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Soy Food Intake and Circulating Levels of Inflammatory Markers in Chinese Women

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Abstract

Background—Soy and some of its constituents, such as isoflavones, have been shown to affect the inflammatory process in animal studies. The association between soy food intake and inflammatory markers has not been evaluated adequately in humans.

Objective—Our aim was to evaluate whether higher intake of soy foods was inversely associated with inflammatory markers in 1,005 middle-aged Chinese women.

Design—In this cross-sectional study, dietary intake of soy foods was assessed by a validated food frequency questionnaire and by a 24-hour recall when biospecimens were procured. A general linear model was used to estimate the geometric means of selected inflammatory markers, including interleukin-6 (IL-6), IL-1β, tumor necrosis factor-α (TNFα), soluble IL-6 receptor, soluble GP130, soluble TNF receptors 1 and 2, and C-reactive protein, across categories of soy food intake after adjusting for age, lifestyle and dietary factors, and history of infectious or inflammation-related diseases.

Results—We found that multivariable-adjusted geometric mean concentrations of IL-6 and TNFα were inversely associated with quintiles of soy food intake, with a difference between the highest and lowest quintiles of 25.5% for IL-6 (*P* for trend = 0.008) and 14% for TNFα (*P* for trend = 0.04). Similar inverse associations were found for TNFα (*P* for trend = 0.003), soluble TNF receptor 1 (*P* for trend=0.01), soluble TNF receptor 2 (*P* for trend=0.02), IL-1β (*P* for trend=0.05), and IL-6 (*P* for trend=0.04) when soy food consumption was assessed by the frequency of consumption in the preceding 24 hours. No significant associations were found for other markers studied.

Conclusions—This study suggests that soy food consumption is related to lower circulating levels of IL-6, TNFα, and soluble TNF receptors 1 and 2 in Chinese women.

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STATEMENT OF POTENTIAL CONFLICT OF INTEREST

No potential conflict of interest was reported by the authors.

Keywords

Soy; Inflammation; Interleukin-1β; Interleukin-6; Tumor necrosis factor-α

Low-grade chronic inflammation has been associated with increased risk of cardiovascular disease, type 2 diabetes mellitus, Alzheimer's disease, and many types of cancer.[1–8] Ahallmark of inflammation is increased production of proinflammatory cytokines, which induces a range of inflammatory enzymes.[9] Clinical and epidemiologic studies suggest that dietary factors such as n-3 polyunsaturated fatty acids, antioxidant vitamins and minerals, and dietary fiber can exert health effects, in part, by modulating inflammation.[1]

Soy and its products are high in polyunsaturated fat, fiber, calcium, and vitamins, but low in saturated fat. In particular, soybeans and soy-based products are the richest dietary sources of isoflavones, the most common and extensively studied phytoestrogens in human diets.[10] Consumption of soy foods has been shown to have beneficial effects on multiple aspects of human health, including reduced risk of inflammation-related diseases, such as cardiovascular disease, diabetes, and certain cancers.[11–16] It has been hypothesized that the anti-inflammatory and antioxidative activity of soy constituents might explain some of its health benefits.[16–19] Studies have shown that soy and its isoflavones can inhibit cell adhesion molecule expression in cultured endothelial cells,[17,18] reduce production of proinflammatory cytokines, and decrease oxidative stress in animal models.[20–23] Several recent clinical trials have found that a soy-rich diet substantially lowers levels of tumor necrosis factor-α (TNFα), interleukin (IL)-6, C-reactive protein (CRP), IL-18, and nitric oxide,[15,24,25] although results are not entirely consistent.[26,27] Most of these trials investigated the effects of specific supplemental soy components administered for a short period of time.

Inflammatory markers such as CRP, IL-6, TNFα, and soluble TNF receptor 2 (sTNF-R2) have been shown to be relatively stable within individuals over time.[6,28–32] Intraclass correlation coefficients for these markers ranged from 0.48 to 0.77 in our study population.[28] This range is similar to intraclass correlation coefficients for serum cholesterol level (intraclass correlation coefficient = 0.60),[6] which is generally accepted as being measured reasonably well by a single blood sample. In this study, we evaluated the association between concentrations of selected inflammatory markers and dietary intake of soy foods measured by a validated food frequency question-naire (FFQ) and by a 24-hour recall of soy food consumption among 1,005 middle-aged Chinese women, hypothesizing that intake of soy foods would be inversely associated with circulating levels of inflammatory markers.

METHODS

Study Participants

This cross-sectional analysis was conducted among 1,005 healthy participants of the Shanghai Women's Health Study, a population-based cohort study. The design and methods of the Shanghai Women's Health Study have been described in depth elsewhere.[33,34] Briefly, at the baseline survey conducted between 1997 and 2000, 74,941 women aged 40 to 70 years were recruited from seven urban communities of Shanghai (participation rate: 92.7%). All women completed a detailed baseline survey that collected information on demographic characteristics, lifestyle and dietary habits, medical history, and other exposures. Anthropometric measurements, including current weight, height, and circumferences of the waist and hip, were also taken.[35] The study was approved by the relevant Institutional Review Boards for human research in both China and the United States. Written informed consent was obtained from all study participants.

