects higher intake of refined grains, red and processed meats, fried potatoes, and sugar

sweetened beverages (Model 3b). Third, we additionally adjusted for the status of baseline individual components of MetS (Model 4). BMI was excluded in this analysis because it is highly correlated to waist circumference.

We also examined intakes of LCω3PUFAs and non-fried fish in relation to each component of MetS. For example, we considered participants to have incident abnormal BP if their systolic BP was ≥ 130 mmHg or diastolic BP was ≥ 85 mmHg or if they were using antihypertensive medications in any of the follow-up examinations. Prevalent events at baseline were excluded in the analyses for each component.

All analyses were performed by using SAS version 9.3 (SAS Institute Inc., Cary, North Carolina, USA). $P \leq 0.05$ was considered statistically significant.

## Results

Baseline characteristics by quintiles of LCω3PUFA intake are shown in Table 1. The average intakes of LCω3PUFAs were 0.03, 0.07, 0.11, 0.18 and 0.40 g/day across quintiles. Compared with participants in the lowest quintile of LCω3PUFA intake, those in the highest quintile were slightly older, less likely to be female, and less likely to be current smokers. They had more years of education, a higher amount of alcohol consumption, and more physical activities. In addition, they reported higher intakes of total energy, fiber, saturated fat, polyunsaturated fat, and protein. For the five components of MetS, no significant differences across quintiles of LCω3PUFA intake were found except HDL cholesterol level, which was higher among participants in the highest quintile of LCω3PUFA intake. There was no significant difference in BMI, either.

During the 25-year follow-up, a total of 1069 incident cases of MetS were identified. LCω3PUFA intake was inversely associated with the incidence of MetS in a dose–response manner. The incidence of MetS was 46 % lower for participants in the highest quintile of LCω3PUFA intake as compared with those in the lowest quintile after adjustment for potential non-dietary confounders (Model 2: HR 0.54; 95 % CI 0.44, 0.67; $P$ for trend < 0.01). When examining EPA and DHA separately, DHA intake (HR 0.36; 95 % CI 0.29, 0.44; $P$ for trend < 0.01) showed a greater inverse association with incidence of MetS than that of EPA (HR 0.69; 95 % CI 0.56, 0.84; $P$ for trend < 0.01). For non-fried fish consumption, a significant inverse threshold association with incidence of MetS was observed. The multivariable adjusted HRs (95 % CIs) from quintile 1 to quintile 5 were 1.00 (reference); 0.70 (0.51, 0.95), 0.68 (0.52, 0.91), 0.67 (0.53, 0.86), and 0.71 (0.56, 0.89) ($P$ for linear trend = 0.49) (Table 2). When stratifying data by gender or race, the inverse associations were not appreciably modified (data not shown).

For the individual components of MetS, the identified incident events numbered 1607, 736, 1384, 1248 and 1641 for meeting abnormal criterion of BP, fasting glucose, HDL cholesterol, triglycerides, and waist circumference, respectively. LCω3PUFA intake was inversely associated with all five components of MetS in a dose–response manner in this cohort. For non-fried fish consumption, a dose–response relationship was documented with

abnormal HDL and triglycerides, and a threshold association was observed with abnormal blood pressure, glucose, and waist circumference (Table 3).

In sensitivity analyses, we first considered potential dietary confounders. After additional adjustment for intakes of protein, saturated fat, polyunsaturated fat, and total energy, the results remained (Model 3a in Table 2). Second, we explored if a dietary pattern would affect our results. After additionally adjusted for two dietary patterns, the observed associations were unchanged (Model 3b in Table 2). Third, we additionally adjusted for the status of baseline individual components of MetS based on model 2. The findings were not materially altered (Model 4 in Table 2). Finally, statin use may affect the levels of HDL cholesterol and triglycerides. However, the results for fish or LCω3PUFA intake in relation to HDL cholesterol and triglycerides levels were similar after adjustment for statin use (data not shown).

## Discussion

In this prospective cohort study with 25 years of follow-up, we found that LCω3PUFA intake and non-fried fish consumption were inversely associated with the incidence of MetS and its individual components. The inverse associations were independent of the status of baseline individual components of MetS and were consistent across gender and racial groups.

A few cross-sectional studies have been conducted to investigate the correlation between fish or LCω3PUFA intake and risk of MetS, and the results were inconsistent [4–9]. Although one prospective cohort study conducted in a Korean population reported an inverse association between fish consumption and the incidence of MetS in male Koreans, the duration of follow-up (4 years) was relatively short and the results might not be generalizable to other ethnicities [10]. In addition, most of the previous studies were conducted in middle-aged or elderly populations, who were likely to have already had onset of metabolic abnormalities and may have modified their lifestyle for disease prevention or treatment. Our study adds new evidence that fish consumption in young adulthood may be beneficial to primary prevention of MetS later in life.

