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Intakes of long-chain omega-3 (n−3) PUFAs and fish in relation to incidence of asthma among American young adults: the CARDIA study[1,2,3]

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Abstract

Background: Although long-chain ω-3 (n−3) PUFAs (LCω3PUFAs) have been linked to the prevention of some inflammatory disorders, little is known about the association between these fatty acids and incidence of asthma.

Objective: The objective was to prospectively investigate the association between LCω3PUFAs and fish intake and incidence of asthma among American young adults.

Design: A 20-y follow-up longitudinal analysis was conducted in a biracial cohort of 4162 Americans, aged 18–30 y, with a history of asthma at baseline in 1985. Diet was assessed by a validated interviewer-administered quantitative food-frequency questionnaire at the examinations in 1985, 1992, and 2005. Incident self-reported asthma was defined as having a physician diagnosis of asthma and/or the use of asthma medications between 1985 and 2005.

Results: During the 20-y follow-up, 446 incident cases of asthma were identified. LCω3PUFA intake was significantly inversely associated with incidence of asthma after adjustment for sociodemographic, major lifestyle, and dietary confounders. The multivariable-adjusted HR for the highest quintile of LCω3PUFA intake as compared with the lowest quintile was 0.46 (95% CI: 0.33, 0.64; *P*-trend < 0.01). However, a higher frequency of nonfried fish consumption was not significantly associated with the risk of asthma. DHA showed a greater inverse association than did EPA. The association between LCω3PUFAs and incident asthma was not appreciably modified by sex, race, BMI, smoking status, or atopic status.

Conclusion: This study showed that intakes of LCω3PUFAs are inversely longitudinally associated with the incidence of asthma in American young adults.

INTRODUCTION

Asthma is characterized by chronic inflammation of the airways that results in narrowing of the bronchial tubes (1). One in 12 Americans of all ages suffers from this health disorder, and an increase of 12.3% occurred during the past decade according to the CDC (2). The increased prevalence of asthma highlights the need for devising effective preventative strategies. Long-chain ω-3 (n−3) PUFAs (LCω3PUFAs)[4], including EPA (20:5ω-3), docosapentaenoic acid (22:5ω-3), and DHA (22:6ω-3), are abundant in fish and have been shown to be antiinflammatory (3, 4). Because asthma is an inflammatory process, it has been hypothesized that a high intake of LCω3PUFAs may have beneficial effects on asthma development (5).

Data relating LCω3PUFA or fish intake to the risk of asthma are sparse in humans (6). Most previous studies on LCω3PUFA or fish intake and asthma were cross-sectional (7–12). Three prospective studies, including 2 long-term studies (13, 14) and 1 short-term study (15), have evaluated the incidence of asthma in adults but failed to find a clear association with LCω3PUFA intake. These 2 studies were conducted in well-educated middle-aged women (34–68 y at baseline) (13) or older men (>65 y at baseline), a substantial proportion (92%) of whom were smokers (14). Some misclassification of asthma and chronic obstructive pulmonary disease may have occurred in smokers (16). Because these 2 diseases share some common features, they may be difficult to distinguish in older patients clinically (17). Therefore, we used data from the Coronary Artery Risk Development in Young Adults (CARDIA) study to examine the association between intakes of LCω3PUFAs and fish and the 20-y incidence of asthma among young American adults.

SUBJECTS AND METHODS

Study population

The CARDIA study is a prospective multicenter cohort study designed to investigate cardiovascular disease risk factors in African American and white men and women (18). The CARDIA cohort comprised 5115 Americans aged 18–30 y who were recruited from 4 US cities in 1985–1986; the recruitment was balanced within each center on sex and race. Six follow-up examinations were conducted, in 1987, 1990, 1992, 1995, 2000, and 2005. Approximately 70% of the participants in the original cohort returned for the sixth follow-up visit in 2005.