Seventy-six percent of cohort members (n = 56,942) donated a 10-mL blood sample at baseline. After collection, samples were kept at 0 to 4°C and processed within 6 hours. Immediately after processing, all samples were stored at −70°C until laboratory analyses were conducted.

Measurement of Inflammatory Markers and Their Receptors

The sample preparation was performed at Vanderbilt Survey and Biospecimen Shared Resource. Cytokines and their receptors were assayed by using the Millipore's MILLIPLEX MAP High Sensitivity Human Cytokine multiplex kit (Millipore Corporation) for IL-1β, IL-6, and TNFα[28] and the MILLIPLEX MAP Human Soluble Cytokine Receptor Panel multiplex kits (Millipore Corporation) for soluble IL-6 receptor (sIL-6R), soluble GP130 (sGP130, a regulator of IL-6/sIL-6R complex signaling), soluble TNF-R1, and sTNF-R2[36] at the Hormone Assay & Analytical Services Core, Vanderbilt University, following manufacturer's instructions. Plasma samples and standards were assayed in duplicate. All laboratory assays were performed in 2009 to 2010. High-sensitivity CRP measurements were performed using ACE High Sensitivity C-Reactive Protein Reagent (ACI-22) on an ACE Clinical Chemistry System (Alfa Wassermann, Inc).[28] A second batch of samples was analyzed using the CRP (HS) Wide Range kit (Pointe Scientific) on ACE Clinical Chemistry System following the manufacturer's protocol. We adjusted for batch in all analyses. Limits of detection were as follows: TNFα, 0.05 pg/mL; sTNF-R1, 9.6 pg/mL; sTNF-R2,16.9 pg/mL; IL-1β,0.06 pg/mL; IL-6,0.10 pg/ mL; sGP130,7.2 pg/mL; sIL-6R, 3.6 pg/mL; and CRP, 0.1 mg/L Intra-assay coefficients of variation were 11.8% for TNFα, 7.5% for sTNF-R1, 5.5% for sTNF-R2,17.4% for IL-1 β,15.5% for IL-6, 3.6% for sGP130, and 3.8% for sIL-6R in this study; inter-assay coefficients of variation were <21% in our validation study conducted in the same core laboratory.[28]

Assessment of Diet

Habitual dietary intakes during the preceding 12 months were collected during in-person interviews using a validated FFQ.[33] For each food item or food group, participants were asked how frequently (daily, weekly, monthly, yearly, or never) they consumed the food or food groups, followed by a question on the amount consumed in liang (1 liang = 50 g) per unit of time. For seasonal foods (mainly vegetables and fruits), an in-season consumption pattern was elicited. The FFQ included a comprehensive list of soy foods (11 soy food items) commonly consumed in Shanghai, including soy milk, tofu, fried tofu, dried or pressed tofu, fresh green soy beans, dry soy beans, soy sprouts, and other soy products. Nutrient intakes, including soy protein and isoflavones, were calculated by summing nutrient intake amounts for each food item or food group. This was calculated by multiplying the reported amount of food intake by the nutrient content of the food item reported in the Chinese Food Composition Tables (2002).[37] Because the water content of soy foods varies widely (96.4% for soy milk, 82.8% for tofu, 65.2% for dried/pressed tofu, 10.2% for dry soybeans), we also calculated total intake of the dry weight of soy foods.[37] Neither soy protein isolate nor isoflavone supplements are commonly consumed in our study population[13] and they were not included in the study. In addition to the FFQ survey, information on the frequency of soy food consumption in the preceding 24 hours was collected in person by trained interviewers when biospecimens were procured.

Statistical Analysis

Participants with less than the detectable limits of inflammatory markers were excluded from the analysis (TNFα, n = 4; sTNF-R1, n = 5; sTNF-R2, n = 1; IL-1β, n=102; IL-6, n=71; sGP130, n = 1; sIL-6R, n = 3; and CRP, n = 90), as were participants with outliers according to a box plot (sTNF-R1, n = 1; sTNF-R2, n = 3; sGP130, n = 1; and sIL-6R, n = 6). Log-transformation was conducted to normalize the distribution of inflammatory markers

studied. Geometric means of these markers were obtained based on the least square means estimated using a general linear model according to quintiles of soy food, soy protein, and isoflavone intake assessed by the FFQ or frequency (0,1, or ≥2 times) of soy food consumption in the 24 hours before the blood sample collection. Tests for trend were performed by entering the categorical variables as continuous variables in the linear regression model. We also used a restricted cubic spline linear regression analysis[38] to evaluate the association between selected biomarkers and soy food intake on a continuous basis. Knots were placed at the 5th, 50th, and 95th percentiles of the distribution of soy food intake. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for a cross-sectional analysis were followed (http://www.strobe-statement.org/).

