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Dietary intake of *trans* fatty acids and systemic inflammation in women[1,2,3]

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Abstract

Background: *trans* Fatty acid (TFA) intake predicts risks of coronary artery disease and diabetes. Systemic inflammation may be involved in the pathogenesis of such conditions; however, relations between TFA intake and systemic inflammation are not well established.

Objective: We investigated the relations between TFA intake and inflammatory markers.

Design: In 823 generally healthy women in the Nurses' Health Study I and II, concentrations of soluble tumor necrosis factor α receptors 1 and 2 (sTNF-R1, sTNF-R2), interleukin 6 (IL-6), and C-reactive protein (CRP) were measured. Usual dietary intakes assessed from 2 semiquantitative food-frequency questionnaires were averaged for each subject.

Results: In age-adjusted analyses, TFA intake was positively associated with sTNF-R1 and sTNF-R2 (*P* for trend < 0.001 for each): sTNF-R1 and sTNF-R2 concentrations were 10% (+108 pg/mL; 95% CI: 50, 167 pg/mL) and 12% (+258 pg/mL; 138, 377 pg/mL) higher, respectively, in the highest intake quintile than in the lowest. These associations were not appreciably altered by adjustment for body mass index, smoking, physical activity, aspirin and nonsteroidal antiinflammatory drug use, alcohol consumption, and intakes of saturated fat, protein, n–6 and n–3 fatty acids, fiber, and total energy. Adjustment for serum lipid concentrations partly attenuated these associations, which suggests that they may be partly mediated by effects of TFAs on serum lipids. TFA intake was not associated with IL-6 or CRP concentrations overall but was positively associated with IL-6 and CRP in women with higher body mass index (*P* for interaction = 0.03 for each).

Conclusions: TFA intake is positively associated with markers of systemic inflammation in women. Further investigation of the influences of TFAs on inflammation and of implications for coronary disease, diabetes, and other conditions is warranted.

Keywords

trans Fatty acids; diet; inflammation; tumor necrosis factor receptors; women

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INTRODUCTION

trans Fatty acids (TFAs) are unsaturated fats with at least one double bond in the *trans* configuration that are formed during the industrial hydrogenation of vegetable oils for food manufacturing. Average consumption in industrialized countries is 4–7% of total dietary fat (1,2), with the major sources being fast foods, bakery products, packaged snacks, and margarines. TFA intake independently predicts risks of both coronary artery disease and diabetes (3,4). An elevated risk of coronary artery disease may be related to effects of TFAs on serum lipids; in feeding studies, TFA consumption lowers HDL-cholesterol concentrations and raises LDL-cholesterol, triacylglycerol, and lipoprotein(a) concentrations (5). However, associations of TFA consumption with coronary artery disease risk in observational studies are stronger than would be predicted on the basis of lipid changes alone (3); in addition, lipid effects of TFA intake would not account for the observed elevated risk of diabetes.

Systemic inflammatory activation is an emerging risk factor for coronary artery disease, insulin resistance, diabetes, dyslipidemia, and heart failure. In both healthy persons and persons with coronary artery disease, elevated C-reactive protein (CRP) concentrations independently predict poor outcomes (6,7). Elevated interleukin 6 (IL-6) concentrations are associated with insulin resistance, lipid abnormalities, coronary artery disease risk, and heart failure mortality (8–12). CRP and IL-6 concentrations also predict incident diabetes (13). Soluble tumor necrosis factor α receptors 1 and 2 (sTNF-R1 and sTNF-R2)—which in their natural monomeric form increase the half-life and bio-availability of TNF, reflecting TNF system activation (14–17)—and their gene polymorphisms are independently associated with insulin resistance, diabetes, lipid abnormalities, coronary artery disease, and heart failure mortality (11,16–24).