In the current analyses, we excluded participants with prevalent asthma at baseline (n = 474). We also excluded participants who lacked information for defining asthma in any follow-up (n = 176). In addition, we excluded participants who *1*) had missing data on LCω3PUFA and/or total energy intake (n = 4), *2*) reported implausible total energy intake in dietary assessments (<800 or >8000 kcal/d for men and <600 or >6000 kcal/d for women; n = 38), or *3*) had missing information on key covariates, including smoking status (n = 28), alcohol consumption (n = 15), and physical activity (n = 1). We further excluded women who were pregnant at any examination (n = 217). After these exclusions, at baseline, a total of 4162 participants (81.4% of 5115) remained for analyses. All participants provided informed consent at each examination. The study design and data collection and analyses were approved by the institutional review boards of the centers involved.

Assessment of diet

The CARDIA diet-history questionnaire, a validated interviewer-administered quantitative food-frequency questionnaire (FFQ), was designed to assess habitual eating patterns. The validity and reproducibility of CARDIA FFQ were described in previous studies (19, 20). Briefly, dietary information was collected in 1985, 1992, and 2005. Nutrient intake was estimated by using an adaptively updated nutrient database from the Nutrition Coordinating Center at the University of Minnesota (NCC Nutrient Database, version 20, October 1991; Nutrition Coordinating Center,

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University of Minnesota, Minneapolis). In this study, LCω3PUFA represented the sum of EPA, docosapentaenoic acid, and DHA. Previous data suggested that the preparation method, particularly deep frying, may substantially alter the fatty acid content of fish (ie, by reducing LCω3PUFA levels and producing *trans* fatty acids) (21). Therefore, we categorized fish consumption into 2 groups: nonfried fish and fried fish.

Assessment of asthma

The incidence of asthma was identified if a participant reported that he or she had asthma diagnosed by a physician and/or reported the use of any asthma-control medicine (medicine containers were examined) at any follow-up exam (22). In this study, we could not define atopic asthma based on available information. However, we used a self-reported diagnosis of hay fever as an indicator of atopic history and considered atopic status as a modifier in the analysis.

Assessment of covariates

Standard questionnaires were used to maintain consistency in the assessment of demographic and behavioral information, including age, sex, race, and education level (<13, 13–15, or ≥16 y) across all CARDIA examinations. Smoking status was classified into 3 groups: current, former, or never. Alcohol consumption was measured by using a validated questionnaire and classified into 4 groups according to the total daily consumption: 0 (never drink), 0.1–9.9, 10–19.9, or ≥20 mL/d. BMI was calculated as weight (in kg) divided by height (in m) squared. Weight and height were directly measured while the participant stood in light clothes and no shoes. In this study, BMI was classified into 3 groups: <25, 25–29.9, or ≥30 kg/m^2 (23). Physical activity was assessed by using the interview-based, validated CARDIA physical activity history questionnaire. A score of 100 exercise units is approximately equivalent to participation in vigorous activity for 2 to 3 h per week during 6 mo of the year (24). Self-reported diagnosis of hay fever was used as an indicator of atopic history (25).

Statistical analyses

Participants were divided into quintiles (≤0.050, 0.051–0.090, 0.091–0.145, 0.146–0.239, or ≥0.240 g/d) according to the distribution of the cumulative average LCω3PUFA intake. Group comparisons of baseline characteristics were performed by ANOVA, the Kruskal-Wallis test, or the chi-square test when appropriate.

Cox proportional hazards regression models were used to estimate the HRs and 95% CIs by comparing participants in higher quintiles of LCω3PUFA intake to the lowest quintile. Each participant contributed follow-up time from the date of the baseline examination until the date in which asthma was first identified or first censored or until the end of the follow-up period. To best represent long-term dietary intake and to reduce measurement errors, we used cumulative average intakes of nutrients in the main analyses (26). For example, we related baseline LCω3PUFA intake to incident asthma identified at years 2 and 5; average LCω3PUFA intake at baseline and exam year 7 to new cases occurring at years 7, 10, and 15; and average LCω3PUFA intake at baseline and years 7 and 20 to new cases occurring at year 20. For the noncases, we also used average LCω3PUFA intake from all the 3 visits.