Categorical covariates adjusted for in multivariable models included education (college and beyond vs less than college), occupation (professional and clerical vs manual laborer), history of infectious or inflammation-related diseases (including coronary heart diseases, hypertension, diabetes mellitus, tuberculosis, bronchitis, asthma, gastritis, ulcerative colitis, and hepatitis; yes or no), menopausal status (pre- or postmenopausal), cigarette smoking (yes or no), alcohol consumption (yes or no), aspirin and other nonsteroid anti-inflammatory drug use (yes or no), vitamin supplement use (yes or no), season of interview (Spring vs other seasons), and assay batch. Continuous covariates adjusted for included age, body mass index (BMI; calculated as kg/m^2), physical activity (measured as metabolic equivalent hours per week per year),[39] total calories, and total fruit and vegetable intakes. Overall metabolic equivalents from physical activity were calculated as the sum of metabolic equivalents from recreational activity and nonrecreational activity. Nonrecreational activity included walking, cycling, stair climbing, and household activities.

In sensitivity analyses, participants with CRP >10 mg/L were excluded to reduce the influence of potential acute infectious conditions on our results,[40] and participants with less than the detectable limits of markers were included to check whether nondetection differed by soy food intake. We also evaluated potential effect modification by age, BMI, menopausal status, and self-reported history of infectious or inflammation-related diseases. Tests for interaction were performed by including cross-product terms of covariates and soy food intake in the main effect model. Multicollinearity was not a concern because the variance inflation factors for all variables were <3 (the variance inflation factors were about 1 for most covariates).[41] All statistical tests were two-sided and performed using SAS statistical software (version 9.2, 2010, SAS Institute).

RESULTS

Characteristics of study participants by quintiles of total soy food intake are presented in Table 1. Women with high intake of soy foods were likely to be older and consume more vegetables. There were no significant differences in other variables across categories of soy food intake, including BMI, waist-to-hip ratio, physical activity, cigarette smoking, or history of infectious or inflammation-related diseases. In addition, there were no significant differences in season of interview across categories of soy food intake. Apart from age, the characteristics of this selected subset of the cohort were not significantly different from the rest of the cohort (data not shown).

After adjustment for age, batch of biomarker measurement, and total energy intake, we found that women in higher quintiles compared with the lowest quintile of soy food intake had lower concentrations of IL-6, TNFα, and IL-1 β (*P* for trend <0.05 for IL-6 and TNFα; *P* for trend=0.05 for IL-1 β) (data not shown). Further adjustment for lifestyle and other dietary factors did not appreciably alter the results for IL-6 and TNFα, but attenuated the

association with IL-1 β (Table 2). The fully adjusted geometric mean of IL-6 was inversely associated with quintiles of soy food intake (4.39, 4.00, 3.77, 3.39, and 3.27 pg/mL for the lowest to highest quintiles, respectively; *P* for trend = 0.008), with a difference between the highest and lowest quintiles of 25.5%. Similar inverse associations were observed for TNFα across quintiles of soy food intake (6.37, 6.13, 5.82, 5.48, and 5.46 pg/mL for the lowest to highest quintiles, respectively; *P* for trend=0.04). Women in the highest quintile of soy food intake had 14% lower TNFα levels compared with women in the lowest quintile. Inverse associations with concentrations of IL-6 and TNFα were also found for dietary intake of soy protein and isoflavones (Table 2).

When intake of soy foods was analyzed on a continuous basis in a restricted cubic spline linear regression model, the concentrations of IL-6 were inversely associated with soy food intake (Figure 1, available online at www.andjrnl.org), with an apparent monotonic trend (*P* for overall significance = 0.02 and *P* for linear relation = 0.02). A similar inverse association between TNFα level and soy food intake was found, but TNFα levels remained unchanged beyond 28 g/day dry weight of soy food intake (at the 80th percentile of the distribution of intake). Tests for overall significance and linear trend were not statistically significant (Figure 2, available online at www.andjrnl.org).

Similar inverse associations were found for TNFα (*P* for trend = 0.003), sTNF-R1 (*P* for trend=0.01), sTNF-R2 (*P* for trend=0.02), IL-1 β (*P* for trend=0.05), and IL-6 (*P* for trend=0.04) when soy food consumption was assessed by the frequency of consumption in the preceding 24 hours (Table 3). Geometric mean concentrations of inflammatory markers in women consuming soy foods two or more times vs none in the preceding 24 hours were 18.7% lower forTNFα, 16.3% lower for sTNF-R1, 9.4% lower for sTNF-R2,11.9% lower for IL-1β, and 29.1% lower for IL-6, after adjusting for socioeconomic and lifestyle factors, health conditions, and other factors collected for the preceding 24 hours, including cigarette smoking and use of antibiotics, vitamin supplements, and nonsteroidal anti-inflammatory drugs. The association with soy food consumption in the preceding 24 hours was attenuated, but persisted significantly after further adjustment for usual intake of soy foods assessed by the FFQ (data not shown). No significant associations were found between soy food consumption and levels of sIL-6R, sGP130, or CRP (Table 2 and Table 3).

In stratified analyses, the observed inverse associations between soy food intake and levels of selected inflammatory biomarkers were not modified by age, BMI, menopausal status, postmenopausal hormone use, or history of infectious or inflammation-related diseases (data not shown).

