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Omega 3 fatty acids and periodontitis in U.S. adults

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Introduction

Periodontitis is a common, chronic inflammatory disease caused by the accumulation of bacterial matrix at the gum line. It is characterized by gum tissue separation from the tooth, which forms a periodontal pocket and can lead to bone and tooth loss. Traditional therapies for periodontitis focus on targeting the bacterial infection, which may be the initiating event responsible for the ensuing inflammation and tissue destruction. More recent therapeutic strategies have targeted the host response to the bacterial infection, which may play a more crucial role in the pathogenesis of periodontitis and its associated systemic effects. In animal models, induced periodontitis induces fatty plaque build up in blood vessels, (1) which appears to be due to host inflammatory responses to the bacteria, rather than the bacteria.(2)

Polyunsaturated fatty acids (PUFAs) are fatty acids with more than 1 carbon-carbon double bond, including omega 3 (n-3), omega 6 (n-6) and omega 9 (n-9) fatty acids. N-3s from marine sources, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and vegetable sources, such as linolenic acid (LNA), which includes alpha-linolenic acid (ALA) and a related n-6 fatty acid, gamma-linolenic acid (GLA), have all been shown to have anti-inflammatory properties.(3-5) Indeed, topical application of bioactive products derived from

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Roger B. Davis provided statistical and programing expertise.

Kenneth J. Mukamal provided guidance on the primary analysis plan, data interpretation and preparation of the manuscript.

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n-3 fatty acids (including DHA and EPA) confer dramatic protection against inflammation-induced tissue and bone loss associated with periodontitis in experimental models.(6)

In humans, one trial randomized 30 subjects with periodontitis to receive 12 weeks systemic therapy of EPA, GLA, both EPA and GLA, or olive oil placebo.(7) The study showed a significant decrease in probing depth in patients receiving GLA alone and a trend towards decreased probing depth in subjects receiving EPA alone. However, it is unknown if LNA or DHA intake is also inversely associated with periodontitis in humans. Moreover, there are no large population studies of periodontitis and the PUFAs that are thought to have anti-inflammatory properties, such as DHA, EPA and LNA. This study aims to examine the association between these n-3s and prevalence of periodontitis in a nationally representative sample of adults.

Methods

Study Sample

This cross-sectional study used data from 9,182 adults aged 20 years and older who participated in the National Health and Nutrition Examination Survey (NHANES) between 1999 and 2004. The survey provides information on the health and nutritional status of the United States' civilian, non-institutionalized population by using a complex, stratified, multistage, probability-sampling design.(8-10) The NHANES includes both an initial in-home interview followed by an examination and personal interview at a mobile examination center for those who are eligible. A total of 31,126 individuals participated in the in-home interview. For this study, we excluded subjects less than 20 years of age (n=15,794), lacking periodontal exams or edentulous (n=4118), lacking physical exams (n=1119), having missing data from covariates of interest (n=426), not meeting minimal criteria for reliability of the dietary recall (n=314), lacking interpretable periodontal exams (n=98) or having incomplete periodontal exams (n=75), leaving 9182 for analysis.

Periodontitis

Periodontitis was assessed during the periodontal exam by dentists trained in the survey examination protocol.(11-13) Briefly, periodontal examinations during the NHANES 1999–2000 were conducted in the midbuccal and mesiobuccal sites for each tooth in two randomly chosen quadrants, one maxillary and one mandibular, on the assumption that conditions in these two quadrants represent the mouth. Third molars were excluded because of their frequent extraction in young adulthood, so a maximum of 14 teeth and 28 sites per individual were examined. For the NHANES 2001–2002 and the NHANES 2003–2004, the periodontal examination was conducted in three sites, midbuccal, mesiobuccal and distobuccal for each tooth, although we only used the midbuccal and mesiobuccal sites to be consistent with the 1999-2000 examination. Periodontal measurements were rounded to the lowest whole millimeter and were made with a color-banded periodontal probe graduated at 2, 4, 6, 8, 10, and 12 millimeters. Detailed information on the NHANES dental examinations for the survey periods is available elsewhere.(11-13)