The initial analyses (model 1) were adjusted for age, sex, race, and study center; model 2 additionally adjusted for education, smoking status, alcohol consumption, physical activity, BMI, and total energy intake; and model 3 additionally adjusted for linoleic acid. Linoleic acid is the primary essential ω-6 fatty acid and has been shown to be proinflammatory (27). The competition for desaturases and elongases in ω-3 and ω-6 PUFA metabolism results in opposite effects on tissue concentration of these ω3-and ω-6 PUFA (28). In a supplemental analysis, we assessed the potential modification of ω-6 PUFA intake on the association of LCω3PUFA intake with incident asthma and the association between the ratio of LCω3PUFA to ω-6 PUFA and incidence of asthma. The median values in each quintile were used as continuous variables for trend estimates.

In addition, we evaluated the possible interactions between LCω3PUFAs and sex, race (African American and white), BMI (<25 or ≥25 kg/m^2), smoking status (current, former, or never smoker), atopic history (with or without hay fever) (25), and ω-6 PUFA intake (above compared with below median) by adding corresponding multiplicative interaction terms in the models, followed by the likelihood ratio test. All analyses were conducted by using SAS (version 9.2; SAS Institute Inc). $P \leq 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics of the study population according to quintiles of LCω3PUFA intake are shown in **Table 1**. Compared with participants in the lowest quintile, those in the highest quintile were slightly older, were more likely to be males and African Americans, and had relatively high education levels. During the 20-y follow-up, 446 incident cases of asthma were identified. LCω3PUFA intake was inversely associated with incidence of asthma after adjustment for potential dietary and nondietary confounders (**Table 2**). The multivariable-adjusted HR of asthma reduced monotonically and inversely by quintiles of LCω3PUFA intake. Participants in the highest quintile of LCω3PUFA intake had a significantly lower incidence of asthma (HR: 0.46; 95% CI: 0.33, 0.64; *P*-trend < 0.01) than did those who were in the lowest quintile. DHA had a greater inverse association with incidence of asthma than did EPA (HR with DHA: 0.30; 95% CI: 0.22, 0.41; $P < 0.01$; HR with EPA: 0.71; 95% CI: 0.52, 0.97; $P = 0.0496$). Because of the narrow distribution (the great majority of participants reported no fried fish consumption), we were not able to examine fried fish consumption separately. No statistically significant associations were found between nonfried fish consumption and incidence of asthma after adjustment for fried fish and other potential confounders.

TABLE 1

Baseline characteristics of the study population according to quintiles of LCω3PUFA intake: CARDIA study, 1985–2005[1]

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[1]CARDIA, Coronary Artery Risk Development in Young Adults; DPA, docosapentaenoic acid; LA, linoleic acid; LCω3PUFA, long-chain omega-3 PUFA.
[2]Reflects differences across the quintiles of LCω3PUFA intake (ANOVA, Kruskal-Wallis test, or chi-square test as appropriate).
[3]Mean ± SD (all such values).
[4]Reflects 25th−75th percentiles.

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TABLE 2

Multivariable-adjusted HRs (95% CIs) of incidence of asthma by cumulative intakes (quintiles)[1] of LCω3PUFAs, EPA, DHA, and nonfried fish: CARDIA study, 1985–2005 (n = 4162)

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[1]All models were constructed by the Cox proportional hazards model. CARDIA, Coronary Artery Risk Development in Young Adults; DPA, docosapentaenoic acid; LCω3PUFAs, long-chain omega-3 PUFAs.
[2]Variables using medians in each quintile were created for the trend test.
[3]Defined as EPA + DPA + DHA.
[4]Model 1: adjusted for age (continuous), sex, race (African American or white), and study center.
[5]Model 2: additionally adjusted for education (<13, 13–15, or ≥16 y), smoking status (never, former, or current), alcohol consumption (0, 0.1–9.9, 10–19.9, or ≥20 mL/d), physical activity (quintile), BMI (in kg/m^2; <25, 25–29.9, or ≥30), and total energy intake (quintile).
[6]Model 3: additionally adjusted for dietary intake (quintiles) of linoleic acid.
[7]Fried fish intake (yes or no) was adjusted only in models when studying nonfried fish.