To reduce the influence of potential acute infection on measures of these biomarkers, we conducted a sensitivity analysis by excluding participants with CRP >10 mg/L (n = 29, 2.89%). The exclusion did not markedly change the results for IL-6 (*P* for trend=0.02), but the inverse association for TNFα became weaker (*P* for trend=0.06). With this exclusion, the inverse association of IL-1 β level with soy food intake became statistically significant; adjusted geometric means were inversely associated with quintiles of soy food intake (1.35, 1.46, 1.23, 1.11, and 1.09 pg/mL for the lowest to highest quintiles, respectively; *P* for trend=0.02). In another sensitivity analysis, inclusion of participants with less than the detectable limits of markers (assigning one half the detectable limits to the missing data) did not markedly change the results for TNFα (*P* for trend=0.04) or IL-1β (*P* for trend = 0.02). However, the inverse association for IL-6 became weaker (*P* for trend=0.10) (Table 4, available online at www.andjrnl.org.andjrnl.org).

DISCUSSION

In this large, population-based, cross-sectional study of Chinese women, we found that concentrations of IL-6, TNFα, and sTNF-R1 and 2 were inversely associated with intake of soy foods. These associations were independent of age, lifestyle factors, and history of infectious or inflammation-related diseases and were not explained by differences in other dietary factors, such as intakes of fruits, non–soy vegetables, or total calories.

To our knowledge, this is the first population-based study of soy food intake and inflammatory markers. Clinical trials of dietary supplementation with various soy foods or specific constituents of soy have been conducted and reported mixed results.[15,16,24–26] Consumption of soy milk or soy nuts by postmenopausal women was associated with decreases in circulating levels of TNFα and CRP.[24,25] Pasta enriched with isoflavone aglycons from soy germ reduced levels of CRP in middle-aged adults with hypercholesterolemia[15] and 8-iso-PGF2α in patients with type 2 diabetes.[16] However, taking purified phytoestrogens in the form of tablets or isolated soy protein did not substantially affect levels of inflammatory markers.[26,42] This inconsistency might be explained, in part, by variations in the types, doses, or periods of intervention in these studies.

The potential mechanisms through which soy and its constituents affect inflammatory biomarkers remain to be clarified. In vitro data suggest that the effects of soy on modulating inflammatory markers such as TNFα are likely attributable to two phytoestrogens in soy, daidzein and genistein.[24] Soy phytoestrogens, which are structurally similar to 17β-estradiol,[43] may resemble hormone-replacement therapy regimens, reducing cell adhesion molecules and inflammatory markers.[43] Soy daidzein and genistein have been found to inhibit prostaglandin E2 expression in a dose-dependent manner[20,21] and improve oxidative stress.[16,21] In addition, soy foods contribute 37% of total intake of polyunsaturated fat in our study population (data not shown). Diets rich in certain polyunsaturated fats, such as linolenic acid, have been shown to lower levels of inflammatory markers.[44,45] For example, supplements with linolenic acid appear to reduce IL-6 levels in patients with dyslipidemia.[45]

The study population is well suited to the investigation of the soy and inflammation association because of its high, yet diverse, levels of soy food intake. As with any nutritional epidemiology study, measurement error in assessing soy food intake is a possible concern. However, the FFQ used in the study was found to have reasonably good validity for the measurement of usual dietary intake of soy foods.[33] Soy food intake assessed by the FFQ and multiple 24-hour dietary recalls was moderately correlated (r=0.49). In addition, the inverse associations between inflammatory markers and usual intake of soy foods assessed by the FFQ were consistently observed in another analysis of the frequency of soy food consumption in the preceding 24 hours. Another concern is the exclusion of participants with less than detectable limits of markers from our primary analyses. The purpose of the exclusion was to avoid the influence of imprecise measurements of markers on the results. When including participants with below detectable limits of markers in a sensitivity analysis, the results for most markers studied were not markedly changed, although the association with IL-6 became slightly weaker for the highest quintile of intake. In addition, we could not completely rule out the possibility of residual confounding due to unmeasured or inaccurately measured covariates, although careful adjustment for a wide range of potential confounding factors did not appreciably change the results.

CONCLUSIONS

We found that soy food consumption was related to lower circulating levels of IL-6, TNFα, and sTNF-R1 and 2, pivotal cytokines in the inflammatory cascade, which have been associated with many chronic diseases.[1–8,46,47] Women in the highest quintile of soy food intake had 26% lower levels of IL-6 and 14% lower levels of TNFa compared with women in the lowest quintile, which can have major implications for public health. For example, a 27% reduction in circulating levels of IL-6 between two extreme quartiles of the marker was associated with a 37% lower risk of lung cancer,[48] a 32% reduction in IL-6 level was related to a 25% reduction in risk of type 2 diabetes,[49] and a 15% reduction in TNFα level was associated with an 18% decreased risk of acute myocardial infarction.[50] Further investigation of the soy-inflammation association and related potential health benefits are warranted.