Previous studies have used several combinations of clinical attachment loss and pocket depth to establish periodontitis case definitions.(14-20) We defined periodontitis as ≥4 mm pocket depth and ≥3 mm attachment loss in any mid-facial or mesial tooth, as in previous studies.(14, 16, 20) For consistency across study cohorts, we used the two sites measured in NHANES 1999–2000, NHANES 2001–2002, and NHANES 2003–2004 to define periodontitis. We also validated the diagnosis by examining levels of circulating C-reactive protein (CRP) according to periodontitis status since elevated levels of CRP are known to be associated with periodontitis.(21, 22)

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In post-hoc analyses, we evaluated prevalence of moderate periodontitis, defined as 4-5 mm pocket depth and 3-4 mm attachment loss; and severe periodontitis, defined as >5 mm pocket depth and >4 mm attachment loss in any mid-facial or mesial tooth.

Dietary Fatty acids

Fatty acid intake in grams per day was assessed by a 24-hour dietary recall. From 1999 to 2001, dietary intake data were collected using the NHANES computer-assisted dietary interview system (CADI). The CADI is a multiple pass recall method which provides instructions to interviewers for recording information about foods. Additional information about the CADI system is provided in the NHANES 1999-2000 Dietary Interviewers Procedures manual.(8) From 2002-2004, data were collected using the USDA's dietary data collection instrument, the Automated Multiple Pass method,(9, 10) which was found to provide valid measures of group total energy and PUFA intake in twenty highly motivated premenopausal women using doubly labeled water total energy expenditure, the Block food-frequency questionnaire, the National Cancer Institute's Diet History Questionnaire and 14-day dietary record.(23) The variable for linolenic acid (18:3 octadecatrienoic acid, LNA) includes both ALA and GLA, which were not assessed separately in NHANES.

Supplemental Fatty acids

Supplemental fatty acid intake was assessed by self-reported dietary supplement use. The interviewer entered the supplement's name and manufacturer into a computer database, which contained information on individual ingredients. Trained nutritionists at the National Center for Health Statistics matched the product names to a known product when possible.

Other Covariates

We analyzed covariates that have been found to be related to periodontitis in previous studies, including age, race-ethnicity, socio-economic status, physical activity, smoking status, diabetes mellitus, alcohol intake, body mass index (BMI) and pregnancy status.(14-16, 19, 24) In secondary analyses, we included intake of various dietary factors based upon possible relations with the exposure and outcome.(17, 25) We categorized age as 20-39, 40-59, 60-79 & ≥80 years. We assigned self-reported race-ethnicity as white, black, Mexican-American, and other; the latter included non-Mexican-American Hispanic and multi-racial individuals. Income was categorized as <$20,000, $20,000 - $44,999, $45,000 - $74,999, ≥ $75,000, and unreported. Education was assigned as <high school, high school, and some college education. Country of birth was self-reported and grouped as within the U.S., Mexico, or other locations. Physical activity was assessed by questions regarding vigorous activity (i.e. jogging, sports, etc. causing a substantial increase in heart rate and heavy perspiration) and moderate activity (i.e. brisk walking, dancing, etc. causing moderate increase in heart rate and perspiration) for at least 10 minutes over the past 30 days; we divided physical activity into 3 categories: sedentary (no moderate or vigorous activity), moderate activity alone, and vigorous activity. We categorized smoking as never, former, and current. Participants reported their general health, which we collapsed into excellent/very good, good/fair and poor. Diabetes was defined as a self-report of a diagnosis of diabetes by a doctor or use of medication to lower blood sugar. We categorized alcohol intake into 4 groups: 0 drinks/day, >0-<2 drinks/day, 2-5 drinks/day and >5 drinks/day. BMI was calculated from measured height (m) and weight (kg) and categorized as <25, 25-29.9, and ≥30. Pregnancy status was ascertained from self report or urine pregnancy tests. Dietary vitamin E (mg/d), vitamin C (mg/d), monounsaturated fatty acids (gm/d), saturated fat (gm/d), carbohydrates (gm/d) and linoleic acid (gm/d) were assessed using the same 24-hour dietary recall as described above. We dichotomized aspirin and/or non-steroidal anti-inflammatory drug (NSAID) use as regular (“daily or nearly every day”) and chronic use (“greater than 21 days”) or non-use.