Thus, systemic inflammatory activation as measured by CRP, IL-6, sTNF-R1, and sTNF-R2 is integrally related to coronary artery disease, the metabolic syndrome, and heart failure. TFA intake also predicts risks of coronary disease and diabetes, but the mechanisms of these observed elevated risks are not well established. We wondered whether TFAs influence systemic inflammation, which might then partly account for the relations between TFAs and these conditions. We therefore investigated the associations between TFA intake and concentrations of CRP, IL-6, sTNF-R1, and sTNF-R2 in 823 generally healthy women enrolled in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII).

SUBJECTS AND METHODS

The NHS and NHSII have been described previously (25,26). The NHS is a prospective cohort study of 121 700 female US registered nurses aged 30–55 y at baseline in 1976, and the NHSII is a prospective cohort study of 116 671 female US registered nurses aged 25–42 y at baseline in 1989. A total of 32 826 women in the NHS and 29 614 women in the NHSII also provided blood samples in 1989–1990 and 1996–1998, respectively; these women were similar to those who did not provide samples (25). Health information and disease status are assessed every 2 y, and diet is assessed approximately every 4 y, by self-administered questionnaires. The studies were approved by the Harvard School of Public Health Human Subjects Committee, and all participants gave written informed consent.

The present analysis used data from NHS participants who were selected as control subjects for a study of myocardial infarction (MI) and from NHSII participants who were selected for a study on alcohol consumption (27). In the NHS, 498 participants were randomly selected as control subjects for women with incident MI, and the controls were matched to the cases on age, smoking, and blood-draw characteristics. Potential control subjects were excluded if they had a history of MI, angina, coronary revascularization, stroke, or nonmelanoma cancer at the time of blood collection (1989–1990). Body mass index (BMI; in kg/m^2), smoking habits,

alcohol consumption, and use of medications were assessed from the 1990 questionnaire; physical activity was assessed from the 1988 questionnaire because the 1990 questionnaire assessed only walking and stair climbing (25–29). These women were similar to the overall NHS cohort except for being older (61.2 y compared with 57.4 y) and more likely to be a current smoker (20% compared with 13%) due to matching criteria. We excluded 16 women with diabetes and 109 women with missing data on diet, inflammatory markers, BMI, smoking, or physical activity, and thus 373 NHS participants were included in this analysis.

In the NHSII, 473 premenopausal participants were randomly selected, stratified by alcohol drinking patterns (frequency, amount, with or without meals), for a study on alcohol consumption (27). Women were excluded if they were taking hormones or had a history of MI, angina, stroke, diabetes, intermittent claudication, peptic ulcer disease, gallbladder or liver disease, or nonmelanoma cancer at the time of blood collection (1996–1998). BMI, physical activity, smoking habits, alcohol consumption, and medication use were assessed from the 1997 questionnaire (25–29). These women were similar to the overall NHSII cohort except for having a greater average alcohol intake (11.4 compared with 3.5 g/d) due to the selection criteria. We excluded 23 women with missing data on diet, inflammatory markers, BMI, smoking, or physical activity, and thus 450 NHSII participants were included in this analysis.

Dietary assessment

To minimize misclassification, usual dietary intakes assessed from 2 semiquantitative food-frequency questionnaires that were closest in time to the blood draw were averaged for each participant (1986 and 1990 in NHS; 1995 and 1999 in NHSII). The reproducibility and validity of this food-frequency questionnaire have been described previously (30–32). The participants were asked to indicate how often, on average, they had consumed given amounts of various specified foods during the past year. Intakes of TFAs and other nutrients were computed by using composition values from the US Department of Agriculture (33) and the Harvard University Food Composition Database, including specific information on the types and brands of margarines, fats, and oils used by each subject for frying, cooking, and baking. Nutrient intakes were preadjusted for total energy by using separate regression analyses (34). Correlation coefficients between the estimates of intake of total fat and types of fat from the food-frequency questionnaire and the averge of 4 one-week dietary records ranged from 0.48 to 0.68 (32). The correlation between the calculated dietary TFA intake from the food-frequency questionnaire and the proportion of TFAs in adipose tissue was 0.51 (32). The range of reported total energy intake was 763–3368 kcal/d.