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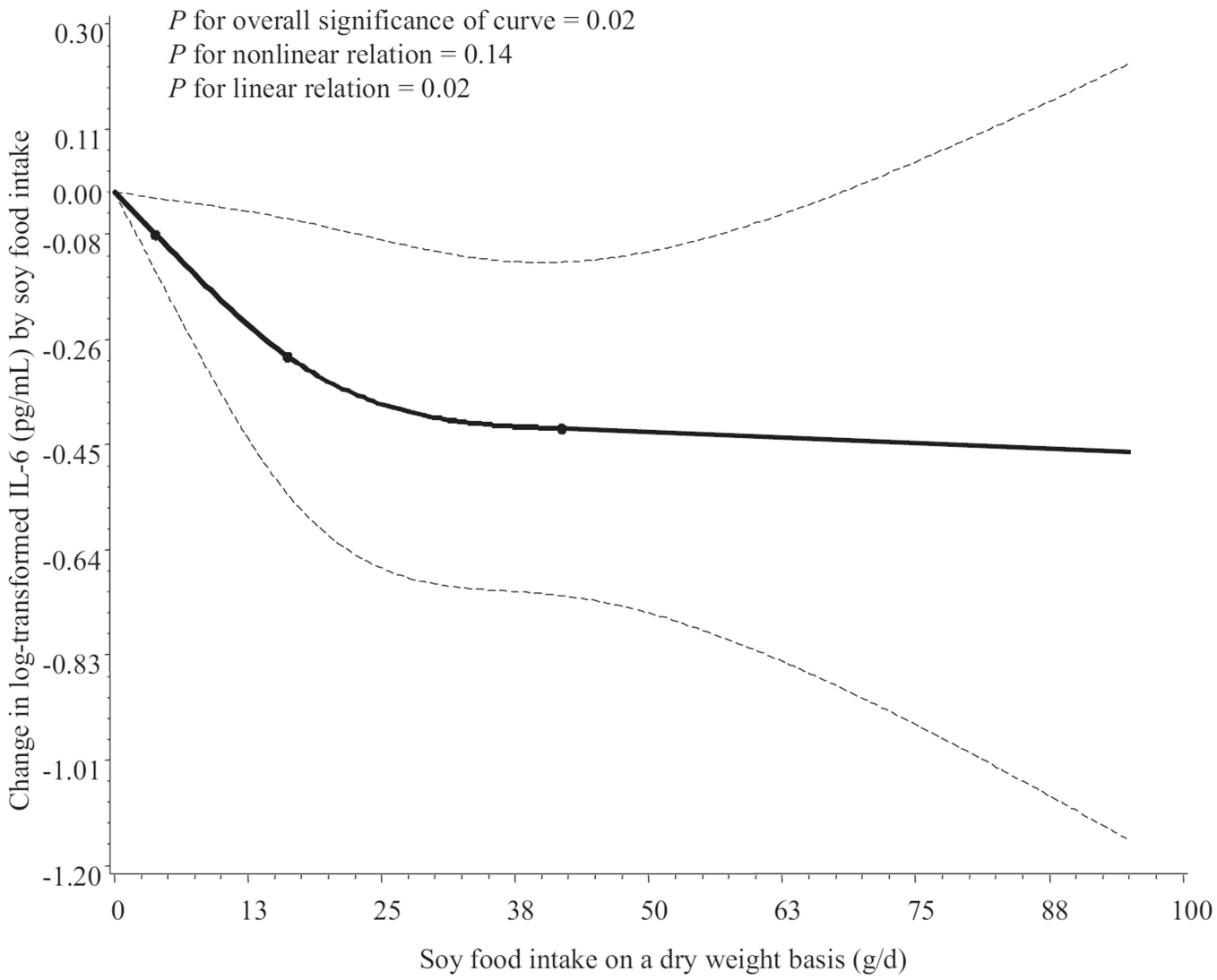

Figure 1.

Smoothed plot of changes in logarithmically transformed interleukin-6 (IL-6) levels (pg/mL) according to intake of soy foods. The amount of soy food intake was assessed on a dry-weight basis (g/day). Changes in IL-6 concentration relative to that in nonconsumers of soy foods were estimated by restricted cubic-spline linear regression analysis with knots placed at the 5th, 50th, and 95th percentiles of intake, after adjustment for age, education, occupation, cigarette smoking, alcohol consumption, body mass index, vitamin supplement use, menopausal status, aspirin and other nonsteroidal anti-inflammatory drug use, seasons of interview, total intake of fruits and vegetables, total energy intake, physical activity, history of infectious and/or inflammation-related diseases, and assay batch. Point estimates are indicated by a solid line and 95% confidence intervals by dashed lines.