The observed inverse associations between LCω3PUFA intake and incidence of asthma were not appreciably modified by atopic history, sex, race, BMI, or smoking status. However, the inverse association between LCω3PUFA intake and incidence of asthma was attenuated by a high intake of ω-6 PUFA (*see* Supplemental Table 1 under "Supplemental data" in the online issue). In addition, the ratio of ω-3 to ω-6 was inversely associated with asthma development (*see* Supplemental Table 2 under "Supplemental data" in the online issue). To test the robustness of our findings, several sensitivity analyses (data not shown) were conducted. First, our findings persisted after we further adjusted for nicotine levels and for other nutrients, including folic acids, magnesium, zinc, sodium, and several antioxidants (β-carotene, vitamin A, vitamin C, vitamin D, and vitamin E). We adjusted for these nutrients because fish is a good source of vitamins and minerals in addition to being an excellent source of the marine-derived ω-3 fatty acids (29). Some previous studies have suggested effects of those nutrients on inflammatory disorders and lung function (30–32). Second, when we excluded participants with self-reported other allergic diseases at baseline (n = 6), the results were essentially unchanged. Third, because the time of events is interval censored, we used midpoint imputation rather than right-point imputation in the main analyses (33). The results were robust to these changes.

DISCUSSION

This longitudinal study showed an inverse association between intake of LCω3PUFAs and incidence of asthma, independently of major lifestyle, sociodemographic, and other dietary confounders. The observed inverse association was modified by ω-3 PUFA intake, but not appreciably modified by sex, race, BMI, smoking status, or atopic history.

Data directly relating LCω3PUFAs to asthma are limited. A cross-sectional study found that plasma LCω3PUFAs were not associated with prevalence of asthma among young adults (34). Dietary fish intake had a beneficial effect on wheezing; however, adjustment for vitamin C made this association statistically nonsignificant (11). Moreover, no significant association was found between childhood fish intake and adult-onset asthma (35). Similarly, 3 prospective studies that examined adult intake of LCω3PUFAs and incident asthma (13–15) found no significant association. Of note, in these studies performed in middle-aged or older men and/or women [women 35–65 y and men 40–65 y (15) of age; women 34–68 y (13) or men older than 65 y (14)], asthma may be difficult to be differentiated from chronic obstructive pulmonary diseases (36), particularly, when the prevalence of smoking is high (74%) (14). In addition, some evidence suggests that cigarette smoking is a major risk factor for asthma (37). Residual confounding from this risk factor may attenuate or mask any association of asthma with

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LCω3PUFAs. The inconsistent results between our study and the previous studies may not be explained by the sex and atopic history of participants because we found that these 2 factors did not materially modify the observed associations.

Our findings of the potential beneficial effect of LCω3PUFA intake on asthma development are biologically plausible. Evidence from both experimental and observational studies suggested that LCω3PUFAs are antiinflammatory (3, 4, 27). A possible mechanism for the effect of LCω3PUFAs on inflammation is that LCω3PUFAs inhibit arachidonic acid (AA) metabolism competitively via enzymatic pathways (38) and suppress the production of active inflammatory eicosanoid mediators from AA (29, 39, 40). This effect was further investigated recently (30). Whereas most of the products of AA are endowed with proinflammatory activity, some are antiinflammatory and others have contrasting activities (eg, prostaglandin E2 has both pro- and antiinflammatory actions). Recently, lipid mediators derived from EPA and DHA have been identified as playing a role in inflammation (41).