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Statistical Analyses

We calculated normality tests on the outcome variables and found CRP to be right skewed. We transformed the CRP data by taking the natural logarithm. We calculated descriptive statistics on the dietary intake of n-3s and other characteristics. We compared the distributions of these characteristics between patients with and without periodontitis using chi-square tests of independence. We calculated unadjusted odds ratios (ORs) for the relation between tertiles of each dietary n-3 intake (1^{st} tertile referent) and prevalence of periodontitis in contingency tables. For multivariable analyses, we used two sequential logistic regression models. The first model adjusted for total energy intake (kcal/24 hr), age (yr) and sex. The second multivariable model additionally adjusted for general health status, race, smoking, diabetes mellitus, origin of birth, income, education, physical activity, pregnancy, BMI, alcohol intake and intake of the other n-3s of interest.

Sampling weights were used to generate weighted effect estimates, including odds ratios (ORs) and 95% confidence intervals (CIs). We used SAS (v9.1, 2002, Cary, NC) and SAS-callable SUDAAN (v9.0, 2007, Research Triangle Park, NC) to analyze dietary recall data with appropriate 6-year weight assignment from years 1999 to 2004.(8-10)

Given suggestions of an interaction between n-3 and n-6 intakes on inflammatory conditions,(25) we tested for interaction with linoleic acid, a commonly consumed omega-6 fatty acid. We also tested the number of teeth lost and regular, chronic aspirin and/or NSAID use as potential confounders. To adjust further for possible confounding, we constructed a dietary model in which linoleic acid (n-6 fatty acid; gm/d), vitamin C (mg/d) and vitamin E (mg/d), and total carbohydrate intake (gm/d), monounsaturated fats (gm/d) and saturated fats (gm/d) were forced into the model.

Due to the high correlations between EPA and DHA intake,(26) one or the other was used in multivariable models; we also evaluated the association between combined EPA/DHA and periodontitis. To evaluate dose-response relationships, we introduced a centered quadratic term and evaluated intake in finer categories beyond tertiles chosen a priori. We also analyzed the association between tertiles (individually and 1^{st} tertile versus 2^{nd} and 3^{rd} combined) dietary plus supplement n-3 intake (for DHA, EPA and LNA) and prevalence of periodontitis and performed an analysis restricted to non-supplement users. In post-hoc analyses, we evaluated the association of DHA intake with periodontitis severity. To evaluate whether observed associations of n-3 intake and periodontitis had the expected systemic anti-inflammatory effects, we examined the association of n-3s and logCRP in a multivariable linear model. Lastly, we evaluated the association between periodontitis severity and logCRP.

Results

Of the 9182 adults studied, a total of 1024 had periodontitis. The weighted prevalence was 8.2% (95% CI 7.0-9.4). As Table 1 shows, periodontitis was most strongly associated with age, male sex, non-white race, lower socioeconomic status, smoking and lower physical activity. As hypothesized, there was a positive association between presence of periodontitis and CRP (adjusted difference in logCRP 0.17 ±0.05, p=0.002).

The median (interquartile range) dietary PUFA intakes (gm/d) among the 9182 subjects were 1.274 gm/d (0.77-1.98) for linolenic acid, 0.003 gm/d (0.00-0.01) for EPA, and 0.020 gm/d (0.00-0.06) for DHA. Spearman correlations between DHA & EPA, DHA & LNA and EPA & LNA were 0.86, 0.24 and 0.21, respectively (all p-values <0.001).

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We found that higher dietary intake of DHA was associated with a lower odds of periodontitis (Table 2), with no statistical difference in effect between the second and third tertiles (p=0.39). Dietary EPA intake was more modestly associated with lower prevalence of periodontitis. We did not observe a statistically significant association between tertiles of LNA and periodontitis. For both DHA and EPA, there was little change in the ORs with multivariable adjustment. For LNA, a significant association in initial models were chiefly attributable to confounding by education, income and race/ethnicity.