Findings from the present study are biologically plausible. Studies suggest that fish oil supplementation may have anti-hypertensive effects especially in hypertensive patients [23, 24]. Also, the hypotriglyceridemic effects of fish oil supplementation are well documented from both epidemiological and intervention studies [2, 3, 25]. Although findings from previous studies were inconsistent, systematic reviews found that fish oil supplementation led to a modest, but significant increase in HDL cholesterol levels (0.01 mmol/L; 95 % CI 0.00–0.02 mmol/L) [26], and an averaged increment of 13 % in LDL cholesterol levels [27]. Also, experimental studies suggest that LCω3PUFA intake may attenuate weight gain with aging or reduce energy intake [28–30]. In addition, the effect of LCω3PUFA on glucose metabolism has become a subject of debate. Despite a number of studies suggesting that dietary LCω3PUFA intake or fish oil supplementation may improve glucose metabolism and insulin sensitivity [31, 32], some other studies did not show significant changes in indices of glucose metabolism [33, 34], and one study even suggested that intake of LCω3PUFAs may

increase the risk of diabetes [35]. Nevertheless, our study adds evidence to the literature in favor of the beneficial effects of LCω3PUFA intakes on glucose metabolism.

In the present study, DHA suggested a greater benefit on MetS and its components as compared to EPA (Table 2 and appendix Table in Online Resource). Although evidence is not entirely consistent, some previous studies provide plausible explanations for these results. DHA was suggested to be more effective in lowering BP than EPA [12, 36]. In addition, several studies reported significant effects of DHA, but not EPA supplementation on HDL cholesterol [37, 38]. Moreover, a recent meta-analysis reported that DHA raised HDL cholesterol levels compared with a placebo, whereas EPA did not [39]. That meta-analysis also reported a greater reduction of triglyceride levels by DHA as compared to EPA in pooled analyses [39]. Furthermore, a study found a significant inverse correlation between phospholipid DHA levels, but not EPA, and BMI change, suggesting that DHA may be more effective than EPA [40].

Because of the extra double bond and increased carbon length, DHA takes much more space than does EPA in the membrane. In addition, potency of the metabolites of EPA and DHA are often markedly different to the parent LCn-3PUFA, and divergence in efficiency of enzymes to metabolize EPA and DHA can contribute to observed diversity in cellular response [41].

Most of the previous studies did not report information on the preparation method for fish consumption. Frying, especially deep frying, may reduce LCω3PUFA content and potentially generate *trans*-fatty acids and/or oxidative factors that could substantially attenuate or even reverse the benefits of fish intake [16]. These studies might underestimate or confound the true effects of fish consumption by combining non-fried and fried fish. Our study found an inverse threshold association between non-fried fish consumption and incidence of MetS. The mechanisms for this threshold relation are not completely understood. Presumably, the potential beneficial effects of fish consumption on MetS in the higher intake groups were attenuated by the relatively high contaminants in fish. However, in the present study, the association between non-fried fish consumption and incidence of MetS was not appreciably changed after adjustment for toenail mercury levels measured at exam year 2 (data not shown).

The strengths of our study include the prospective design, a relatively large sample size, and 25-years of follow-up. In addition, we used cumulative average dietary intakes from multiple measurements during the follow-up, which should reduce the random measurement error and provide a better estimate of habitual intake than a single estimate. Several limitations should be highlighted. First, the possibility of residual confounding or bias from unknown or unmeasured factors cannot be completely ruled out even though we considered a number of dietary and non-dietary potential confounders and did some sensitivity analyses. Second, dietary measurement errors are inevitable. However, this may not substantially bias our results because this non-differential measurement error is likely to attenuate rather than accentuate the potential benefits. In addition, we could not assess LCω3PUFA intake and non-fried fish consumption simultaneously due to a relatively high correlation between them. Thus, we could not determine whether the association of non-fried fish intake is still

present, after taking into account the intake of LCω3PUFAs. In addition, the great majority of LCω3PUFA intake in this study is from fish consumption. Only approximately 5 % of participants used fish oil supplements. The association between the dietary and total LCω3PUFA intake and incidence of MetS are similar (data not shown). However, our capability of examining the effect of fish oil supplementation is limited.

