Original Article

Associations between eicosapentaenoic acid and docosahexaenoic acid consumption and inflammatory bowel disease in adults: The National Health and Nutrition Examination Survey (NHANES) 2009–2010

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Background and Objectives: Current evidence on the associations of dietary eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) consumption with the risk of inflammatory bowel disease (IBD) is inconsistent. This study aimed to investigate the relationship between dietary EPA and DHA consumption with the incidence of IBD in a population of the United States, which potentially provides insights for global nutritional prevention and control strategies for IBD. **Methods and Study Design:** Data were sourced from the National Health and Nutrition Examination Survey for the years 2009-2010. EPA and DHA consumption was measured using twice 24-h dietary recall questionnaires. In the arthritis questionnaire, the incidence of IBD was inquired via a sub-analysis for arthropathy. To assess the relationship between dietary EPA and DHA consumption with the incidence of IBD, binary logistic regression and limited cubic spline models were used. **Results:** A total of 4,242 individuals aged 20 years and older participated in this survey. IBD was diagnosed in 52 individuals, representing a prevalence of 1.23%. The 95% confidence interval for crude odds ratios (ORs) of IBD in quartiles 2 and 3 of dietary EPA consumption was 0.14 (0.04-0.55) (p<0.05) and 0.36 (0.18-0.73) (p<0.05) when compared to quartile 1, respectively. The 95% confidence interval for crude ORs of IBD in quartile 4 of dietary DHA consumption was 0.09(0.02-0.35) (p<0.05) when compared to quartile 1. **Conclusions:** For the National Health and Nutrition Examination Survey in 2009-2010, increased dietary EPA and DHA consumption may be related to a decreased risk of IBD in Americans aged 20 and above.

Key Words: inflammatory bowel disease, eicosapentaenoic acid, docosahexaenoic acid, dose-response, National Health and Nutrition Examination Survey (NHANES)

INTRODUCTION

Inflammatory bowel disease (IBD) is a term used to describe chronic gastrointestinal disorders with unknown causes, which increase the risk of bowel failure and may even lead to bowel cancer.[1] In North America, the Pacific region, and several European countries, the incidence of IBD surpassed 0.3%, and is also increasing in Asian countries. The incidence of ulcerative colitis is higher in North America than in the Asia-Pacific region.[2-5] IBD aetiology appears to be complicated by interactions between the immune system, the environment, and some host genetic risk factors.[6] At present in addition to traditional treatments, other treatments for IBD include anti-TNF-α monoclonal antibody therapy,[7] stem cell therapy,[8] and targeted therapies.[9] However, their therapeutic effect is still limited.

Nutrition and the environment can influence genetic susceptibility. The concept of gene-nutrition-based therapy for IBD treatment and prevention has also emerged.[10,11] Omega-3 polyunsaturated fatty acids (n-3 PUFAs) have anti-inflammatory features and play a crucial role in the control of inflammation, making them medicinal candidates in chronic inflammatory diseases.[12,13] Diets high in two kinds of N-3 PUFAs (eicosatetraenoic acid (EPA) and docosahexaenoic acid (DHA)) have been shown to improve chronic illnesses in animal models.[14-16]

The National Health and Nutrition Examination Survey (NHANES) was a two-year cross-sectional survey study conducted by the Centres for Disease Control and Prevention (CDC) of America to evaluate nutritional and health conditions of this population. Participants were first interviewed at home before attending a mobile examination centre to finish their health examination.[17]

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Although their anti-inflammatory properties have been confirmed in experimental studies, the relationship between EPA and DHA intake and the development of IBD in epidemiological studies has remained controversial and even yielded opposite results.[18-21] In addition, few previous studies have analysed age stratification. Therefore, this research investigated the dietary intake of EPA and DHA among Americans aged 20 years and older within the NHANES dataset to explore their association with the incidence of IBD. This represents a pioneering effort to examine this specific correlation using the NHANES cohort. In addition, our study is the first to investigate the effects of n-3 PUFAs on the incidence of IBD by age stratification.