As Figure 1 shows, DHA and EPA were associated with lower logCRP in multivariable linear models. These associations were not significant in tests of heterogeneity but were significant in tests of linear trend. LNA was not associated with CRP levels in initial or multivariable models.

Only 145 subjects reported taking any dietary supplements containing DHA, EPA, ALA or GLA. The median (interquartile range) dietary + supplementary PUFA intakes (gm/d) among the 9182 subjects were 1.276 gm/d (0.77-1.99) for linolenic acid, 0.003 gm/d (0.00-0.02) for EPA, and 0.021 gm/d (0.00-0.06) for DHA. Similar associations in the 2nd and 3rd tertiles of n-3s and periodontitis were found when using dietary plus supplemental DHA, EPA or LNA (ALA plus GLA) intake or in analyses restricting to those who did not use supplements (Table 2). Similar associations in the second and third tertiles of combined EPA/DHA and periodontitis were found in multivariable models [0.74 (0.59-0.93) and 0.78 (0.61-1.02), respectively]. There were no significant interactions between DHA, EPA & LNA intake and linoleic acid (p=0.16, 0.14 & 0.32), respectively] with respect to prevalence of periodontitis.

In additional sensitivity analyses, we found no significant difference in the prevalence of periodontitis between the 2nd and 3rd tertiles of DHA, EPA or LNA (p=0.39, 0.55 and 0.11, respectively). When categorized in quintiles, the inverse association of DHA and periodontitis appeared to be similar across quintiles 2-5 (data not pictured). Tests of quadratic trend for DHA, EPA & LNA and periodontitis were p=0.25, p=0.05 and p=0.17, respectively. Additional adjustment for additional dietary factors slightly strengthened the observed associations (Table 2), chiefly due to partial negative confounding by carbohydrate intake. Adjustment for the number of teeth lost, linoleic acid (n-6 fatty acid) or regular, chronic aspirin and/or NSAID use did not change these associations.

In post-hoc analyses, multivariable associations between tertile of DHA intake and prevalence of severe periodontitis were not significant (p=0.33). Finally, increasing periodontitis severity was associated with increased logCRP (p<0.001): 0.17 (SE=0.06) for moderate periodontitis and 0.26 (SE=0.11) for severe periodontitis.

Discussion

Dietary DHA was associated with a lower prevalence of periodontitis in this nationally representative cross-sectional study of adults. This inverse association was not strengthened with higher intake beyond the second tertile nor with the addition of supplemental DHA, suggesting a threshold effect similar to what has been found in studies of fish intake for sudden cardiac death (27), where no further benefit is achieved beyond modest fish intake. Additionally, dietary EPA had a more modest inverse association with periodontitis, whereas dietary LNA was not associated with periodontitis.

Both n-3s and n-6s have been found to have anti-inflammatory effects through the production of nuclear transcription factors, enzymes and cytokines in human cells.(28) For example, Marion-Letellier et al found that DHA, EPA, GLA and ALA increased levels of peroxisome proliferator-activated receptor-gamma (PPAR-γ) and reduced production of the

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pro-inflammatory cytokines interleukin-8 and interleukin-6. The strongest anti-inflammatory effects tended to coincide with longer, more desaturated n-3 and n-6 carbon chains, effects that are consistent with our primary analysis. In addition, we found DHA and EPA to be associated with lower CRP in linear secondary analyses.

Furthermore, n-3s have been found in animal models of periodontitis to be substrates for neutrophil production of resolvins and protectins, which appear central to the resolution of inflammation.(29, 30) Other animal studies have suggested n-3s may have a protective effect on periodontitis by decreasing the host inflammatory responses to common asaccharolytic microbial pathogens, such as Porphyromonas gingivalis. This decreased inflammatory reaction may result in less tissue breakdown, rendering these microbes unable to sustain their protein-derived energy source.(6, 31)

Our findings expand upon the one human study of PUFA's for the treatment of periodontitis (7) by providing information on DHA intake in a large, generalizable sample of adults. The trial showed a significant decrease in probing depth (change in mean score -0.50) in patients receiving GLA alone and a trend toward decreased probing depth (change in mean score -0.41) in subjects receiving EPA alone. This trend toward reduced periodontitis prevalence with EPA is again consistent with our findings. However, our results also suggest that DHA (doses recommended by the American Heart Association of two servings per week of fatty fish i.e. salmon, mackerel, herring, albacore tuna, etc. would be sufficient) may be as or more potent in influencing periodontitis.

