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Impact of the dietary fatty acid intake on C-reactive protein levels in US adults

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Abstract

Growing evidence suggests that the effects of diet on cardiovascular disease (CVD) occur through mechanisms involving subclinical inflammation. We assessed whether reported dietary fatty acid intake correlates with a serum high-sensitivity C-reactive protein (hs-CRP) concentration in a population-based sample of US men and women.

In this cross-sectional analysis, participants were selected from the US National Health and Nutrition Examination Survey (NHANES) and restricted to those with available data on dietary intake, biochemical and anthropometric measurements from 2001 to 2010. All statistical analyses accounted for the survey design and sample weights by using SPSS Complex Samples v22.0 (IBM Corp, Armonk, NY).

Of the 17,689 participants analyzed, 8607 (48.3%) were men. The mean age was 45.8 years in the overall sample, 44.9 years in men, and 46.5 years in women ($P = 0.047$). The age-, race-, and sex-adjusted mean dietary intakes of total polyunsaturated fatty acids (PUFAs), PUFAs 18:2 (octadecadienoic), and PUFAs 18:3 (octadecatrienoic) monotonically decreased across hs-CRP quartiles ($P < 0.001$), whereas dietary cholesterol increased across hs-CRP quartiles ($P < 0.001$)

This study provides further evidence of an association between fatty acid intake and subclinical inflammation markers. hs-CRP concentrations are likely modulated by dietary fatty acid intake. However, the causality of this association needs to be demonstrated in clinical trials.

Abbreviations: AMPM = automated multiple-pass method, ANCOVA = analysis of co-variance, ANOVA = analysis of variance, BMI = body mass index, CVD = cardiovascular disease, HDL = high-density lipid, hs-CRP = high-sensitivity C-reactive protein, IL-6 = interleukin 6, MEC = mobile examination center, MetS = metabolic syndrome, MUFA = monounsaturated fatty acids, n-6 fAs = N-6 fatty acids, NCEP/ATPIII = National Cholesterol Education Program's Adult Treatment Panel III report, NCHS = National Center for Health Statistics, NHANES = National Health and Nutrition Examination Survey, PPARs = peroxisome proliferator-activated receptors, PUFAs = polyunsaturated fatty acids, SFA = saturated fatty acid, US = United States.

Keywords: cholesterol, high-sensitivity C-reactive protein, polyunsaturated fatty acids

1. Introduction

Subclinical chronic inflammation is known to play an important role in the development of atherosclerotic cardiovascular disease (CVD).[1] Serum concentrations of high-sensitivity C-reactive protein (hs-CRP) and proinflammatory cytokines, including interleukin 6 (IL-6), are associated with an increased risk of CVD.[1,2] There have been several reports of associations between dietary factors and the level of serum CRP and other inflammatory biomarkers.[1,3] Dietary guidelines recommend the consumption of n-3 and n-6 polyunsaturated fatty acids (PUFAs), in preference, saturated and trans-fatty acids; however, it has been reported that a high intake of n-6 PUFAs may increase subclinical inflammation.[4,5] The relationship between hs-CRP and dietary n-6 fatty acids (n-6 FAs) remains controversial.[6–8]

A recent systematic review and meta-analysis found that short-term marine-derived omega-3 supplementation decreases systemic inflammatory biomarkers, including hs-CRP, IL-6, and tumor necrosis factor-α (TNF-α) in different populations.[9] However, another systematic review provided weak support for omega-3 fatty acid supplementation in reducing chronic inflammation, reporting no convincing evidence supporting that a low intake of specific omega-3 fatty acids is associated with increased inflammation.[10] International dietary guidelines provide varying recommendations on the amounts and types of fatty acids for decreasing inflammatory markers and improving cardiovascular health.[11–13] This lack of consensus may reflect the lack of conclusive scientific evidence regarding the effects of dietary fatty acids intake on levels of hs-CRP.[11–13]

To our knowledge, no previous study has comprehensively examined the association of dietary fatty acids intake with hs-CRP level in the US population. We aimed to explore the

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association between reported dietary intake of fatty acids and serum hs-CRP concentrations in the NHANES population sample.