METHODS

Data gathering

The NHANES database is a publicly available set of data used worldwide.[22] Before completing the questionnaire and investigation phases, all respondents provided informed consent. Ethical approval was not required for this study as we utilized a public database.

The selection criteria used for this study are shown in Figure 1. Between 2009 and 2010, a total of 10,537 individuals participated in the NHANES, however this study only focused on 6,218 individuals who were aged 20 years and older. Among these, excluded cases included participants who did not have an IBD diagnosis (n = 1,861), had insufficient or inconsistent day-one information upon recruitment (n = 45), had colorectal tumours (n = 12), or were pregnant (n = 58 women). Excessive overall energy consumption of less than 500 or over 5000 kcal/day for women (n = 0) and less than 500 kcal/day or over 800 kcal/day for men (n = 0) was also excluded. After these exclusions, a total of 4,242 individuals aged 20 years and older were included in the subsequent analysis.

Definition of presence and absence of IBD

The existence of ulcerative colitis (UC) or Crohn's disease (CD) was specifically queried in the “arthritis questionnaire” in the 2009-2010 NHANES. Consistent with previous studies,[23,24] participants were asked if they were diagnosed with IBD.

Dietary consumption assessment

Daily dietary EPA and DHA consumption were assessed using a multi-pathway approach during a 24-h dietary recall. This is an interviewee-driven method that collects a precise and comprehensive list of all food and beverages consumed in a 24-h period. Although this method is dependent on the memory ability of the respondents, it can reflect the recent dietary situation of the respondents relatively accurately and comprehensively when compared with other methods (such as Food Frequency Questionnaire, etc.); it is therefore widely used in some studies.[25-28] All participants were required to take part in twice 24-h comprehensive nutrition recall interviews. The total amount of EPA and DHA was calculated by averaging the total amount of EPA and DHA in twice 24-h dietary review surveys. If there was only one 24-h dietary review record, then it was taken to represent the respondent's total daily EPA and DHA.[29]

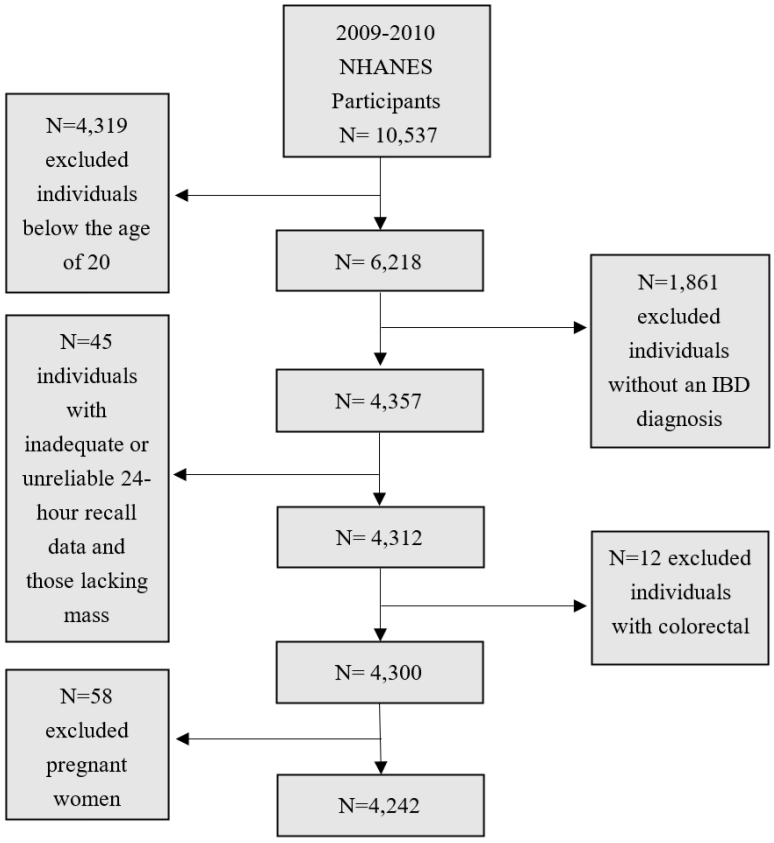

Figure 1. Chart depicting the selection criteria used for this study

Covariates

Age, gender, ethnic background, degree of education, family status, BMI, physical activities,[30] smoking, drinking, high blood pressure, and Type 2 diabetes mellitus (T2DM) were investigated as possible confounding variables.