In conclusion, findings from this prospective cohort study suggest that LCω3PUFA intake and non-fried fish consumption in young adulthood are associated with lower incidence of MetS later in life. This study provides evidence supporting the recommendations of fish consumption or LCω3PUFA intake for the primary prevention of MetS.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## References

1. Mozumdar A, Liguori G. Persistent increase of prevalence of metabolic syndrome among U.S. adults: NHANES III to NHANES 1999–2006. Diabetes Care. 2011; 34:216–219. [PubMed: 20889854]
2. Carpentier YA, Portois L, Malaisse WJ. n-3 fatty acids and the metabolic syndrome. Am J Clin Nutr. 2006; 83:1499S–1504S. [PubMed: 16841860]
3. Saravanan P, Davidson NC, Schmidt EB, Calder PC. Cardiovascular effects of marine omega-3 fatty acids. Lancet. 2010; 376:540–550. [PubMed: 20638121]
4. Ruidavets JB, Bongard V, Dallongeville J, Arveiler D, Ducimetière P, Perret B, Simon C, Amouyel P, Ferrières J. High consumptions of grain, fish, dairy products and combinations of these are associated with a low prevalence of metabolic syndrome. J Epidemiol Community Health. 2007; 61:810–817. [PubMed: 17699537]
5. Kouki R, Schwab U, Hassinen M, Komulainen P, Heikkilä H, Lakka TA, Rauramaa R. Food consumption, nutrient intake and the risk of having metabolic syndrome: the DR's EXTRA Study. Eur J Clin Nutr. 2010; 65:368–377. [PubMed: 21119694]
6. Noel SE, Newby PK, Ordovas JM, Tucker KL. Adherence to an (n-3) fatty acid/fish intake pattern is inversely associated with metabolic syndrome among Puerto Rican adults in the Greater Boston area. J Nutr. 2010; 140:1846–1854. [PubMed: 20702744]
7. Fonseca MJ, Gaio R, Lopes C, Santos AC. Association between dietary patterns and metabolic syndrome in a sample of Portuguese adults. Nutr J. 2012; 11:64. [PubMed: 22943133]
8. Mirmiran P, Hosseinpour-Niazi S, Naderi Z, Bahadoran Z, Sadeghi M, Azizi F. Association between interaction and ratio of ω-3 and ω-6 polyunsaturated fatty acid and the metabolic syndrome in adults. Nutrition. 2012; 28:856–863. [PubMed: 22459553]
9. Lai YH, Petrone AB, Pankow JS, Arnett DK, North KE, Ellison RC, Hunt SC, Djoussé L. Association of dietary omega-3 fatty acids with prevalence of metabolic syndrome: the National

Heart, Lung, and Blood Institute Family Heart Study. Clin Nutr. 2013; 32:966–969. [PubMed: 23711994]

10. Baik I, Abbott RD, Curb JD, Shin C. Intake of fish and n-3 fatty acids and future risk of metabolic syndrome. J Am Diet Assoc. 2010; 110:1018–1026. [PubMed: 20630158]
11. Friedman GD, Cutter GR, Donahue RP, Hughes GH, Hulley SB, Jacobs DR Jr, Liu K, Savage PJ. CARDIA: study design, recruitment, and some characteristics of the examined subjects. J Clin Epidemiol. 1988; 41:1105–1116. [PubMed: 3204420]
12. Xun P, Hou N, Daviglus M, Liu K, Morris JS, Shikany JM, Sidney S, Jacobs DR, He K. Fish oil, selenium and mercury in relation to incidence of hypertension: a 20-year follow-up study. J Intern Med. 2011; 270:175–186. [PubMed: 21205024]
13. McDonald A, Van Horn L, Slattery M, et al. The CARDIA dietary history: development, implementation, and evaluation. J Am Diet Assoc. 1991; 91:1104–1112. [PubMed: 1918764]
14. Liu K, Slattery M, Jacobs D Jr, et al. A study of the reliability and comparative validity of the cardia dietary history. Ethn Dis. 1994; 4:15–27. [PubMed: 7742729]
15. Nutrition Coordinating Center, University of Minnesota. Nutrition Data System for Research (NDSR), Food and Nutrient Database. http://www.ncc.umn.edu/products/ndsr.html.
16. Mozaffarian D, Lemaitre RN, Kuller LH, Burke GL, Tracy RP, Siscovick DS. Cardiac benefits of fish consumption may depend on the type of fish meal consumed: the Cardiovascular Health Study. Circulation. 2003; 107:1372–1377. [PubMed: 12642356]
17. Pereira MA, FitzerGerald SJ, Gregg EW, Joswiak ML, Ryan WJ, Suminski RR, Utter AC, Zmuda JM. A collection of Physical Activity Questionnaires for health-related research. Med Sci Sports Exerc. 1997; 29:S1–S205. [PubMed: 9243481]
18. Gunderson EP, Chiang V, Lewis CE, Catov J, Quesenberry CP Jr, Sidney S, Wei GS, Ness R. Long-term blood pressure changes measured from before to after pregnancy relative to nonparous women. Obstet Gynecol. 2008; 112:1294–1302. [PubMed: 19037039]
19. Donahu RP, Jacobs DR, Sidney S, Wagenknecht LE, Alers JJ, Hulley SB. Distribution of lipoproteins and apolipoproteins in young adults. Arteriosclerosis. 1989; 9:656–664. [PubMed: 2783079]
20. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of The National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA. 2001; 285:2486–2497. [PubMed: 11368702]
21. Fang J, Austin P, Tu J. Test for linearity between continuous confounder and binary outcome first, run a multivariate regression analysis second. 2009 http://support.sas.com/resources/papers/proceedings09/252-2009.pdf.
22. He K, Rimm EB, Merchant A, Rosner BA, Stampfer MJ, Willett WC, Ascherio A. Fish consumption and risk of stroke in men. JAMA. 2002; 288:3130–3136. [PubMed: 12495393]
23. Cicero AF, Ertek S, Borghi C. Omega-3 polyunsaturated fatty acids: their potential role in blood pressure prevention and management. Curr Vasc Pharmacol. 2009; 7(3):330–337. [PubMed: 19601857]
24. Mori TA. Dietary n-3 PUFA and CVD: a review of the evidence. Proc Nutr Soc. 2014; 73:57–64. [PubMed: 24119287]
25. Harris WS. n-3 fatty acids and serum lipoproteins: human studies. Am J Clin Nutr. 1997; 65:1645S–1654S. [PubMed: 9129504]
26. Eslick GD, Howe PR, Smith C, Priest R, Bensoussan A. Benefits of fish oil supplementation in hyperlipidemia: a systematic review and meta-analysis. Int J Cardiol. 2009; 136:4–16. [PubMed: 18774613]
27. Oelrich B, Dewell A, Gardner CD. Effect of fish oil supplementation on serum triglycerides, LDL cholesterol and LDL subfractions in hypertriglyceridemic adults. Nutr Metab Cardiovasc Dis. 2013; 23:350–357. [PubMed: 21924882]
28. Buckley JD, Howe PR. Long-chain omega-3 polyunsaturated fatty acids may be beneficial for reducing obesity—a review. Nutrients. 2010; 2:1212–1230. [PubMed: 22254005]

