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Long-chain omega-3 fatty acids and headache in the U.S. population

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ABSTRACT

The objective of this study was to assess whether dietary intake of long-chain omega-3 polyunsaturated fatty acids (PUFAs) is associated with lower prevalence of headache in the U.S. population. This cross-sectional study used data for a nationally representative sample of 12,317 men and women aged ≥ 20 years participating in the National Health and Nutrition Examination Surveys of 1999–2004. Interviewers recorded self-report of severe headache or migraine in the past three months. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were quantified from 24-hour dietary recall using the U.S. Department of Agriculture National Nutrient Database. Serum concentration of C-reactive protein, a marker of inflammation and potential mediator of PUFA's analgesic properties, was quantified by latex-enhanced nephelometry. Multivariable generalized linear models estimated prevalence ratios (PR) with 95% confidence limits (CL) for severe headache or migraine adjusting for NHANES cycle, sociodemographic characteristics, body mass index and total energy intake. The unadjusted prevalence of severe headache or migraine was 22.0% (females 28.2%, males 15.5%). In multivariable analysis, greater intake of omega-3 PUFAs was associated with lower prevalence of severe headache or migraine: PR 0.94 (95% CL: 0.88, 0.99, p = 0.035) per log unit increase in EPA, and PR 0.94 (95% CL: 0.90, 0.99, p = 0.023) per log unit increase in DHA. The strength of association was greater for non-Mexican Hispanics than for other racial/ethnic groups but was not attenuated after adjustment for C-reactive protein. In conclusion, higher dietary intakes of EPA and DHA were associated with lower prevalence of headache supporting the hypothesis that omega-3 PUFAs may prevent or reduce headache.

1. Introduction

Severe headache and migraine are common neurological disorders, strongly patterned by age and gender, and profoundly disabling. From among 328 disorders assessed in the 2016 Global Burden of Diseases Study, tension-type headache ranked third for prevalence, while migraine was the second leading cause of disability [1].

The discovery that lipid derivatives of long chain omega-3 polyunsaturated fatty acids (PUFAs) have analgesic properties, in addition to their pro-resolving properties, raises the exciting possibility of a therapeutic benefit to headache and migraine [2]. Eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) are long-chain omega-3 PUFAs, found in oily cold water fish and fish oil supplements, and precursors to specialized pro-resolving lipid mediators known as resolvins, protectins and maresins. These lipid mediators have immunomodulatory activities and regulatory roles in biochemical and metabolic processes for the resolution of inflammation [3,4]. Among their specific activities, they reduce adhesion molecule expression [5], inhibit leukocyte chemotaxis [6], dampen inflammatory cytokine production and signaling [7,8], and regulate inflammatory gene expression [9]. Such effects make omega-3 PUFAs useful adjuncts in management of inflammatory pain disorders such as rheumatoid arthritis [10] and dysmenorrhea [11] and minimize the need for non-steroidal anti-inflammatory drugs [10,11].

Evidence of the analgesic effect of omega-s or their downstream metabolites comes primarily from rodent models. These studies demonstrate that omega-3 PUFAs suppress sensitivity to thermal, [12–14] chemical [12], and mechanical [15] pain stimuli. In particular, resolvin D1 inhibits transient receptor potential channels that detect noxious stimuli and activate nociceptors [16].

The strongest study design to find an analgesic effect of omega-3 PUFAs in humans was a randomized controlled trial [17] (RCT) in

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Table 1
Associations between population **c**haracteristics and prevalence (s.e.) of severe headache or migraine, and mean (s.e.) daily dietary intake of EPA and DHA, NHANES 1999–2004 (N = 12,317 aged ≥ 20 years).