Statistical analysis

Stata 15.0 software (Stata Corporation, College Station, TX) was used for all statistical analyses. The Kolmogorov-Smirnov normality tests were used to determine the normality of continuous variables, and normally distributed variables were shown as mean plus standard deviations, while non-normally distributed variables were shown as median plus standard deviation (interquartile range). If variables were normally distributed, Student's t-tests were performed to compare mean levels between IBD and non-IBD populations; if not, Mann-Whitney U tests were performed. Chi-square tests were used to compare percentages of categorical variables between IBD and non-IBD populations. Statistically significant differences were defined as $p < 0.05$.

RESULTS

The characteristics of the cohort were displayed in Table 1, which included individuals with and without IBD. This study contained a total of 4,242 participants. Among the participants, 52 individuals were diagnosed with IBD, indicating a prevalence of 1.23%. IBD patients were found to be older (51.5 years vs. 44.1 years) (p<0.001), had higher smoking rates (p = 0.0428), and higher high blood pressure rates (p<0.001). Other measures, such as gender, race, BMI, alcohol consumption, physical work, and T2DM, revealed no significant differences. The average consumption of dietary EPA and DHA was reported to be higher in the non-IBD cohort than in the IBD cohort, as shown in Table 1.

Table 2 depicted the association between dietary EPA and DHA consumption and the incidence of IBD. The 95% confidence interval for crude ORs of IBD in quartiles 2 and 3 of dietary EPA consumption was 0.14 (0.04-0.55) (p<0.05) and 0.36 (0.18-0.73) (p<0.05) when compared to quartile 1, respectively. The OR comparing individuals with the highest dietary intake of EPA with those with the lowest intake was found to be 0.45 (0.18-1.12) (p > 0.05). After age and gender adjustments (model 1), dietary EPA consumption remained positively correlated

Table 1. Participant characteristics in the NHANES based on the presence of IBD, NHANES 2009-2010 (N =4,242)[†‡]

Item	Presence of IBD	Absence of IBD	*p*-value
Participants, n (%)	52	4,190	
Age (year)	51.5 ± 13.2	44.1 ± 14.1	<0.001*
Gender (%)			0.0844
Male	20 (38.5)	2,116 (50.5)	
Female	32 (51.5)	2,074 (49.5)	
Race (%)			0.2610
Mexican American	15 (28.8)	834 (19.9)	
Other Hispanic	8 (15.4)	473 (11.3)	
Non-Hispanic White	22 (42.3)	1,896 (45.3)	
Non-Hispanic Black	6 (11.5)	775 (18.5)	
Other race	1 (1.9)	212 (5.1)	
BMI (kg/m^2)	2.2 ± 0.7	2.1 ± 0.8	0.7089
Smoking over 100 cigarettes during lifespan			0.0428*
Yes	31 (59.6)	1,908 (45.5)	
No	21 (40.4)	2,282 (54.5)	
Consuming over 12 alcoholic drinks per year			0.7883
Yes	39 (75.0)	3,209 (76.6)	
No	13 (25.0)	981 (23.4)	
Work activity (%)			0.9098
Vigorous activity	10 (19.2)	859 (20.5)	
Moderate Activity	13 (25.0)	945 (22.6)	
Other	29 (55.8)	2,386 (56.9)	
Recreation activity (%)			0.1359
Vigorous activity	6 (11.5)	919 (21.9)	
Moderate activity	13 (25.0)	1,110 (26.5)	
Other	33 (63.5)	2,161 (51.6)	
Diabetes (%)			0.0702
Yes	9 (17.3)	410 (9.8)	
No	42 (80.8)	3,702 (88.4)	
Hypertension (%)			<0.001*
Yes	31 (59.6)	1,191 (28.4)	
No	21 (40.4)	2,993 (71.4)	
EPA (g per day)	0.024 ± 0.056	0.035 ± 0.082	0.3594
DHA (g per day)	0.047 ± 0.077	0.073 ± 0.136	0.1755