Measurement of inflammatory markers

CRP concentrations were measured spectrophotometrically by using a high-sensitivity assay (Hitachi 911 analyzer; Roche Diagnostics, Indianapolis) with reagents and calibrators from Denka Seiken (Niigata, Japan); day-to-day CVs were 9.4% and 1.1% at 0.65 and 13.4 mg/L, respectively. IL-6 concentrations were measured with an ultrasensitive enzyme-linked immunosorbent assay (R&D Systems, Minneapolis) with a sensitivity of 0.094 pg/mL and CVs of 12%, 15%, 7%, and 7% at 0.67, 1.4, 2.69, and 7.48 pg/mL, respectively. sTNF-R1 and sTNF-R2 concentrations were measured with enzyme-linked immunosorbent assays (R&D Systems) with CVs of 8.7% and 9.3%, respectively. Processing times did not substantially affect concentrations of these inflammatory markers (35). Intraclass correlations over a period of 4 y were 0.7 for CRP, 0.5 for IL-6, and 0.8 for sTNF-R1 and sTNF-R2 (36).

Statistical analysis

Linear regression with robust variance estimates (accounting for heteroscedasticity) (37) was used to evaluate associations between TFA intake and concentrations of sTNF-R1, sTNF-R2, IL-6, and CRP; analyses were also repeated by using log-transformed concentrations. TFA

intake was evaluated in quintiles as a percentage of total fat intake; analyses were also repeated with TFA intake evaluated as a percentage of total energy or after adjustment for total energy by using regression. Tests for linear trend were calculated by assigning the median value for each quintile of intake treated as a continuous variable. All results were age adjusted (5-y categories). To assess for confounding, 2 prespecified models were evaluated: *1*) adjusted for age, BMI (5 categories), smoking (4 categories), and physical activity (quintiles); and *2*) further adjusted for aspirin use, nonsteroidal anti-inflammatory drug use, alcohol use (5 categories), and consumption of saturated fat, protein, n–6 polyunsaturated fat, n–3 polyunsaturated fat, fiber, and total energy (each in quintiles). We also evaluated associations after adjustment for LDL and HDL cholesterol, triacylglycerols, and lipoprotein(a) (each in quintiles) to assess potential mediation and confounding by these serum lipoproteins. Potential effect modification was evaluated for age, BMI, and aspirin use (prespecified) and for n–6 fatty acid consumption and nonsteroidal antiinflammatory drug use (post hoc) by using multiplicative (continuous) interaction terms and likelihood ratio testing. Relations were initially evaluated separately in the NHS and the NHSII; analyses were then performed on the combined dataset. Analyses were performed by using SAS 8.2 (SAS Institute Inc, Cary, NC). All *P* values are two-tailed ($\alpha = 0.05$).

RESULTS

The mean age of the NHS participants was 61 y (range: 44–70 y), and the mean age of the NHSII participants was 42 y (range: 32–50 y). Relations between TFA intake and inflammatory markers were similar in the NHS and NHSII; therefore, combined results are presented. Mean TFA intake was 4.7% of dietary fat (range: 1.5–9.2%), and most TFAs came from fried foods consumed away from home (18%); cookies, donuts, or sweet rolls (17%); margarine (10%); beef eaten as a meal or in a sandwich (9%); and crackers (4%). Mean (±SD) concentrations of inflammatory markers were 1123 ± 319 pg/mL for sTNF-R1, 2279 ± 597 pg/mL for sTNF-R2, 1.9 ± 2.6 pg/mL for IL-6, and 2.6 ± 4.6 mg/L for CRP.

TFA intake was inversely associated with physical activity, HDL cholesterol, and intakes of alcohol, protein, n–3 fatty acids, and dietary fiber and was positively associated with BMI and the ratio of LDL to HDL cholesterol (Table 1). Assessed as a percentage of total fat intake, TFA intake was not associated with the intakes of saturated fat or n–6 fatty acids, thus minimizing potential confounding by these dietary factors.