29. Harden CJ, Dible VA, Russell JM, Garaiova I, Plummer SF, Barker ME, Corfe BM. Long-chain polyunsaturated fatty acid supplementation had no effect on body weight but reduced energy intake in overweight and obese women. Nutr Res. 2014; 34:17–24. [PubMed: 24418242]
30. Garaulet M, Pérez-Llamas F, Pérez-Ayala M, Martínez P, de Medina FS, Tebar FJ, Zamora S. Site-specific differences in the fatty acid composition of abdominal adipose tissue in an obese population from a Mediterranean area: relation with dietary fatty acids, plasma lipid profile, serum insulin, and central obesity. Am J Clin Nutr. 2001; 74:585–591. [PubMed: 11684525]
31. Fedor D, Kelley DS. Prevention of insulin resistance by n-3 polyunsaturated fatty acids. Curr Opin Clin Nutr Metab Care. 2009; 12:138–146. [PubMed: 19202385]
32. Ramel A, Martinéz A, Kiely M, Morais G, Bandarra NM, Thorsdottir I. Beneficial effects of long-chain n-3 fatty acids included in an energy-restricted diet on insulin resistance in overweight and obese European young adults. Diabetologia. 2008; 51:1261–1268. [PubMed: 18491071]
33. Krebs JD, Browning LM, McLean NK, Rothwell JL, Mishra GD, Moore CS, Jebb SA. Additive benefits of long-chain n-3 polyunsaturated fatty acids and weight-loss in the management of cardiovascular disease risk in overweight hyperinsulinaemic women. Int J Obes. 2006; 30:1535–1544.
34. Giacco R, Cuomo V, Vessby B, Uusitupa M, Hermansen K, Meyer BJ, Riccardi G, Rivellese AA. Fish oil, insulin sensitivity, insulin secretion and glucose tolerance in healthy people: is there any effect of fish oil supplementation in relation to the type of background diet and habitual dietary intake of n-6 and n-3 fatty acids? Nutr Metab Cardiovasc Dis. 2007; 17:572–580. [PubMed: 17127043]
35. Djoussé L, Gaziano JM, Buring JE, Lee IM. Dietary omega-3 fatty acids and fish consumption and risk of type 2 diabetes. Am J Clin Nutr. 2011; 93:143–150. [PubMed: 20980491]
36. Mori TA, Woodman RJ. The independent effects of eicosapentaenoic acid and docosahexaenoic acid on cardiovascular risk factors in humans. Curr Opin Clin Nutr Metab Care. 2006; 9:95–104. [PubMed: 16477172]
37. Conquer JA, Holub BJ. Supplementation with an algae source of docosahexaenoic acid increases (n-3) fatty acid status and alters selected risk factors for heart disease in vegetarian subjects. J Nutr. 1996; 126:3032–3039. [PubMed: 9001371]
38. Grimsgaard S, Bonaa KH, Hansen JB, Nordøy A. Highly purified eicosapentaenoic acid and docosahexaenoic acid in humans have similar triacylglycerol-lowering effects but divergent effects on serum fatty acids. Am J Clin Nutr. 1997; 66:649–659. [PubMed: 9280188]
39. Wei MY, Jacobson TA. Effects of eicosapentaenoic acid versus docosahexaenoic acid on serum lipids: a systematic review and meta-analysis. Curr Atheroscler Rep. 2011; 13:474–483. [PubMed: 21975919]
40. Kunesová M, Braunerová R, Hlavatý P, et al. The influence of n-3 polyunsaturated fatty acids and very low calorie diet during a short-term weight reducing regimen on weight loss and serum fatty acid composition in severely obese women. Physiol Res. 2006; 55:63–72. [PubMed: 15857162]
41. Russell FD, Burgin-Maunder CS. Distinguishing health benefits of eicosapentaenoic and docosahexaenoic acids. Mar Drugs. 2012; 10:2535–2559. [PubMed: 23203276]