Mean ± SD is shown for continuous variables and numbers (percentage) is shown for categorical variables.
[†]Chi-square tests were used to compare the percentage of participants who had (inflammatory bowel disease) IBD and those who did not.
[‡]Mann-Whitney U tests were used to compare the mean values of participants who had (inflammatory bowel disease) IBD and those who did not.

Table 2. Weighted ORs (95% confidence intervals) for IBD prevalence across quartiles of dietary EPA and DHA consumption, NHANES 2009-2010 (N =4,242)

	Case/Participants	Crude	Model 1†	Model 2‡
EPA (g/day)				
<0.0045	24/1115	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
0.0045 to<0.01	11/1100	0.14 (0.04-0.55) *	0.16 (0.04-0.60) *	0.17 (0.41-0.70) *
0.01 to<0.0225	7/972	0.36 (0.18-0.73) *	0.42 (0.22-0.80) *	0.52 (0.27-0.99) *
≥0.0225	10/1055	0.45 (0.18-1.12)	0.50 (0.21-1.19)	0.53 (0.25-1.14)
DHA (g/day)				
<0.009	17/1066	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
0.009 to<0.0315	13/1059	0.68 (0.23-1.96)	0.67 (0.23-1.92)	0.75 (0.25-2.22)
0.0315 to<0.073	15/1057	1.14 (0.44-2.94)	1.18 (0.47-3.02)	1.43 (0.57-3.56)
≥0.073	7/1060	0.09 (0.02-0.35) *	0.09 (0.02-0.33) *	0.10 (0.02-0.46) *

†Model 1 was adjusted for age and gender.
‡Model 2 was adjusted for age, gender, race, BMI, work activity, recreational activity, smoking, drinking, hypertension, and diabetes.
*$p < 0.05$.

with a lower incidence of IBD in quartiles 2 and 3 of dietary EPA consumption. Results were similar after further adjustment of all confounding factors (model 2).

The 95% confidence interval for crude ORs of IBD in quartile 4 for dietary DHA consumption was 0.09 (0.02-0.35) (p<0.05) when compared to quartile 1. After age and gender adjustments (model 1), dietary DHA consumption was still inversely associated with a lower occurrence of IBD. Similar findings were found after further adjustment of all confounding factors, as was seen in model 2. When compared to the quartile 1 group, the multivariable-adjusted ORs between the incidence of IBD and dietary DHA consumption were 0.09 (0.02-0.33), 0.10 (0.02-0.46).

Findings stratified by age were displayed in Table 3. For participants below the age of 60, quartile 2 of dietary EPA consumption was linked to a decreased risk of IBD, of which the ORs were 0.14(0.02–0.80). For participants below the age of 60, quartile 4 of dietary DHA consumption was also linked to a decreased risk of IBD, of which the ORs were 0.12 (0.02–0.72).

Figure 2 depicted the findings of the limited cubic spline dose-response relationship between dietary EPA and DHA consumption and IBD onset. Dietary EPA consumption and the onset of IBD had a nonlinear negative correlation and an L-shaped affiliation.