We did not observe a statistically significant decrease in the prevalence of periodontitis with higher LNA (primarily ALA with minimal GLA) intake. However, this lack of association may be due to a relatively low median intake of LNA (1.27 gm/d) compared to the GLA dose (3 gm/d) found to be protective for periodontitis in the previously mentioned trial.(7)

Limitations of our study include the cross-sectional design, which permits the detection of associations but not a temporal relationship nor causation. It is also possible that tooth loss due to periodontitis could have affected diets. However, we excluded edentulous subjects and found no change in associations when adjusting the analyses for tooth loss. Participants of the NHANES who did not have a periodontal exam reported older age, higher income, greater alcohol consumption and less tobacco use. Nonetheless NHANES is likely the most representative study of periodontitis currently conducted. Individuals' dietary intakes vary from day to day, so a 24-hour dietary recall does not necessarily provide an ideal estimate of an individual's long-term average or “usual” daily intake. However, dietary recalls tend to provide highly reliable estimates of recent intake, and the mean of a group's recent intake yields a reasonable estimate of the mean of the group's usual nutrient intake if the dietary recalls are collected on all days of the week and seasons of the year, as is the case with NHANES. As a result, the mean nutrient intakes reported here for groups (i.e. tertiles) approximate their mean usual nutrient intakes. Also, NHANES provides no quantitative assessment of sugar or other refined carbohydrates, which may bias our results toward the null given the negative confounding observed with total carbohydrate intake in the model.

Lastly, ALA and GLA are combined into one variable, linolenic acid, which could represent opposing effects on chronic inflammation since ALA is an n-3, whereas GLA is an n-6 fatty acid.(25) However, the great majority of dietary LNA intake is from ALA.(32, 33) Moreover, as noted above, GLA has been found to have anti-inflammatory effects in vitro (28) and a protective effect on periodontitis in one randomized controlled trial.(7) Moreover, we found no effect modification or confounding by a much more common dietary source of n-6, linoleic acid.

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Strengths of our study include the large and representative sample of civilian, noninstitutionalized US adults. Also, detailed periodontal assessments were conducted with a number of quality control procedures, including calibration of dentists prior to and tri-annually throughout the survey and periodic replications of dental exams by dental experts to monitor consistancy of examinations. Finally, detailed information on potentially confounding covariates was available in a systematic manner.

In summary, we found that n-3 intake, particularly DHA and EPA, are inversely associated with periodontitis in the US population. To date, the treatment of periodontitis has primarily involved mechanical cleaning and local antibiotic application. Thus, a dietary therapy, if effective, might be a less expensive and safer method for the prevention and treatment of periodontitis. Given the evidence indicating a role for n-3s in other chronic inflammatory conditions, (27, 34-38) it is possible that treating periodontitis with n-3s could have the added benefit of preventing other chronic diseases associated with inflammation, including ischemic cerebrovascular disease,(39) as well. Both of these questions warrant further investigation in prospective cohort and randomized clinical trials.