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**Table 1**

Baseline characteristics of the study population by quintile of LCω3PUFA intake, the CARDIA study, 1985–2010 ($n$ = 4356)

| Characteristics | Quintile of LCω3PUFA intake | | | | | Total | *P* value[a] |
|---|---|---|---|---|---|---|---|
| | Q1 (lowest) | Q2 | Q3 | Q4 | Q5 (highest) | | |
| *n* | 868 | 870 | 871 | 877 | 870 | 4356 | |
| LCω3PUFA intake (g/day) | 0.03 (0.01) | 0.07 (0.01) | 0.11 (0.02) | 0.18 (0.03) | 0.40 (0.28) | 0.16 (0.18) | NA |
| EPA (g/day) | 0.01 (0.01) | 0.03 (0.01) | 0.04 (0.02) | 0.07 (0.02) | 0.17 (0.13) | 0.06 (0.08) | NA |
| DHA (g/day) | 0.01 (0.01) | 0.03 (0.01) | 0.05 (0.02) | 0.08 (0.03) | 0.19 (0.14) | 0.07 (0.08) | NA |
| Non-fried fish (servings/day) | 0.17 (0.19) | 0.46 (0.33) | 0.78 (0.52) | 1.18 (0.64) | 2.21 (1.55) | 0.96 (1.07) | NA |
| Fried fish (servings/day) | 0.03 (0.13) | 0.06 (0.28) | 0.08 (0.42) | 0.08 (0.33) | 0.06 (0.29) | 0.06 (0.31) | NA |
| Age (year) | 24.25 (3.84) | 24.87 (3.61) | 24.76 (3.69) | 25.39 (3.43) | 25.09 (3.53) | 24.88 (3.64) | <0.01 |
| Female (%) | 59.10 | 57.82 | 54.54 | 48.35 | 43.22 | 52.59 | <0.01 |
| Education (year) | 13.29 (2.13) | 13.86 (2.20) | 13.82 (2.18) | 14.11 (2.31) | 14.11 (2.40) | 13.84 (2.26) | <0.01 |
| Body mass index (kg/m$^2$) | 24.50 (4.86) | 24.28 (4.98) | 24.26 (4.90) | 24.18 (4.71) | 24.16 (4.10) | 24.28 (4.72) | 0.57 |
| Smoking status (%) | | | | | | | |
| Never | 56.22 | 58.16 | 57.52 | 56.44 | 55.86 | 56.84 | <0.01 |
| Former | 10.71 | 12.07 | 12.86 | 16.99 | 14.14 | 13.36 | |
| Current | 33.06 | 29.77 | 29.62 | 26.57 | 30.00 | 29.80 | |
| Alcohol intake (g/day) | | | | | | | |
| Median | 2.39 | 2.73 | 2.73 | 5.16 | 7.59 | 4.77 | <0.01 |
| IQR[b] | 0.00–12.53 | 0.00–12.61 | 0.00–14.31 | 0.00–17.04 | 0.00–21.84 | 0.00–15.00 | |
| Physical activity (exercise unit) | | | | | | | |
| Median | 306 | 340 | 354 | 374 | 464 | 366 | <0.01 |
| IQR[b] | 166–500 | 182–558 | 193–566 | 220–576 | 260–704 | 201–579 | |
| Family history of diabetes (%) | 14.86 | 12.53 | 15.04 | 13.57 | 11.95 | 13.59 | 0.23 |
| Daily intake | | | | | | | |
| Total energy (kcal/day) | 2559.72 (1259.56) | 2606.26 (1286.04) | 2916.90 (1637.87) | 3063.96 (1528.82) | 3480.91 (1825.92) | 2925.94 (1558.75) | <0.01 |
| Fiber (g/day) | 4.67 (2.98) | 5.01 (2.72) | 5.69 (3.53) | 6.18 (3.55) | 7.14 (3.88) | 5.74 (3.47) | <0.01 |
| Saturated fat (g/day/1000 kcal) | 15.79 (3.59) | 15.76 (3.09) | 15.91 (3.33) | 15.61 (3.33) | 15.61 (3.12) | 15.76 (3.30) | 0.13 |
| PUFA (g/d/1000 kcal) | 7.09 (2.23) | 7.54 (2.33) | 7.70 (2.33) | 7.83 (2.31) | 8.06 (2.47) | 7.65 (2.36) | <0.01 |
| Protein (g/d/1000 kcal) | 34.93 (6.58) | 36.72 (6.53) | 37.21 (6.64) | 37.43 (6.15) | 38.26 (6.84) | 36.91 (6.64) | <0.01 |