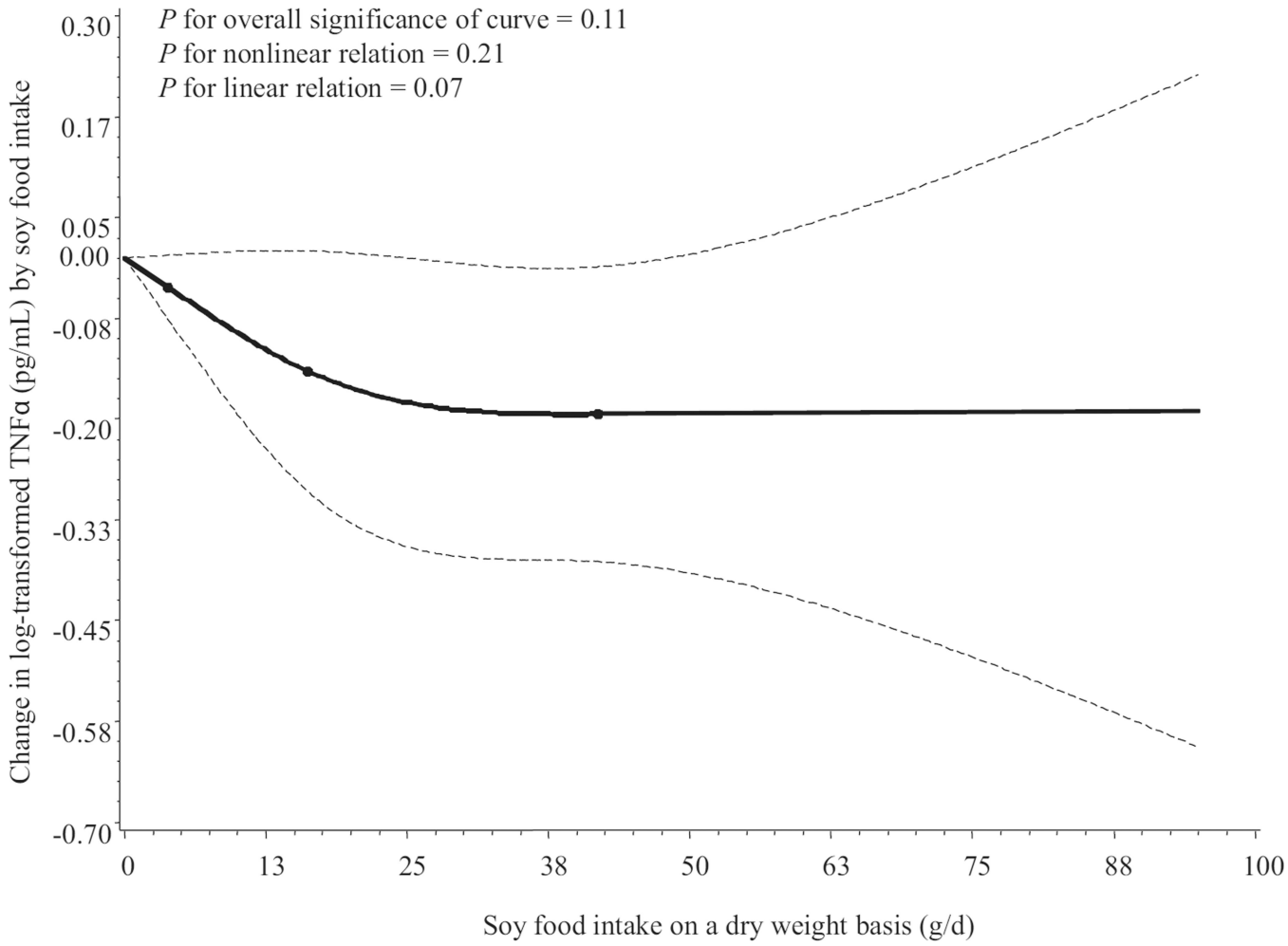

Figure 2.

Smoothed plot of changes in logarithmically transformed tumor necrosis factor-α (TNFα) concentration (pg/mL) according to intake of soy foods. The amount of soy food intake was assessed on a dry-weight basis (g/day). Changes in TNFα concentration relative to that in nonconsumers of soy foods were estimated by restricted cubic-spline linear regression analysis with knots placed at the 5th, 50th, and 95th percentiles of intake, after adjustment for age, education, occupation, cigarette smoking, alcohol consumption, body mass index, vitamin supplement use, menopausal status, aspirin, and other nonsteroidal anti-inflammatory drug use, seasons of interview, total intake of fruits and vegetables, total energy intake, physical activity, history of infectious and/or inflammation-related diseases, and assay batch. Point estimates are indicated by a solid line and 95% confidence intervals by dashed lines.

Table 1

Characteristics of study participants according to total soy food intake: Shanghai Women's Health Study[a]