After adjustment for age, TFA intake was positively associated with concentrations of both sTNF-R1 and sTNF-R2 (*P* for trend < 0.001 for each): sTNF-R1 and sTNF-R2 concentrations were 10% (+109 pg/mL; 95% CI: 50, 167 pg/mL) and 12% (+258 pg/mL; 95% CI: 138, 377 pg/mL) higher, respectively, in the highest intake quintile than in the lowest intake quintile (Table 2). These relations were not greatly altered by adjustment for other factors that might influence inflammation, including BMI, smoking, and physical activity (model 1; *P* for trend = 0.001 for sTNF-R1, and *P* for trend < 0.001 for sTNF-R2) and medication use and dietary factors (model 2; *P* for trend = 0.002 for sTNF-R1, and *P* for trend < 0.001 for sTNF-R2). In similar analyses, TFA intake was not associated with CRP or IL-6 concentrations (Table 2). Results were not appreciably different when inflammatory marker concentrations were log transformed before evaluation (data not shown).

TFA intake influences concentrations of several serum lipoproteins (5). We therefore adjusted for LDL-cholesterol, HDL-cholesterol, triacylglycerol, and lipoprotein(a) concentrations to evaluate the extent to which these lipoproteins might mediate the relations of TFA intake with sTNF-R1 and sTNF-R2. After this additional adjustment (model 2 plus lipoproteins), TFA intake was still positively associated with sTNF-R1 and sTNF-R2 concentrations (*P* for trend = 0.007 for each), although the magnitude of the association was partly attenuated: sTNF-R1

and sTNF-R2 concentrations were 8% (+74 pg/mL; 95% CI: 10, 137 pg/mL) and 9% (+177 pg/mL; 95% CI: 49, 305 pg/mL) higher, respectively, in the highest intake quintile than in the lowest.

We evaluated how different food groups contributing to TFA intake related to sTNF-R1 and sTNF-R2 concentrations (Table 3). After adjustment for potential confounders, each serving of margarine/d was associated with trends toward higher concentrations of sTNF-R1 (+26 pg/mL; 95% CI: − 1, 53 pg/mL) and sTNF-R2 (+28 pg/mL; 95% CI: − 24, 80 pg/mL). However, there were no significant associations, and broad CIs limited detection of potential relations.

We also individually evaluated *trans* isomers of palmitoleic acid (*trans* 16:1), oleic acid (*trans* 18:1), and linoleic acid (*trans* 18:2); *trans* 18:1 accounted for 71% of total TFA intake. After adjustment for potential confounders (as in model 2), *trans* 16:1 intake was not associated with sTNF-R1 ($P = 0.89$) or sTNF-R2 ($P = 0.51$) concentrations, whereas the intakes of *trans* 18:1 and *trans* 18:2 were positively associated with concentrations of sTNF-R1 ($P < 0.001$ for each) and sTNF-R2 ($P < 0.001$ for *trans* 18:1, and $P < 0.001$ for *trans* 18:2).

When we evaluated potential interactions, TFA intake was positively associated with IL-6 and CRP concentrations in women with higher BMI (P for interaction = 0.03 for each): higher TFA intake (each 1% of dietary fat) was associated with 0.06-pg/mL (95% CI: 0.01, 0.11 pg/mL) higher IL-6 concentrations and 0.09-mg/L (95% CI: 0.01, 0.17 pg/mL) higher CRP concentrations for each 1 unit of higher BMI (adjustments as in model 2). There was little evidence that relations between TFA intake and sTNF-R1 or sTNF-R2 varied according to BMI or that relations between TFA intake and any of the inflammatory markers varied according to age, aspirin use, nonsteroidal antiinflammatory drug use, or n–6 fatty acid intake ($P > 0.15$ for each interaction). The findings were not appreciably different if TFA intake was evaluated as a percentage of total energy or after adjustment for total energy by using regression (data not shown).

DISCUSSION

In this cross-sectional study among generally healthy women, higher TFA intake was associated with higher sTNF-R1 and sTNF-R2 concentrations independently of various other factors that might influence systemic inflammation, such as age, BMI, smoking, physical activity, medication use, alcohol consumption, and other dietary factors. The observed patterns were similar in the 2 separate cohorts (NHS and NHSII), which decreases the likelihood that the findings were solely due to chance and indicates similar relations in both younger (premenopausal) and older (largely postmenopausal) women.