| Characteristics | Quintile of LCω3PUFA intake | | | | | Total | *P* value[a] |
|---|---|---|---|---|---|---|---|
| | Q1 (lowest) | Q2 | Q3 | Q4 | Q5 (highest) | | |
| Metabolic syndrome components | | | | | | | |
| Triglycerides (mg/dL) | 72.06 (37.12) | 70.24 (52.95) | 69.75 (40.29) | 68.71 (35.05) | 70.67 (45.32) | 70.28 (42.62) | 0.57 |
| HDL cholesterol (mg/dL) | 51.66 (12.86) | 52.65 (12.78) | 52.77 (12.27) | 53.80 (13.06) | 55.67 (13.55) | 53.31 (12.98) | <0.01 |
| Glucose (mg/dL) | 81.85 (8.45) | 81.53 (8.47) | 81.40 (8.11) | 81.53 (7.87) | 82.06 (8.08) | 81.67 (8.20) | 0.42 |
| Systolic blood pressure (mmHg) | 109.99 (10.87) | 109.70 (11.03) | 110.28 (10.44) | 110.46 (10.81) | 110.91 (10.26) | 110.27 (10.69) | 0.17 |
| Diastolic blood pressure (mmHg) | 68.26 (9.30) | 68.26 (9.30) | 68.48 (8.90) | 68.87 (9.37) | 68.56 (9.23) | 68.48 (9.22) | 0.62 |
| Waist circumference (cm) | 77.37 (11.14) | 76.93 (10.78) | 76.94 (10.81) | 77.63 (10.65) | 77.76 (9.91) | 77.32 (10.66) | 0.34 |

Data are means (SD), unless otherwise specified

*CARDIA* Coronary Artery Risk Development in Young Adults, *DHA* docosahexaenoic acid, *EPA* eicosapentaenoic acid, *HDL* high-density lipoprotein, *IQR* inter-quartile range, *LCω3PUFAs* long-chain omega-3 polyunsaturated fatty acids, *NA* not applicable, *PUFA* polyunsaturated fatty acids

[a] *P* values were any difference across the quintiles of LCω3PUFA intake by using analysis of variance, Kruskal–Wallis test or Chi-squared test, as appropriate

[b] 25th–75th percentiles

**Table 2**

Multivariable-adjusted HRs (95 % CIs) of incident metabolic syndrome by intakes of LCω3PUFA, EPA, DHA and non-fried fish, the CARDIA study, 1985–2010 ($n$ = 4356)