2. Methods

2.1. Population

The National Health and Nutrition Examination Survey (NHANES) is an ongoing, repeated set of cross-sectional surveys conducted by the National Center for Health Statistics (NCHS). NHANES uses a multistage probabilistic sampling strategy that oversamples certain segments of the population, including African-Americans, Mexican-Americans, and those of lower socioeconomic status. Approximately, 5000 subjects are recruited into NHANES each year, and the data are publicly available in 2-year cycles. Demographic, dietary, and behavioral information are gathered through in-home questionnaires, whereas anthropometric and biomarker data are collected by trained staff using mobile examination units. The NCHS Research Ethics Review Board approved the underlying protocol, and written informed consent was obtained from all subjects. The interview consists of questions on sociodemographic characteristics and previously diagnosed medical conditions. More detailed information on the NHANES survey design and questionnaires is reported elsewhere.[14]

The present study is based on analysis of data for two, 2-year NHANES survey cycles between 2001 and 2010 using data from the day 1 dietary recall. Overall response rates for these years ranged from 73% to 84% for interviews, and from 70% to 80% for examinations.[15,16] We identified 17,689 eligible participants aged 18 years or older for the analyses.

Details on NHANES Laboratory/Medical Technologists Procedures and Anthropometry Procedures are described elsewhere.[17,18] Moreover, complete laboratory procedures for collection, storage, calibration, and quality control of blood samples for determination of hs-CRP concentrations are available elsewhere (http://www.cdc.gov/NCHS/data/nhanes/nhanes_09_10/CRP_F_met.pdf. [accessed August 19, 2013]). In this study National Cholesterol Education Program's Adult Treatment Panel III report (NCEP/ATPIII) have been used to describe metabolic syndrome (MetS).[19] If a subject has at least 3 of the following 5 criteria, then he was classified as having MetS: waist circumference ≥102 cm in men or ≥88 cm in women; triglycerides ≥150 mg/dL; high-density lipid (HDL) cholesterol <40 mg/dL in men or <50 mg/dL in women; systolic blood pressure ≥130 or diastolic blood pressure ≥85 mmHg; fasting blood glucose ≥100 mg/dL.

For assessment of the diet 24-h recall was applied by a skilled assessor throughout the mobile examination center (MEC) as described previously.[20,21] In this study, we have used the data on fatty acids intake such as total daily fat intake, total saturated fatty acid intake, total monounsaturated fatty acid (MUFA) intake, total PUFA intake, cholesterol intake, saturated fatty acids (SFA) 4:0 (butanoic), SFA 6:0 (hexanoic), SFA 8:0 (octanoic), SFA 10:0 (decanoic), SFA 12:0 (dodecanoic), SFA 14:0 (tetradecanoic), SFA 16:0 (hexadecanoic), SFA 18:0 (octadecanoic), MUFA 16:1 (hexadecenoic), MUFA 18:1 (octadecenoic), MUFA 20:1 (eicosenoic), MUFA 22:1 (docosenoic), PUFA 18:2 (octadecadienoic), PUFA 18:3 (octadecatrienoic), PUFA 18:4 (octadecatetraenoic), PUFA 20:4 (eicosatetraenoic), PUFA 20:5 (eicosapentaenoic), PUFA 22:5 (docosapentaenoic), PUFA 22:6 (docosahexaenoic).

2.2. Statistical analysis

Analyses were conducted according to the guidelines set by the Centers for Disease Control and Prevention for analysis of the NHANES dataset, accounting for the masked variance and using their suggested weighting methodology.[22] Continuous and categorical demographic variables were compared across quartiles of hs-CRP using analysis of variance (ANOVA) and χ^2 tests, respectively. Age-, sex-, race-, body mass index (BMI)- and energy-adjusted mean intakes of nutrients were compared across quartiles of serum hs-CRP using analysis of co-variance (ANCOVA). Comparison of dietary intakes across quartile of Serum hs-CRP scores was conducted using ANCOVA with Bonferroni correction. All tests were 2-sided, and $P<0.05$ was the level of significance unless otherwise stated. Results were analyzed using SPSS complex sample module version 22.0 (IBM Corp, Armonk, NY). Sample weights were applied to account for unequal probabilities of selection, nonresponse bias, and oversampling.

3. Results

The weighted distributions of study population characteristics are shown in Table 1. Of the 17,689 eligible participants, 48.3% (n = 8607) were men. The mean age was 45.8 years overall, 44.9 years in men and 46.5 in women ($P = 0.047$). The distribution of the clinical, biochemical, and anthropometrical characteristics across quarters of serum hs-CRP is shown in Table 2, with significant differences (all $P < 0.001$) in a linear manner (all $P < 0.001$ for linear trends). This reflects monotonically increasing trend (decreasing for high-density lipoprotein cholesterol) across increasing quarters of hs-CRP level for a range of measures including BMI, waist circumference, and triglycerides. The prevalence of diabetes, hypertension, and MetS increased across quarters of hs-CRP.