Although administration of dimeric Fc fusion constructs of the TNF receptor or of high concentrations of natural monomeric sTNF-R1 and sTNF-R2 competitively inhibits TNF activity, at physiologic concentrations sTNF-R1 and sTNF-R2 prevent TNF decay, preserving the active form of TNF and increasing TNF bioavailability (14,15). Thus, concentrations of endogenously produced sTNF-R1 and sTNF-R2 reflect the activity of the TNF system (16, 17), and concentrations of these receptors correlate with numerous disease states including coronary artery disease, diabetes, and heart failure (11,16–24). Our results show higher sTNF-R1 and sTNF-R2 concentrations with higher TFA intake, indicating a link between TFA intake and TNF activity. These findings are consistent with those of an experimental study in 19 subjects in which consumption of a soybean margarine diet (6.7% of energy from TFAs) increased TNF production by cultured mononuclear cells in comparison with consumption of a soybean oil diet (0.6% of energy from TFAs) (38).

The associations of TFA consumption with coronary artery disease risk reported in prior studies are greater than would be predicted by effects on serum lipoproteins alone (3). In our study,

relations between TFA intake and TNF receptor concentrations were only partly attenuated by adjustment for serum lipid concentrations, suggesting that this relation is not wholly mediated through effects on serum lipids. In experimental studies, TFAs also increase insulin resistance, reduce postprandial tissue plasminogen activator activity, impair endothelial cell function, and increase lipid oxidation (39–42). Each of these abnormalities can be caused by activation of the TNF system (43–47). The TNF system may also promote atherosclerosis via effects on plaque stability, endothelial cell permeability and receptors, and monocyte and macrophage activation (48,49). In addition, TFA intake is associated with an elevated risk of new-onset diabetes (4), and activation of the TNF system is a risk factor for diabetes, independent of adiposity (22,23). Thus, activation of the TNF system may represent a mediating step between TFA consumption and risks of coronary artery disease and diabetes.

In the present study, *trans* 16:1 was not associated with TNF receptor concentrations. In contrast, *trans* 18:2 and *trans* 18:1—the predominant TFA in the diet and generally consumed from margarine, partially hydrogenated vegetable oils, and bakery sweets—each predicted higher TNF receptor concentrations. Among the different food groups, margarine tended to be associated with higher TNF receptor concentrations; CIs were broad, however, for each of the food groups. These potential differences in the influence of different *trans* isomers and different foods on the TNF system require confirmation in additional studies and should be viewed as hypothesis generating. Interestingly, *trans* 18:1 and *trans* 18:2 are stronger predictors of sudden cardiac death than is *trans* 16:1 (50).

How might TFA consumption influence inflammation? TFAs are incorporated into endothelial cell membranes (51), which have numerous cell-specific pathways relating to TNF activation (49). TFAs may also modulate TNF biology via effects on macrophage membrane phospholipids and signaling pathways, in a manner analogous to mechanisms seen with n–3, n–6, and monounsaturated fatty acids (52). Thus, there are biologically plausible mechanisms for an association between TFA intake and activation of the TNF system. Furthermore, although we did not observe an association between TFA intake and IL-6 or CRP concentrations overall, higher TFA intake predicted higher IL-6 and CRP concentrations in women with higher BMI. IL-6 and CRP are both linked to adiposity and the metabolic syndrome, which may be related to the production and release of IL-6 by adipose tissue (53). Thus, our findings raise the biologically interesting hypothesis that women with higher BMI may be more susceptible to effects of TFA intake on IL-6 and CRP production, which may be related to effects on or responses of adipose tissue. Further investigation of these relations, including the potential mechanisms of effect, is warranted.

Our study had several strengths. TFA intake was estimated by using a well-established, validated dietary instrument. Exclusion of women with known significant medical conditions at baseline reduced potential bias from changes in diet due to known disease. Standardized assessment of other participant characteristics increased our ability to adjust for potential confounding factors.