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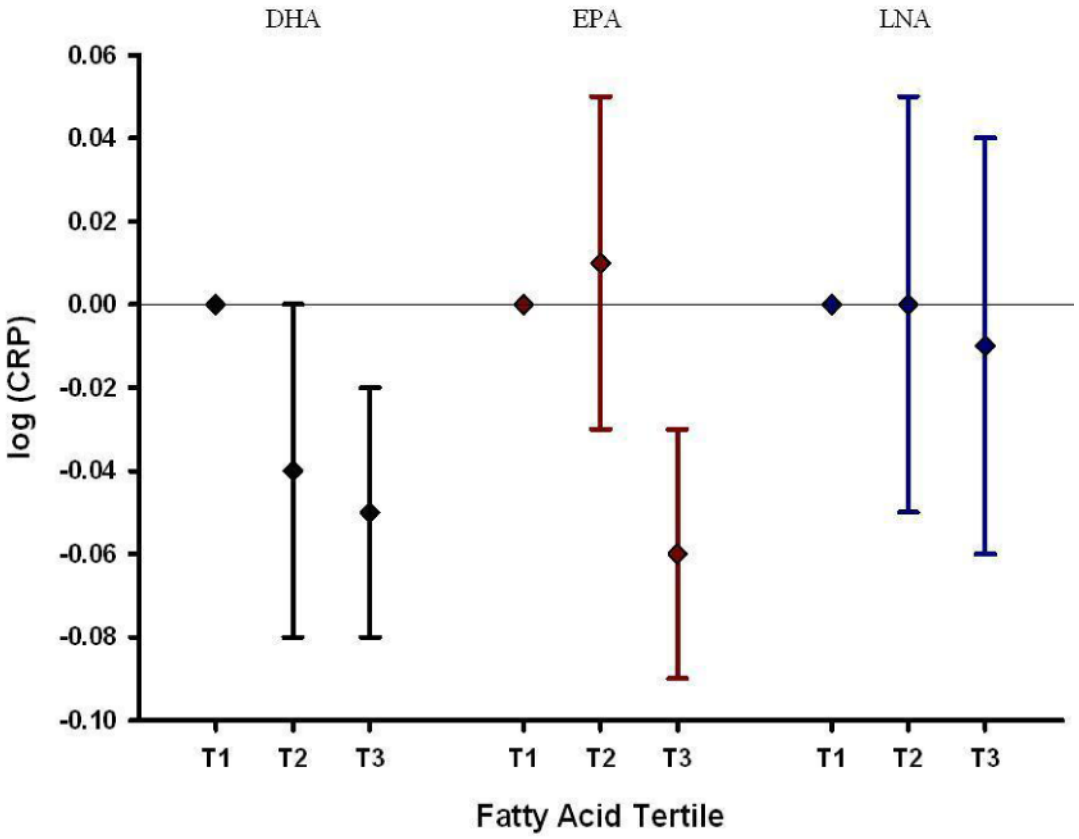

Figure 1. Multivariable[a] Linear Association between Tertile of PUFA Intake and logCRP (n=9183)

Abbreviations: PUFA: Polyunsaturated fatty acid; CRP: C-reactive protein; T: Tertile; DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; LNA: Linolenic Acid (alpha-linolenic acid and gamma-linolenic acid);

[a]Multivariable model: adjusted for age, sex, total energy intake (kcal/day), race/ethnicity, smoking, education, income, physical activity, pregnancy, self-reported health status, diabetes mellitus, body mass index, origin of birth, alcohol and tertiles of other fatty acid intake.

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Table 1

Sample Characteristics among U.S. Adults With and Without Periodontitis; NHANES[a] 1999-2004 (n=9182)

	Periodontitis n (%):	No Periodontitis n (%):
Age, group, y		
20-39	276 (32)	3732 (49)
40-59	435 (49)	2491 (36)
60-79	276 (17)	1620 (13)
≥80	37 (2)	315 (2)
Sex		
Male	620 (61)	3821 (49)
Female	404 (39)	4337 (51)
Race/ethnicity		
Non-Hispanic white	295 (52)	4168 (73)
Non-Hispanic black	291 (21)	1399 (10)
Mexican American	333 (12)	1932 (8)
Other	105 (15)	659 (10)
Income, $		
<20,000	404 (35)	2261 (21)
20,000-34,999	347 (31)	2469 (28)
35,000-74,999	135 (17)	1638 (23)
>75,000	94 (14)	1498 (25)
Refused to disclose	44 (3)	292 (3)
Education		
<High school	479 (35)	2147 (15)
High school	225 (26)	1950 (25)
Some college	320 (39)	4061 (60)
Alcohol intake, drinks/day		
0	385 (32)	2703 (28)
>0-<2	180 (17)	1899 (23)
2-5	330 (38)	2914 (41)
>5	129 (13)	642 (8)
Smoking status		
Never	437 (37)	4509 (54)
Former	266 (23)	1940 (23)
Current	321 (40)	1709 (23)
BMI[b], kg/m2		
<25	270 (29)	2662 (36)
25-29.9	379 (35)	2935 (34)
≥30	375 (36)	2561 (30)
Activity level		
None	580 (53)	3167 (31)