The association of fatty acid intake with serum hs-CRP is summarized in Table 3. Mean dietary intakes of total PUFA, PUFA 18:2 (octadecadienoic), and PUFA 18:3 (octadecatrienoic) monotonically decreased across hs-CRP quarters ($P < 0.001$), and dietary cholesterol increases across hs-CRP quartiles ($P < 0.001$), whereas intake of total fat, MUFA, and SFA was not correlated with serum hs-CRP levels (Table 3).

In models adjusted for BMI, age, race, and sex, we found that total daily fat intake, total MUFA intake, total PUFA intake,

Table 1

Sample size and weighted characteristics of NHANES 2001–2010 adult participants.

		All n	Weighted distributions of the participants
Sex	Men	8607	48.3%
	Women	9082	51.7%
Age, y, mean ± SEM		17,689	45.82 ± 0.33
Education level	Less than high school	4827	19.4%
	Completed high school	3942	24.4%
	More than high school	7743	56.4%
Race/ethnicity	White (non-Hispanic)	8290	69.4%
	Non-Hispanic Black	3724	11.5%
	Mexican-American	3363	8.4%
	Other Hispanic and other	2312	10.7%

NHANES = National Health and Nutrition Examination Survey, SEM = standard error mean.

Table 2

Clinical and biochemical measures across quartiles of hs-CRP.

Variables	Quarters of serum hs-CRP					
N	1 4164	2 4156	3 4222	4 4066	*P* difference	*P* trend*
Serum hs-CRP, median (95% CI), mg/dL	0.040 (0.039–0.041)	0.128 (0.126–0.129)	0.309 (.306–0.312)	1.27 (1.23–1.31)		
Sex (men, %)	53.5%	54.8%	46.3%	36.3%	<0.001	<0.001
Age, y	41.99 ± 0.38	46.97 ± 0.38	47.72 ± 0.34	48.08 ± 0.49	<0.001	<0.001
Body mass index, kg/m^2	24.67 ± 0.08	27.54 ± 0.10	29.90 ± 0.12	33.10 ± 0.19	<0.001	<0.001
Waist circumference, cm	87.76 ± 0.29	96.16 ± 0.31	101.46 ± 0.34	107.70 ± 0.42	<0.001	<0.001
Fasting blood glucose, mg/dL	91.90 ± 0.41	96.79 ± 0.54	99.49 ± 0.64	106.13 ± 0.93	<0.001	<0.001
HDL cholesterol, mg/dL	57.72 ± 0.36	53.16 ± 0.38	51.08 ± 0.40	49.83 ± 0.34	<0.001	<0.001
Total cholesterol, mg/dL	189.55 ± 0.85	198.18 ± 0.95	202.27 ± 1.06	199.47 ± 0.94	<0.001	<0.001
Triglycerides, mg/dL	125.72 ± 1.88	157.18 ± 3.30	173.85 ± 3.20	169.25 ± 2.84	<0.001	<0.001
Systolic blood pressure, mmHg	117.88 ± 0.29	121.66 ± 0.35	123.01 ± 0.40	123.71 ± 0.41	<0.001	<0.001
Diastolic blood pressure, mmHg	68.62 ± 0.41	70.34 ± 0.29	70.46 ± 0.37	70.06 ± 0.36	<0.001	<0.001
Type-2 diabetes (%)	4.5%	7.2%	9.7%	13.9%	<0.001	<0.001
Hypertension (%)	10.6%	15.4%	17.3%	18.6%	<0.001	<0.001
Metabolic syndrome (%)	12.1%	26.3%	37.2%	42.8%	<0.001	<0.001

CI = confidence interval, HDL = high-density lipoprotein, hs-CRP = high-sensitivity C-reactive protein. Values expressed as estimated mean and standard error.
* *P* values for linear trend across quartiles of hs-CRP. Variables were compared across quartiles of hs-CRP using analysis of variance (ANOVA) and χ^2 tests.

MUFA 18:1 (octadecenoic), PUFA 18:2 (octadecadienoic), and PUFA 18:3 (octadecatrienoic) monotonically decreased across hs-CRP quarters (all $P < 0.001$), whereas dietary total SFA, SFA 4:0 (Butanoic), SFA 6:0 (Hexanoic), SFA 8:0 (octanoic), SFA 10:0 (decanoic), and SFA 14:0 (tetradecanoic) increased across hs-CRP quarters (all $P < 0.001$). In models adjusted for age, race, sex, BMI, and energy, we found that total PUFA intake, PUFA 18:2 (octadecadienoic), and PUFA 18:3 (octadecatrienoic) monotonically decreased across hs-CRP quarters (all $P < 0.001$), whereas total SFA intake, SFA 4:0 (butanoic), SFA 6:0 (hexanoic), SFA 8:0 (octanoic), SFA 10:0 (decanoic), SFA 14:0 (tetradecanoic), and SFA 18:0 (Octadecanoic) increased across

Table 3

Age-, sex-, and race-adjusted mean nutrient intakes across quartiles of hs-CRP levels.