Our findings also have potential limitations. TFA intake was likely estimated with some error due to imperfect estimates of the intakes of specific foods and of their TFA content due to variation in preparation methods and manufacturing processes. In addition, if inflammation is influenced by short-term (days to weeks) rather than long-term (months to years) TFA intake, there may have been misclassification because of variation from the usual diet at the time of blood collection. (On the other hand, the half-life of specific fatty acids in adipose tissue is several months; thus, effects of TFAs in short-term studies could be underestimated or missed entirely.) Thus, potential measurement error in exposure and outcomes may have led to underestimation of the true relations between TFA intake and the inflammatory markers; for example, this may in part explain the lack of observed associations between TFA intake and

IL-6 and CRP overall. Although we adjusted for various clinical and dietary characteristics, residual confounding due to unmeasured or incompletely measured factors cannot be excluded. The women in our study were generally healthy women participating in a longitudinal cohort study, and our findings may not be generalizable to other populations.

Our results suggest that dietary intake of TFAs is associated with systemic inflammation in generally healthy women, as reflected by higher TNF receptor concentrations, as well as higher IL-6 and CRP concentrations in women with higher BMI, and that these associations are independent of various other characteristics including serum lipid concentrations. This observed relation between TFA intake and systemic inflammation may represent a novel potential mechanism for the effects of TFAs on risks of coronary artery disease and diabetes. Further study is indicated to investigate the potential proinflammatory effects of TFAs and the implications of such effects for risks of coronary artery disease, diabetes, and other conditions.

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TABLE 1

Age-adjusted participant characteristics according to quintile (Q) of *trans* fatty acid intake[1]

	Q1 (*n* = 164)	Q2 (*n* = 165)	Q3 (*n* = 165)	Q4 (*n* = 164)	Q5 (*n* = 165)	Overall (*n* = 823)
trans Fatty acid intake						
(% of fat)[2]	3.1	3.9	4.6	5.3	6.6	4.7
(g/d)[2]	1.8	2.3	2.7	3.1	3.9	2.7
BMI (kg/m^2)[3]	23.8	24.1	24.9	24.8	25.0	24.6
Smoking (%)						
Never	49	57	51	46	55	52
Past	34	26	31	33	25	30
Current, 1–14 cigarettes/d	8	7	8	8	10	8
Current, ≥ 15 cigarettes/d	8	11	10	14	9	10
Hypertension (%)	9	11	15	13	10	11
Physical activity (MET/wk)[2]	29	22	16	18	18	20
Aspirin, >2 d/wk (%)	17	19	18	19	20	18
NSAIDs, >2 d/wk (%)	18	16	22	27	23	21
Total cholesterol (mg/dL)	212	206	211	205	212	209
LDL cholesterol (mg/dL)	118	115	123	118	122	119
HDL cholesterol (mg/dL)[2]	70	66	63	63	63	65
LDL:HDL ratio[3]	1.8	1.9	2.1	2.1	2.1	2.0
Triacylglycerols (mg/dL)	96	105	105	107	108	103
Lipoprotein(a) (mg/dL)	20	19	21	17	18	19
Hemoglobin A_{1c} (%)	5.4	5.4	5.5	5.4	5.4	5.4
Intakes						
Energy (kcal/d)	1730	1800	1836	1849	1858	1812
Alcohol (g/d)[3]	12	10	10	10	8	10
Carbohydrates (g/d)[4]	209	208	211	210	216	211
Protein (g/d)[2]	79	80	76	77	74	77
Saturated fat (g/d)	19	20	20	20	20	20
n–6 Fatty acids (g/d)	10	10	10	10	10	10
n–3 Fatty acids (g/d)[2]	1.4	1.2	1.2	1.2	1.2	1.2
Fiber (g/d)[2]	21	19	19	18	17	19

[1] Values for continuous variables are means. MET, metabolic equivalents; NSAIDs, nonsteroidal antiinflammatory drugs.