	Quintiles of Soy Food Intake (g/day)[b]					
	0.01–8.6 (n=201	**8.7–14.0 (n=201**	**14.1–19.2 (n=201**	**19.3–27.4 (n=201**	**27.5–95.0 (n=201**	***P* for trend[c]**
			mean±standard deviation			
Age (y)	57.5±9.2	56.7 ±9.2	58.0±8.8	59.0±8.1	59.2±8.4	0.03
			%			
Education, college, and beyond	9.9	10.9	11.1	12.7	9.3	0.79
Household income >30,000 yuan/y[d]	13.2	15.8	12.6	11.4	16.8	0.58
Professional occupation	22.9	25.2	26.6	25.5	23.9	0.91
Cigarette smoking	3.6	2.8	3.9	2.8	5.1	0.71
Alcohol consumption	2.1	3.2	2.4	1.9	4.7	0.40
Post-menopause	76.2	73.4	75.7	71.7	76.7	0.14
Postmenopausal hormone use	1.5	2.1	2.6	1.9	4.4	0.45
Aspirin and other nonsteroidal anti-inflammatory drug use	4.6	1.2	2.9	4.2	4.1	0.32
History of infectious and/or inflammation-related diseases[e]	56.6	60.5	55.9	57.3	67.5	0.11
Season of interview						
Spring	45.07	36.39	37.35	37.56	36.93	0.80
Summer	24.35	28.95	30.91	27.54	34.75	
Fall	20.72	23.72	20.62	22.22	19.07	
Winter	9.86	10.94	11.12	12.68	9.25	
			mean±standard error of estimate			
Body mass index[f]	24.7 ±0.2	24.6 ±0.2	24.7±0.2	24.7±0.2	24.5 ±0.2	0.66
Waist-to-hip ratio	0.825 ±0.004	0.823 ±0.004	0.816±0.004	0.824±0.004	0.823 ±0.004	0.83
Physical activity (MET[g] h/wk/y)	106.1 ±3.0	102.6±3.0	111.5±3.0	107.0±3.0	110.1 ±3.0	0.20
Dietary intake						
Fruit (g/day)	239.3±11.3	225.411.4	234.0±11.3	252.6±11.3	237.0±11.4	0.54
Vegetables (g/day)	238.3 ±10.8	267.3 ±10.8	272.0±10.8	299.5 ±10.8	344.7 ±10.8	<0.0001
Red meat (g/day)	43.6±2.0	45.4±2.0	46.0±2.0	46.7±2.0	47.4±2.0	0.17
Total calories (kcal/day)	1,665.3 ±28.6	1,683.2 ±28.7	1,678.7 ±28.6	1,697.5±28.6	1,592.1 ±28.7	0.15
Soy protein (g/day)	3.1 ±0.2	5.8±0.2	7.8±0.2	10.6±0.2	17.0±0.2	<0.0001
Isoflavones (mg/day)	9.9±0.7	19.4±0.7	26.8 ±0.7	37.0±0.7	59.6±0.7	<0.0001

[a] Except for mean age, data were standardized to age distribution; data on dietary variables, except for total calories, were further standardized to total calorie intake

[b] The amount of soy food intake was assessed on a dry-weight basis.

[c] Linear regression models were used for continuous variables and the Cochran-Mantel-Haenszel χ^2 test for categorical variables.

[d] US$1=8 yuan, at the time of recruitment.

[e] History of infectious and/or inflammation-related diseases included coronary heartdiseases, hypertension, diabetes mellitus, tuberculosis, bronchitis, asthma, gastritis, ulcerative colitis, and hepatitis

[f] Calculated as kg/m^2

[g] MET=metabolic equivalent.

Table 2

Multivariable-adjusted concentrations of inflammatory markers in women according to quintiles of daily intake of soy foods, soy protein, and isoflavones, the Shanghai Women's Health Study[a]

	By Quintiles of Soy Food Intake[b]				By Quintiles of Soy Protein Intake[b]				By Quintiles of Isoflavone Intake[b]			
Marker	**n**	**Geometric mean±SEE**	**Difference[d] (%)**	***P* for trend**	**n**	**Geometric mean±SEE**	**Difference[d] (%)**	***P* for trend**	**n**	**Geometric mean±SEE**	**Difference[d] (%)**	***P* for trend**
Interleukin-6 (IL-6) (pg/mL)	183	4.39±1.09	Reference	0.008	183	4.30±1.09	Reference	0.007	182	4.35±1.09	Reference	0.006
	188	4.00±1.09	−8.88		187	4.09±1.09	−4.88		190	4.17± 1.09	−4.14	
	186	3.77±1.09	−14.12		184	3.66±1.09	−14.88		183	3.69±1.09	−15.17	
	185	3.39±1.09	−22.78		189	3.74±1.09	−13.02		187	3.34±1.09	−23.22	
	188	3.27±1.09	−25.51		187	3.05±1.09	−29.07		188	3.29±1.09	−24.37	
Soluble GP130 (pg/mL)	193	177,089±1.02	Reference	0.69	193	176,510± 1.02	Reference	0.64	191	177,825 ±1.02	Reference	0.69
	185	183,599±1.02	3.68		185	185,664 ±1.02	5.19		186	181,821 ±1.02	2.25	
	188	179,428 ±1.02	1.32		187	177,329±1.02	0.46		187	179,603 ±1.02	1.00	
	186	178,571 ±1.02	0.84		190	180,048 ±1.02	2.00		187	180,083 ±1.02	1.27	
	192	176,811 ±1.02	−0.16		189	176,039±1.02	−0.27		193	176,105 ±1.02	−0.97	
Soluble IL-6 receptor (pg/mL)	193	21,574±1.04	Reference	0.99	193	210,159± 1.04	Reference	0.96	191	21,867 ±1.04	Reference	0.96
	187	21,664±1.04	0.41		187	22,635 ±1.04	7.70		188	20,813 ±1.04	−4.82	
	188	21,684±1.04	0.51		187	21,560±1.04	2.59		187	22,546 ±1.04	3.11	
	187	21,553±1.04	−0.10		191	21,483 ±1.04	2.22		188	21,105± 1.04	−3.48	
	192	21,644±1.04	0.32		189	21,480±1.04	2.21		193	21,824 ±1.04	−0.20	
Tumor necrosis factor-α (TNFα) (pg/mL)	201	6.37±1.05	Reference	0.04	201	6.31 ±1.05	Reference	0.03	201	6.26±1.05	Reference	0.04
	200	6.13± 1.05	−3.77		201	6.28±1.05	−0.48		200	6.37±1.05	1.76	
	200	5.82±1.05	−8.63		198	5.72±1.05	−9.35		200	5.85 ±1.05	−6.55	
	199	5.48±1.05	−8.79		201	5.91 ±1.05	−6.34		198	5.54±1.05	−11.50	
	197	5.46±1.06	−13.97		196	5.39±1.05	−14.58		198	5.60±1.06	−10.54	
Soluble TNF receptor 1 (pg/mL)	193	1,076.68±1.03	Reference	0.87	193	1,076.26±1.03	Reference	0.94	191	1,091.90± 1.03	Reference	0.79
	187	1,193.36±1.03	10.84		187	1,210.03±1.03	12.43		188	1,172.05±1.03	7.34	
	188	1,101.54±1.03	2.31		188	1,083.47 ±1.03	0.67		188	1,088.54 ±1.03	−0.31	
	189	1,140.33±1.03	5.91		190	1,154.32±1.03	7.25		188	1,148.99± 1.03	5.23	
	193	1,108.40±1.03	2.95		192	1,098.32±1.03	2.05		195	1,116.48±1.03	2.25	
Soluble TNF receptor 2 (pg/mL)	193	4,350.67 ±1.02	Reference	0.16	193	4,344.28 ±1.02	Reference	0.048	191	4,345.17±1.02	Reference	0.15