Variables	Quarters of hs-CRP				
N	1 4164	2 4156	3 4222	4 4066	*P* for trend*
hs-CRP mean (95% CI), mg/dL	0.040 (0.039–0.041)	0.128 (0.126–0.129)	0.309 (0.306–0.312)	1.27 (1.23–1.31)	
Total daily fat intake, g	77.38 ± 1.091	78.17 ± 1.056	77.41 ± 1.088	76.06 ± 1.169	0.326
Total saturated fatty acid intake, g	24.48 ± 0.422	25.35 ± 0.377	25.37 ± 0.403	24.86 ± 0.424	0.352
Total monounsaturated fatty acid intake, g	28.58 ± 0.413	28.73 ± 0.398	28.58 ± 0.434	28.18 ± 0.482	0.419
Total polyunsaturated fatty acid intake, g	17.55 ± 0.258	17.21 ± 0.309	16.62 ± 0.246	16.23 ± 0.261	<0.001
Cholesterol intake, mg	288.76 ± 4.515	296.56 ± 5.042	304.57 ± 6.608	302.71 ± 5.247	<0.001
SFA 4:0 (Butanoic), g	0.464 ± 0.012	0.513 ± 0.017	0.494 ± 0.010	0.478 ± 0.019	0.667
SFA 6:0 (Hexanoic), g	0.258 ± 0.002	0.287 ± 0.007	0.279 ± 0.003	0.266 ± 0.004	0.256
SFA 8:0 (Octanoic), g	0.215 ± 0.001	0.234 ± 0.002	0.222 ± 0.001	0.216 ± 0.002	0.625
SFA 10:0 (Decanoic), g	0.381 ± 0.015	0.412 ± 0.003	0.401 ± 0.013	0.399 ± 0.004	0.326
SFA 12:0 (dodecanoic), g	0.667 ± 0.026	0.684 ± 0.028	0.696 ± 0.037	0.653 ± 0.038	0.856
SFA 14:0 (tetradecanoic), g	1.923 ± 0.048	2.070 ± 0.043	2.030 ± 0.044	1.991 ± 0.042	0.625
SFA 16:0 (hexadecanoic), g	13.482 ± 0.217	13.82 ± 0.201	13.88 ± 0.211	13.64 ± 0.191	0.452
SFA 18:0 (octadecanoic), g	6.304 ± 0.114	6.460 ± 0.106	6.623 ± 0.111	6.507 ± 0.118	0.071
MUFA 16:1 (hexadecenoic), g	1.197 ± 0.023	1.244 ± 0.187	1.237 ± 0.168	1.263 ± 0.103	0.154
MUFA 18:1 (octadecenoic), g	26.719 ± 0.392	26.82 ± 0.374	26.60 ± 0.400	26.22 ± 0.451	0.374
MUFA 20:1 (eicosenoic), g	0.250 ± 0.007	0.256 ± 0.003	0.252 ± 0.003	0.247 ± 0.008	0.202
MUFA 22:1 (docosenoic), g	0.031 ± 0.008	0.038 ± 0.008	0.037 ± 0.007	0.039 ± 0.004	0.656
PUFA 18:2 (octadecadienoic), g	15.522 ± 0.239	15.161 ± 0.270	14.681 ± 0.238	14.301 ± 0.231	<0.001
PUFA 18:3 (octadecatrienoic), g	1.525 ± 0.026	1.535 ± 0.029	1.448 ± 0.029	1.424 ± 0.027	<0.001
PUFA 18:4 (octadecatetraenoic), g	0.018 ± 0.003	0.018 ± 0.003	0.013 ± 0.001	0.019 ± 0.003	0.328
PUFA 20:4 (eicosatetraenoic), g	0.158 ± 0.003	0.152 ± 0.008	0.158 ± 0.002	0.153 ± 0.003	0.226
PUFA 20:5 (eicosapentaenoic), g	0.059 ± 0.002	0.046 ± 0.004	0.042 ± 0.007	0.042 ± 0.001	0.139
PUFA 22:5 (docosapentaenoic), g	0.021 ± 0.007	0.021 ± 0.003	0.025 ± 0.003	0.029 ± 0.009	0.361
PUFA 22:6 (docosahexaenoic), g	0.102 ± 0.008	0.081 ± 0.001	0.089 ± 0.009	0.081 ± 0.005	0.076