DISCUSSION

IBD is a global disease with the highest incidence in Europe and Australia. The association between IBD and iron consumption,[24] zinc consumption,[23] copper consumption,[23] fibre consumption,[31] dietary polyphenols,[32] dairy products, dietary calcium,[33] and body mass index[34] have been investigated in previous studies using databases from Europe and America. In this study, a cross-sectional evaluation of the 2-year NHANES survey (2009-2010) was conducted to determine the relationship between EPA and DHA consumption and the onset of IBD in American adults. The main finding of this study was that dietary EPA and DHA consumption is linked to the development of IBD in American adults. To the best of our knowledge, this is the first observational study of dietary EPA and DHA consumption and IBD using the NHANES database. The main finding of our study was that in dose-response correlations, L-shaped associations between EPA and DHA consumption and IBD risk were evident.

The anti-inflammatory effects of n-3 PUFAs have been long discussed and remain controversial. Several studies have suggested a positive effect of n-3 unsaturated fatty acids on the prevention and treatment of IBD. Salomon et al. conducted clinical trials using n-3 unsaturated fatty acids (2.7 g EPA in three divided doses daily for 8 weeks) for the treatment of UC patients in the early 1990s. Moderate to significant improvement was seen in 7 patients (out of 10).[18] Dichi et al. found that UC patients who consumed fish oil (3.2g EPA per day + 2.16g DHA per day) for 2 months had significantly lower colonoscopic scores.[19] However, these previous studies were single-center, small-sample intervention studies. On the other hand, there were very contradicting results in other studies. In a clinical trial from America including 25,871 participants, fish oil containing EPA and DHA did not significantly reduce the incidence of complex outcomes consisting of IBD and all other autoimmune diseases.[20] In a multicentre case-control study of Asian populations, the intake of DHA (0.21 g/4184 kJ vs 0.15 g/4184 kJ) and EPA (0.12 g/4184 kJ vs 0.09 g/4184 kJ) in UC patients was significantly higher than that in control patients.[21] Therefore, the effects of EPA and DHA on IBD still need to be verified with larger sample data.

Our study was based on an analysis of a database with a large and reliable data covering 4,242 Americans, which leads to us paying more attention to the role of EPA and DHA intake in the prevention of chronic inflammation disease. This is the core innovation of this study. In addition, our study is the first to investigate the effects of n-3 PUFAs on the occurrence of IBD by age stratification. Our study suggested that intake of 0.0045-0.01g of EPA and ≥0.073g of DHA per day in diet are the most effective intakes for preventing the development of IBD.

The mechanisms of the relationship between dietary EPA and DHA intake and the incidence of IBD remain unclear, many scholars consider it related to gut microbiota,[35,36] the metabolism of EPA and DHA,[37] and anti-angiogenic effects.[38] A recent meta-analysis confirmed that n-3 unsaturated fatty acids, such as DHA and EPA, can alleviate the heavy burden caused by high levels of inflammatory factors and overactivation of the immune

Table 3. Weighted ORs (95% confidence intervals) for IBD prevalence across quartiles of dietary EPA and DHA consumption stratified by age, NHANES 2009-2010 (N =4242)

	20 < Age < 60 Years		Age ≥ 60 Years	
	Case/Participants	Model 2†‡	Case/Participants	Model 2†‡
EPA (g/day)				
< 0.0045	16/854	1.00 (Ref.)	8/261	1.00 (Ref.)
0.0045 to < 0.01	7/888	0.14 (0.02-0.80) *	4/212	0.41 (0.04-4.13)
0.01 to < 0.0225	5/828	0.34 (0.11-1.07)	2/144	2.36 (0.21-26.44)
≥0.0225	5/842	0.29 (0.06-1.43)	5/213	2.61 (0.37-18.33)
DHA (g/day)				
< 0.009	11/862	1.00 (Ref.)	6/204	1.00 (Ref.)
0.009 to < 0.0315	10/853	0.83 (0.24-2.85)	3/206	0.33 (0.04-2.83)
0.0315 to < 0.073	8/865	1.04 (0.25-4.35)	7/192	3.62 (0.69-19.03)
≥0.073	4/832	0.12 (0.02-0.72) *	3/228	0.10 (0.01-1.35)

†Calculated using binary logistic regression.
‡Model 2 was adjusted for age, gender, race, (Body Mass Index) BMI, work activity, recreational activity, smoking, drinking, hypertension, and diabetes.
*$p < 0.05$.