| | Quintiles of LCω3PUFA intake | | | | | *P* for linear trend[a] |
|---|---|---|---|---|---|---|
| | Q1 (lowest) | Q2 | Q3 | Q4 | Q5 (highest) | |
| *Total LCω3PUFA* | | | | | | |
| Median (IQR, g/day) | 0.03 (0.02–0.04) | 0.07 (0.06–0.08) | 0.11 (0.10–0.13) | 0.18 (0.16–0.20) | 0.33 (0.27–0.44) | |
| No. of events/participants | 258/868 | 230/870 | 224/871 | 204/877 | 153/870 | |
| Model 1[b] | 1 (referent) | 0.77 (0.64,0.92) | 0.68 (0.56,0.81) | 0.59 (0.49,0.71) | 0.42 (0.35,0.52) | <0.01 |
| Model 2[c] | 1 (referent) | 0.89 (0.75,1.07) | 0.76 (0.64,0.92) | 0.71 (0.59,0.87) | 0.54 (0.44,0.67) | <0.01 |
| Model 3a[d] | 1 (referent) | 0.91 (0.76,1.09) | 0.76 (0.63,0.92) | 0.71 (0.58,0.87) | 0.52 (0.41,0.65) | <0.01 |
| Model 3b[e] | 1 (referent) | 0.90 (0.75,1.07) | 0.75 (0.62,0.90) | 0.69 (0.56,0.84) | 0.50 (0.40,0.63) | <0.01 |
| Model 4[f] | 1 (referent) | 0.91 (0.76,1.09) | 0.76 (0.63,0.91) | 0.71 (0.59,0.86) | 0.55 (0.44,0.68) | <0.01 |
| *EPA* | | | | | | |
| Median (IQR, g/day) | 0.01 (0.00–0.01) | 0.02 (0.02–0.03) | 0.04 (0.04–0.05) | 0.07 (0.06,0.08) | 0.14 (0.11,0.19) | |
| No. of events/participants | 255/873 | 214/869 | 217/889 | 211/848 | 172/877 | |
| Model 1[b] | 1 (referent) | 0.77 (0.64,0.92) | 0.70 (0.58,0.84) | 0.71 (0.59,0.85) | 0.55 (0.45,0.67) | <0.01 |
| Model 2[c] | 1 (referent) | 0.84 (0.70,1.004) | 0.79 (0.66,0.95) | 0.81 (0.67,0.98) | 0.69 (0.56,0.85) | <0.01 |
| Model 3a[d] | 1 (referent) | 0.86 (0.71,1.03) | 0.82 (0.68,0.99) | 0.83 (0.69,1.01) | 0.69 (0.56,0.86) | <0.01 |
| Model 3b[e] | 1 (referent) | 0.85 (0.71,1.03) | 0.82 (0.67,0.99) | 0.82 (0.68,1.004) | 0.69 (0.55,0.85) | <0.01 |
| Model 4[f] | 1 (referent) | 0.86 (0.71,1.03) | 0.76 (0.64,0.92) | 0.79 (0.65,0.95) | 0.69 (0.56,0.85) | <0.01 |
| *DHA* | | | | | | |
| Median (IQR, g/day) | 0.01 (0.00–0.01) | 0.03 (0.02–0.03) | 0.05 (0.04–0.06) | 0.08 (0.07–0.10) | 0.16 (0.13–0.21) | |
| No. of events/participants | 289/832 | 242/909 | 209/882 | 182/852 | 147/881 | |
| Model 1[b] | 1 (referent) | 0.55 (0.46,0.65) | 0.44 (0.37,0.53) | 0.37 (0.30,0.44) | 0.28 (0.23,0.34) | <0.01 |
| Model 2[c] | 1 (referent) | 0.63 (0.53,0.75) | 0.52 (0.43,0.62) | 0.44 (0.36,0.53) | 0.36 (0.29,0.44) | <0.01 |
| Model 3a[d] | 1 (referent) | 0.65 (0.55,0.78) | 0.51 (0.42,0.62) | 0.43 (0.35,0.52) | 0.34 (0.27,0.42) | <0.01 |
| Model 3b[e] | 1 (referent) | 0.64 (0.54,0.77) | 0.50 (0.42,0.61) | 0.42 (0.34,0.51) | 0.33 (0.26,0.41) | <0.01 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Model 4[f] | 1 (referent) | 0.65 (0.55,0.77) | 0.53 (0.44,0.64) | 0.43 (0.36,0.53) | 0.37 (0.30,0.46) | <0.01 |
| | Non-fried fish consumption | | | | | *P* for linear trend[a] |
| | <1 month | 1–3 month | 1 week | 2–4 week | ≥5 week | |
| Median (IQR, serving/day) | 0.00 (0.00–0.01) | 0.09 (0.06–0.12) | 0.21 (0.18–0.25) | 0.48 (0.38–0.59) | 1.32 (0.96–1.93) | |
| No. of events/participants | 87/250 | 81/317 | 111/458 | 293/1257 | 497/2074 | |
| Model 1[b] | 1 (referent) | 0.64 (0.47,0.86) | 0.55 (0.42,0.73) | 0.51 (0.40,0.65) | 0.51 (0.40,0.64) | <0.01 |
| Model 2[c] | 1 (referent) | 0.70 (0.51,0.95) | 0.68 (0.52,0.91) | 0.67 (0.53,0.86) | 0.71 (0.56,0.89) | 0.49 |
| Model 3a[d] | 1 (referent) | 0.69 (0.51,0.94) | 0.68 (0.51,0.90) | 0.69 (0.54,0.88) | 0.73 (0.58,0.93) | 0.80 |
| Model 3b[e] | 1 (referent) | 0.71 (0.53,0.97) | 0.70 (0.53,0.93) | 0.70 (0.55,0.90) | 0.75 (0.59,0.96) | 0.84 |
| Model 4[f] | 1 (referent) | 0.68 (0.50,0.93) | 0.70 (0.53,0.93) | 0.65 (0.51,0.83) | 0.69 (0.55,0.88) | 0.44 |

All models were constructed using Cox proportional hazards regression analysis

*CARDIA* Coronary Artery Risk Development in Young Adults, *CI* confidence interval, *DHA* docosahexaenoic acid, *EPA* eicosapentaenoic acid, *HR* hazard ratio, *IQR* inter-quartile range, *LCω3PUFA* long-chain ω-3 polyunsaturated fatty acid

[a] *P* for trend was examined by using medians in each quintile/subgroup of exposure of interest

[b] Model 1: adjustment for age (years, continuous), gender, ethnicity (African American, Caucasian) and study center