CI = confidence interval, hs-CRP = high-sensitivity C-reactive protein, MUFA = monounsaturated fatty acid, PUFA = polyunsaturated fatty acid, SFA = saturated fatty acid.
Values expressed as estimated mean and standard error.
* *P* values for linear trend across quarters of hs-CRP. Age-, sex-, and race-adjusted mean intakes of nutrients were compared across quartiles of hs-CRP using analysis of co-variance.

hs-CRP quarters (all $P < 0.001$, Supplemental Table 1, http://links.lww.com/MD/B547).

4. Discussion

This study investigated the association between dietary fatty acid intake and serum hs-CRP concentrations in a representative sample of US adults. The main findings were the association of increasing serum hs-CRP levels with increasing cholesterol intake and decreasing PUFA intake, suggesting a relationship between fatty acid intake and subclinical inflammation in this population.

Consistent with our findings, there are reports in the literature to suggest that inflammatory markers such as hs-CRP increase quickly after consumption of an excess amount of dietary lipids, while nutritional cholesterol itself is closely linked to inflammation markers through particular transcriptional regulators and may contribute to increasing the inflammatory component of atherogenesis.[23–25] We also recently reported an inverse relationship between cholesterol intake and hs-CRP in adult Iranians without a history of CVD.[26] Murakami et al[27] stated no significant association between SFA intake and raised hs-CRP, and they ascribed their results to the low baseline degree of raised hs-CRP level in their population (Japanese women). In this regard, a study in an elderly subjects could not detect a significant association between concentration of saturated myristic, palmitic or stearic acids, measured in serum cholesteryl esters, and hs-CRP level.[28] In line with these previous results, an augmented SFA intake was not significantly related with changes in hs-CRP in an Italian subjects. They stated that, in dysmetabolic subjects, the role of dietary factors including PUFA is associated with enhanced postprandial inflammatory factors and lipids profile.[29,30] Moreover, it has been proposed that the Mediterranean diet has a converse correlation with inflammatory factors such as hs-CRP level.[20,31]

Studies have reported that n-3 FAs work both directly by substituting arachidonic acid as an eicosanoid substrate and stopping arachidonic acid metabolism, and indirectly by changing the expression of inflammatory genes via influences on transcription factor activation.[6,32] Additionally, it has been suggested that both n-3 PUFAs and n-6 PUFAs halt the activities of δ-6 desaturase, δ-5 desaturase, and cyclooxygenase, all of which have a role in fatty acid control that affects pro- and anti-inflammatory mediators. Therefore, high intake of both n-3 PUFAs and n-6 PUFAs could lessen inflammation.[5,33] Additional proposed mechanism is that PUFAs can change the action of transcription factors, such as peroxisome proliferator-activated receptors (PPARs) and nuclear factor κB. PPARs via stopping signaling molecules can impact the initiation of nuclear factor κB, and hence obstructs the construction production of pro-inflammatory cytokines.[5,34]

Some inconsistent findings have been reported in different type of studies, with some suggesting no significant differences in subjects with a MUFA-rich diet.[35–37] In line with our study, recently Muke et al,[38] in a prospective study of 4707 individuals, found that higher intakes of PUFAs (mainly n-6 PUFAs) were correlated with lower levels of hs-CRP, which might reflect reduced chronic systemic inflammation. Julia et al[39] hypothesized that the inverse relation found between total n-3 PUFAs and hs-CRP was mostly driven by long-chain n-3 PUFAs.

The present study has some limitations. Its cross-sectional nature does not allow inferences about causality. Also, the use of a single 24-hour dietary recall may not fully capture the usual dietary behaviors. However, this concern is mitigated by the large sample size, increasing the probability of inclusion of diverse dietary behaviors. Moreover, we did not control for chronic diseases that might elevate hs-CRP.

As fatty acid intake has been a topic of interest in relation to CVD risk, understanding the effects of SFA, MUFA, and PUFA on subclinical inflammation could yield useful clinical insights and therapeutic potential. Our findings provide further evidence on the association between fatty acid intake and subclinical inflammation as reflected in hs-CRP levels. This raises the possibility that hs-CRP concentrations could be improved by changes in dietary fatty acid intake. However, these need to be formally tested in well-designed trials to comprehensively understand the impact of dietary fatty acids on subclinical inflammation.

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