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	Periodontitis n (%):	No Periodontitis n (%):
Moderate	226 (24)	2358 (30)
Vigorous	218 (23)	2633 (39)
Health status		
Excellent/very good	407 (46)	4192 (58)
Good	348 (33)	2529 (29)
Fair/poor	269 (22)	1437 (13)
Diabetes		
No	899 (90)	7604 (95)
Yes	125 (10)	554 (5)

Abbreviations:

[a] NHANES: National Health and Nutrition Examination Survey.

[b] BMI: Body Mass Index

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Table 2
Tertiles (T) of Omega-3 Intake and Prevalence of Periodontitis (n=9182)

	Odds Ratios of Periodontitis (95% CI)			
	T1	**T2**	**T3**	**p-value**
DHA	**[0 gm/d]**	**[>0-<0.04 gm/d]**	**[≥0.04 gm/d]**	
Participants	n=2214	n=3391	n=3577	
Cases	n=287	n=332	n=405	
Partial adjustment[a]	1.0	0.65 (0.52, 0.82)	0.84 (0.66, 1.06)	0.002
Multivariable[b]	1.0	0.70 (0.55, 0.88)	0.78 (0.61, 1.00)	0.009
Dietary model[c]	1.0	0.70 (0.56, 0.88)	0.77 (0.61, 0.98)	0.007
Diet + supplement[d]	1.0	0.69 (0.55, 0.87)	0.80 (0.62, 1.02)	0.009
No supplements	1.0	0.70 (0.55, 0.88)	0.76 (0.60, 0.97)	0.009
EPA	[0 gm/d]	[>0-<0.01 gm/d]	[≥0.01 gm/d]	
Participants	n=3378	n=2235	n=3569	
Cases	n=413	n=225	n=386	
Partial adjustment[a]	1.0	0.74 (0.58, 0.95)	0.88 (0.70, 1.11)	0.06
Multivariable[b]	1.0	0.78 (0.61, 1.00)	0.85 (0.67, 1.08)	0.10
Dietary model[c]	1.0	0.77 (0.61, 0.99)	0.84 (0.66, 1.07)	0.08
Diet + supplement[d]	1.0	0.79 (0.64, 0.99)	0.85 (0.66, 1.10)	0.09
No supplements	1.0	0.79 (0.62, 1.01)	0.84 (0.67, 1.05)	0.09
LNA:	[<0.91 gm/d]	[0.91-1.67 gm/d]	[>1.67 gm/d]	
Participants	n=3123	n=3125	n=2934	
Cases	n=388	n=363	n=273	
Partial adjustment[a]	1.0	0.91 (0.69, 1.21)	0.68 (0.48, 0.95)	0.04
Multivariable[b]	1.0	1.08 (0.81, 1.44)	0.86 (0.60, 1.23)	0.28
Dietary Model[c]	1.0	1.06 (0.79, 1.41)	0.79 (0.51, 1.22)	0.27
Diet + supplement	1.0	1.12 (0.85, 1.47)	0.84 (0.59, 1.21)	0.15
No supplements	1.0	1.12 (0.85, 1.48)	0.87 (0.61, 1.24)	0.19

Abbreviations: T: Tertile; DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; LNA: Linolenic Acid (alpha-linolenic acid and gamma-linolenic acid);

[a] Partial adjustment for age, sex and total energy intake (kcal/day).

[b] Multivariable model: adjusted for age, sex, total energy intake (kcal/day), race/ethnicity, smoking, education, income, physical activity, pregnancy, self-reported health status, diabetes mellitus, body mass index, origin of birth, alcohol and tertiles of other fatty acid intake.

[c] Dietary Model: adjusted for all multivariable model covariates as well as dietary carbohydrates, saturated fats, monounsaturated fats and linoleic acid (a common dietary n-6 fatty acid).

[d] Diet + supplement: adjusted for all multivariable model covariates.

P-values shown derive from tests of heterogeneity.