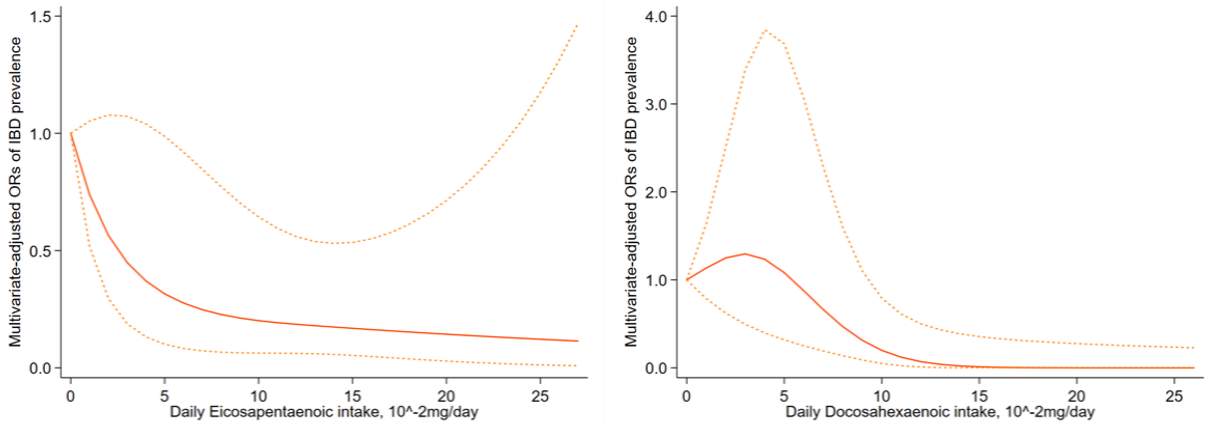

Figure 2. Dose-response relationship between EPA and DHA consumptions and the likelihood of IBD.
This association adjusted for age, gender, race, BMI, work activity, recreational activity, smoking, drinking, hypertension, and diabetes.
The bolded line and discontinued-line refer to the assessed ORs and their 95% certainty intervals (ORs, odds ratios)

system.[39] Therefore, in the prevention and treatment of IBD, we should pay more attention to the adequate intake and supplementation of EPA and DHA in the diet.

This study was the first to examine the relationship between EPA and DHA consumption and IBD in adults using the NHANES database. Nonetheless, it had several limitations. Firstly, for the 24-h recall dietary survey method, although many previous studies[25-28] have confirmed its accuracy, it does not really reflect the accurate content of circulating n-3 unsaturated fatty acids. So, it may underestimate the prevalence of IBD and it was difficult to determine the exact link between EPA and DHA concentration and the occurrence of IBD in a cross-sectional study. At the same time, the accuracy of the results of dietary survey using this method depended on the accuracy of the memory of the respondents. Secondly, while our analysis took several confounding factors into consideration, possible bias from unmeasured confounding elements that were beyond the scope of our study may exist. Thirdly, the NHANES determined the presence of IBD based on a questionnaire, and did not confirm this diagnosis with an endoscopic procedure, thereby likely leading to some misreported data. In the future, endoscopic pathology should be used as a diagnostic method for IBD, and large-scale cohort studies should be conducted to further verify the results of the association between dietary n-3 unsaturated fatty acids and the incidence of IBD. Finally, as the NHANES database was used in this study, results can only reflect the population in and around the United States. In the future, we need to conduct more large sample surveys in the Asian population.

Conclusions

In summary, this study showed that increased dietary EPA and DHA consumption may be related to a decreased risk of IBD in those aged 20 and older in the United States. The associations we investigated in this study were biologically plausible, however the need for validation through additional large-scale, prospective studies remains, to substantiate these preliminary insights with greater certainty.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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