[2] *P* for trend < 0.001.

[3] *P* for trend < 0.01.

[4] *P* for trend < 0.05.

TABLE 2

Inflammatory marker concentrations according to quintile (Q) of *trans* fatty acid intake[1]

	Q1 (*n* = 164)	Q2 (*n* = 165)	Q3 (*n* = 165)	Q4 (*n* = 164)	Q5 (*n* = 165)	*P* for trend
sTNF-R1 (pg/mL)						
Age adjusted	1056 ± 21	1101 ± 21	1141 ± 23[2]	1154 ± 21[2]	1164 ± 21[3]	<0.001
Model 1	1065 ± 22	1105 ± 22	1137 ± 22[4]	1150 ± 20[2]	1159 ± 20[2]	0.001
Model 2	1065 ± 23	1106 ± 20	1135 ± 21[4]	1149 ± 20[2]	1161 ± 20[2]	0.002
sTNF-R2 (pg/mL)						
Age adjusted	2121 ± 43	2259 ± 42[4]	2336 ± 48[2]	2301 ± 36[2]	2379 ± 42[3]	<0.001
Model 1	2139 ± 42	2271 ± 41[4]	2328 ± 46[2]	2294 ± 35[2]	2365 ± 42[3]	<0.001
Model 2	2126 ± 44	2264 ± 42[4]	2322 ± 45[2]	2302 ± 35[2]	2383 ± 44[3]	<0.001
IL-6 (pg/mL)						
Age adjusted	2.04 ± 0.30	1.88 ± 0.20	1.80 ± 0.19	1.77 ± 0.12	1.86 ± 0.14	0.58
Model 1	2.07 ± 0.31	1.92 ± 0.20	1.77 ± 0.19	1.75 ± 0.12	1.85 ± 0.14	0.47
Model 2	2.05 ± 0.29	1.93 ± 0.20	1.84 ± 0.20	1.74 ± 0.13	1.79 ± 0.16	0.40
CRP (mg/L)						
Age adjusted	2.56 ± 0.54	2.64 ± 0.34	2.32 ± 0.23	2.79 ± 0.29	2.89 ± 0.27	0.47
Model 1	2.81 ± 0.53	2.84 ± 0.33	2.18 ± 0.22	2.64 ± 0.27	2.75 ± 0.23	0.90
Model 2	3.12 ± 0.63	2.83 ± 0.33	2.21 ± 0.23	2.51 ± 0.29	2.55 ± 0.24	0.40

[1] All values are $\bar{x}$ ± SE. Model 1 was adjusted for age, BMI, smoking, and physical activity. Model 2 was further adjusted for aspirin use; nonsteroidal antiinflammatory drug use; alcohol use; intakes of saturated fat, protein, n–6 polyunsaturated fat, n–3 polyunsaturated fat, and fiber; and total energy intake. sTNF-R1 and sTNF-R2, soluble tumor necrosis factor α receptors 1 and 2, respectively; IL-6, interleukin 6; CRP, C-reactive protein.

[2–4] Significantly different from Q1: [2]$P < 0.01$, [3]$P < 0.001$, [4]$P < 0.05$.

TABLE 3

Differences in concentrations of soluble tumor necrosis factor α receptors 1 and 2 (sTNF-R1, sTNF-R2) associated with intakes of specific food groups[1]

Food group	sTNF-R1	sTNF-R2
	pg/mL	
Margarine (servings/d)	26 (−1, 53)	28 (−24, 80)
Cookies, donuts, or sweet rolls (servings/d)	12 (−17, 40)	12 (−48, 71)
Beef as a meal or sandwich (servings/d)	11 (−90, 113)	85 (−110, 279)
Crackers (servings/d)	11 (−17, 39)	−18 (−75, 38)
Fried foods consumed away from home (servings/wk)	−7 (−34, 21)	−9 (−55, 37)

[1] 95% CI in parentheses. Values are the differences associated with each serving of higher intake, adjusted for each food item in the table and for the covariates in model 2 (*see* Table 2). There were no significant associations.