Our finding that DHA was superior to EPA with respect to asthma prevention is compatible with previous findings. In vitro studies have shown that DHA was more potent than EPA at decreasing the expression of proinflammatory cytokines, cell-adhesion molecules, and monotype adhesion to endothelial cells (42). Moreover, studies that measured serum or plasma fatty acids as biomarkers for dietary intake showed that a high concentration of DHA but not EPA in serum phospholipids (43) and plasma (44) may have a protective effect on airway hyperresponsiveness (44), lung function (43), and other chronic inflammatory conditions of the lung (44).

Studies suggest that ω-6 PUFAs may compete with ω-3 PUFAs for key enzymes in the metabolisms. Consistently, we found that the inverse associations between LCω3PUFA intake and incidence of asthma were substantially attenuated by high intakes of ω-6 PUFA intake.

In this study, LCω3PUFAs, but not nonfried fish consumption, were significantly associated with reduced incidence of asthma. Fish is a package of nutrients and contaminants, whereas LCω3PUFAs are considered to be the key nutrients responsible for its benefits. The integrative effects of fish consumption may reflect the interactions of LCω3PUFAs with other nutrients and contaminants in fish. Our finding of no association might be explained by contaminants in fish, such as mercury (45, 46) and polychlorinated biphenyls (PCBs) (47), and/or added sodium (48, 49), which could have substantially attenuated or masked a potential beneficial effect of nonfried fish on asthma. The types of fish meal are important with respect to the investigation of contaminants in fish (50). Mercury has been found to be a major factor in allergic/immune reactive conditions, including asthma (45, 46). PCBs have been associated with an increased risk of asthma in Flemish children (47), although the health effects of chronic low-level PCB exposure were less well studied. In addition, intervention studies found an increase in airway responsiveness when dietary sodium was increased (48, 49). Thus, the associations of fish and LCω3PUFAs with health endpoints may not be necessarily consistent.

Our study had many strengths that support the validity of our findings. The main strengths of this study were the prospective design, a relatively large sample size and diverse population, and the high follow-up rates, which reduced the concern that the results were affected by differential follow-up rates. In addition, we used a validated FFQ (19) and cumulative average dietary consumption information from 3 time points that should reduce random measurement error and provide a better estimate of habitual intake than a single estimate (26).

A few limitations in this study should be considered. First, our study was observational by design; thus, we could not rule out residual confounding, nor could we draw conclusive statements about the preventive effect of LCω3PUFA consumption on the development of asthma. Although we controlled for many potential confounders in the analyses, the possibility of unmeasured confounders cannot be excluded. Second, information on fish-oil supplement use is not available in CARDIA. However, the CARDIA baseline diet was assessed in 1985–1986, when few people were using fish-oil supplements. When we used only the baseline diet in the analysis, the results remained. Thus, our results should not be substantially biased by fish-oil supplement use. Third, the definition of asthma was mainly based on a self-reported doctor diagnosis of asthma and could not distinguish atopic asthma from other types,

which may have resulted in some misclassification of asthma status and time of onset; however, it is unlikely that a misclassification other than a random or nondifferential one occurred. Also, when we further adjusted atopic status indicated by hay fever, the results remained. In addition, the measurement error of dietary data are inevitable, but the measurements of LCω3PUFA intake and fish consumption should enable us to rank the participants and estimate the RRs. Also, the measurement error has been largely reduced by using cumulative average intakes.

In conclusion, the results of this prospective study provide evidence that LCω3PUFA intake is inversely associated with incident asthma. Further studies, particularly randomized placebo-controlled clinical trials are needed to establish causal inference.

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Footnotes

[4]Abbreviations used: AA, arachidonic acid; CARDI, Coronary Artery Risk Development in Young Adults; FFQ, food-frequency questionnaire; LCω3PUFA, long-chain ω-3 PUFA; PCB, polychlorinated biphenyl.

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