Characteristics	N (weighted percent)	Headache prevalence% (s.e.)	p	Mean EPA mg/day (s.e.)	Mean DHA mg/day (s.e.)
Total	12,317 (100.0)	22.0 (0.8)		40.8 (2.2)	77.2 (2.8)
Cycle					
1999–2000	3,923 (32.4)	20.7 (1.6)	0.474	38.9 (3.2)	77.9 (3.8)
2001–2002	4,234 (32.8)	23.2 (1.4)		42.3 (4.4)	74.7 (4.5)
2003–2004	4,160 (34.8)	22.1 (1.3)		41.1 (3.7)	79.1 (6.0)
Sex					
Men	6,177 (49.2)	15.5 (0.7)	<0.001	46.8 (2.7)	89.7 (4.0)
Women	6,140 (50.9)	28.2 (1.1)		35.0 (2.9)	65.1 (3.0)
Age, *y*					
20–24	1,053 (10.5)	23.6 (2.5)	<0.001	25.0 (2.8)	55.1 (4.8)
25–34	1,912 (18.9)	26.7 (1.5)		39.5 (4.4)	78.1 (6.1)
35–44	2,162 (21.4)	28.0 (1.6)		45.7 (6.6)	81.5 (6.2)
45–54	2,033 (19.9)	24.2 (1.3)		43.8 (4.8)	83.9 (7.5)
55–64	1,790 (13.0)	16.5 (1.4)		42.7 (5.3)	80.3 (7.5)
64–74	1,793 (9.9)	10.8 (0.8)		42.6 (5.3)	77.6 (7.2)
≥75	1,574 (6.6)	7.3 (0.9)		37.8 (4.8)	69.5 (7.1)
Race/ethnicity					
Mexican American	2,762 (7.0)	24.1 (1.3)	0.012	29.9 (2.7)	63.7 (2.9)
Other Hispanic	549 (5.3)	29.2 (3.3)		31.0 (5.0)	62.6 (8.2)
Non-Hispanic white	6,229 (72.5)	21.0 (1.0)		38.0 (2.8)	72.1 (3.4)
Non-Hispanic black	2,372 (10.8)	23.6 (1.0)		53.7 (3.7)	100.5 (5.9)
Other/Multiple	405 (4.5)	21.9 (2.6)		82.5 (13.3)	141.4 (19.8)
Educational attainment					
High school	6,942 (46.2)	24.9 (1.1)	<0.001	34.3 (1.6)	69.0 (3.3)
More than high school	5,375 (53.8)	19.4 (1.0)		46.3 (3.6)	84.3 (3.9)
Body mass index, *kg/m²*					
<25.0	3,940 (34.7)	21.5 (1.0)	<0.001	42.1 (4.5)	76.8 (4.4)
25.0 to 29.9	4,430 (34.2)	19.7 (1.0)		43.2 (3.3)	82.3 (5.1)
≥30.0	3,947 (31.1)	25.0 (1.2)		36.7 (2.5)	72.1 (3.7)
Total energy intake, *kcal/d*					
≤ 1669.32	4,713 (33.4)	23.3 (1.1)	0.059	27.7 (1.8)	53.2 (2.6)
1669.43 to 2442.42	4,013 (33.4)	22.4 (1.1)		37.3 (2.8)	74.2 (4.0)
≥2442.65	3,591 (33.3)	20.2 (1.1)		57.4 (5.1)	104.3 (5.6)

standard error (s.e.), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), milligrams/day (mg/day).

Table 2
Unadjusted and adjusted associations of eicosapentaenoic acid and docosahexaenoic acid with headache or migraine, NHANES 1999–2004 (N = 12,317 aged ≥ 20 years).

	Unadjusted prevalence ratio (95% CL)[b]	P-value	Adjusted[a] prevalence ratio (95% CL)[b]	P-value
Eicosapentaenoic acid[c]	0.92 (0.87, 0.98)	0.006	0.94 (0.88, 0.99)	0.035
Docosahexaenoic acid[c]	0.93 (0.88, 0.97)	0.003	0.94 (0.90, 0.99)	0.023

[a] Adjusted for NHANES cycle, sex, age group, race/ethnicity, educational attainment, body mass index (continuous), total energy intake (continuous)
[b] Confidence limits (CL)
[c] Eicosapentaenoic acid and docosahexaenoic acid are log (base 10) transformed

which two analgesic food-based interventions were compared in adults with chronic daily headache. One diet was high in omega-3 plus low in omega-6 PUFAs, while the other reduced omega-6 PUFAs without altering omega-3 intake. After 12 weeks, subjects in the high omega-3 plus low omega-6 intervention had significantly greater reductions in headache pain frequency and intensity, than the low omega-6 intervention. Subjects' use of pain-relieving medications decreased from baseline levels by 37% and 43% respectively in the high omega-3 plus low omega-6 group [17]. In biochemical analysis of erythrocytes, the two interventions altered concentrations of circulating omega-6 and omega-3 PUFAs in the expected directions [17]. During the 12-week period, plasma concentrations of antinociceptive endocannabinoids derived from omega-3 PUFAs increased while concentrations of pronociceptive endocannabinoids derived from omega-6 PUFAs decreased [18].

By design, this RCT applied strict dietary controls. Two meals and two snacks provided daily were supplemented by intensive counselling by a registered dietitian at 2-week intervals. [17] While rigorously conducted, this RCT was small (n = 67) and its findings have yet to be replicated. Furthermore, it is unknown whether the levels of omega-3 PUFAs consumed in the population at large are associated with headache in the absence of a strict dietary intervention and counselling. Hence, the purpose of this study is to investigate the association between dietary intake of long-chain omega-3 PUFAs and headache in a nationally representative sample of U.S. adults. We also investigated whether the association was attenuated after adjustment for serum C-reactive protein, a marker of inflammation that we hypothesized might be a mediator of PUFA's analgesic properties.

2. Methods and materials

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines in reporting these findings.

2.1. Study design and participants

The cross-sectional National Health and Nutrition Examination Survey (NHANES) selects a nationally representative sample of non-institutionalized U.S. civilians using a complex, stratified, multistage probability cluster design. Following an in-home interview, participants attend a mobile examination center (MEC) for biospecimen collection and additional interviews including a 24-h dietary recall interview. The present analysis used 1999–2004 NHANES data, because the headache question was limited to these cycles. Study protocols for NHANES were