[c] Model 2: model 1 with additional adjustment for education (years, continuous), smoking status (never, former, current), family history of diabetes (yes or no), physical activity (quintiles), alcohol consumption (0, 0.1–9.9, 10–19.9, ≥20 g/day), and baseline body mass index (<25, 25–29.9, ≥30 kg/m$^2$). Fried fish consumption (yes vs. no) was also adjusted when non-fried fish was the exposure

[d] Model 3a (sensitivity analysis): model 2 with additional adjustment for intakes (quintiles) of protein, saturated fatty acid, polyunsaturated fatty acid, and total energy

[e] Model 3b (sensitivity analysis): model 2 with additional adjustment for “Fruit-Vegetable” pattern (quintiles), meat pattern (quintile) and total energy intake (quintile)

[f] Model 4 (sensitivity analysis): model 2 with additional adjustment for each component of metabolic syndrome at baseline, except baseline body mass index, because it is highly correlated with waist circumference

**Table 3**

Multivariable-adjusted HRs (95 % CIs) of incident abnormal individual components of metabolic syndrome by intakes of LCω3PUFAs and non-fried fish, the CARDIA study, 1985–2010

| Components of metabolic syndrome | Quintiles of LCω3PUFA intake | | | | | *P* for linear trend[a] |
|---|---|---|---|---|---|---|
| | Q1 (lowest) | Q2 | Q3 | Q4 | Q5 (highest) | |
| Blood pressure[b] (*n* = 4154) | 1 (referent) | 0.86 (0.74,1.01) | 0.89 (0.76,1.03) | 0.75 (0.64,0.88) | 0.63 (0.54,0.75) | <0.01 |
| Glucose[c] (*n* = 4593) | 1 (referent) | 0.83 (0.67,1.04) | 0.68 (0.54,0.85) | 0.68 (0.54,0.86) | 0.63 (0.50,0.80) | <0.01 |
| HDL cholesterol[d] (*n* = 3367) | 1 (referent) | 0.63 (0.54,0.73) | 0.53 (0.45,0.61) | 0.45 (0.38,0.54) | 0.36 (0.30,0.44) | <0.01 |
| Triglycerides[e] (*n* = 4289) | 1 (referent) | 0.67 (0.57,0.79) | 0.55 (0.46,0.65) | 0.48 (0.40,0.57) | 0.43 (0.36,0.52) | <0.01 |
| Waist circumference[f] (*n* = 4217) | 1 (referent) | 0.77 (0.67,0.89) | 0.67 (0.58,0.78) | 0.63 (0.54,0.74) | 0.60 (0.51,0.70) | <0.01 |
| | Non-fried fish consumption | | | | | *P* for linear trend[a] |
| | <1 month | 1–3 month | 1 week | 2–4 week | ≥5 week | |
| Blood pressure[b] (*n* = 4154) | 1 (referent) | 0.77 (0.59,1.002) | 0.74 (0.58,0.95) | 0.76 (0.62,0.95) | 0.77 (0.62,0.95) | 0.49 |
| Glucose[c] (*n* = 4593) | 1 (referent) | 0.63 (0.43,0.92) | 0.68 (0.48,0.96) | 0.61 (0.45,0.82) | 0.65 (0.49,0.87) | 0.44 |
| HDL cholesterol[d] (*n* = 3367) | 1 (referent) | 0.94 (0.73,1.19) | 0.70 (0.55,0.88) | 0.66 (0.54,0.81) | 0.62 (0.51,0.75) | <0.01 |
| Triglycerides[e] (*n* = 4289) | 1 (referent) | 0.80 (0.61,1.04) | 0.69 (0.54,0.88) | 0.63 (0.51,0.79) | 0.62 (0.50,0.76) | <0.01 |
| Waist circumference[f] (*n* = 4217) | 1 (referent) | 0.86 (0.68,1.10) | 0.76 (0.61,0.94) | 0.77 (0.64,0.94) | 0.75 (0.62,0.91) | 0.06 |

All models were constructed using Cox proportional hazards regression analysis. The models were adjusted for the covariates listed for model 2 in Table 2

*CARDIA* Coronary Artery Risk Development in Young Adults, *CI* confidence interval, *HDL* high-density lipoprotein, *HR* hazard ratio, *LCω3PUFA* long-chain ω-3 polyunsaturated fatty acid

[a] *P* for trend was examined by using medians in each quintile exposure of interest

[b] Incident abnormal blood pressure: systolic blood pressure ≥130 mmHg or diastolic blood pressure BP ≥ 85 mmHg or if the participants were using antihypertensive medications in any of the follow-up examinations

[c] Incident abnormal glucose: fasting glucose level ≥6.1 mmol/L or if the participants were using antidiabetic medications in any of the follow-up examinations

[d] Incident abnormal HDL cholesterol: HDL cholesterol level <1.3 mmol/L in women or <1.04 mmol/L in men

[e] Incident abnormal triglyceride: triglyceride level ≥1.7 mmol/L

[f] Incident abnormal waist circumference: waist circumference >88 cm for women or >102 cm for men