	By Quintiles of Soy Food Intake[b]				By Quintiles of Soy Protein Intake[b]				By Quintiles of Isoflavone Intake[b]			
Marker	**n**	**Geometric mean±SEE**	**Difference[d] (%)**	***P* for trend**	**n**	**Geometric mean±SEE**	**Difference[d] (%)**	***P* for trend**	**n**	**Geometric mean±SEE**	**Difference[d] (%)**	***P* for trend**
	188	4,391.28± 1.02	0.93		188	4,471.24 ±1.02	2.92		189	4,363.22± 1.02	0.42	
	189	4,307.66±1.02	−0.99		188	4,284.54 ±1.02	−1.38		188	4,353.63 ±1.02	0.19	
	188	4,287.66±1.02	−1.45		191	4,321.26± 1.02	−0.53		189	4,305.27 ±1.02	−0.92	
	194	4,161.54± 1.02	−4.35		192	4,083.33 ±1.02	−6.01		195	4,134.38± 1.02	−4.85	
IL-1β (pg/mL)	183	1.28±1.09	Reference	0.11	182	1.26±1.09	Reference	0.12	183	1.27 ±1.09	Reference	0.17
	182	1.46 ±1.09	14.06		182	1.47 ±1.09	16.67		184	1.55±1.09	22.05	
	183	1.24±1.09	−3.13		180	1.25 ±1.09	−0.79		182	1.12±1.09	−11.81	
	181	1.16±1.09	−9.38		185	1.17±1.09	−7.14		179	1.14±1.09	−10.24	
	170	1.13±1.10	−11.72		170	1.12±1.09	−11.11		171	1.21 ±1.09	−4.72	
C-reactive protein (CRP) (mg/L)	151	1.20±1.10	Reference	0.51	150	1.13±1.10	Reference	0.34	151	1.08±1.09	Reference	0.49
	171	1.08±1.09	−10.00		171	1.17±1.09	3.54		169	1.30±1.09	20.37	
	151	1.25 ±1.09	4.17		155	1.20±1.09	6.19		152	1.15±1.09	6.48	
	155	1.20±1.09	0.00		154	1.14±1.09	0.88		156	1.18±1.09	9.26	
	162	1.25 ±1.09	4.17		160	1.33±1.09	17.70		162	1.25 ±1.09	15.74	

[a] Adjusted for age, education, occupation, cigarette smoking, alcohol consumption, body mass index, vitamin supplement use, menopausal status, aspirin and other nonsteroidal anti-inflammatory drug use, season of interview, total intake of fruits and vegetables, total energy intake, physical activity, history of infectious and/or inflammation-related diseases, and assay batch in general linear regression models.

[b] Quintile cutoffs for soy food intake assessed on a dry-weight basis: 0.01— 8.6,14.0,19.2, and 27.4— 95.0 g/day; quintile cutoffs for soy protein intake: 0.01 — 4.3,6.8,9.5, and 13.2— 47.5 g/day; quintile cutoffs for isoflavone intake: 0.02—14.0, 23.0,33.1, and 46.4— 147.2 mg/day.

[c] SEE=standard error of estimate.

[d] Difference (%)=(geometric mean of inflammatory marker in each quintile— geometric mean in the lowest quintile)/geometric mean in the lowest quintile of soy foods, soy protein, or isoflavone intake.

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Table 3

Concentrations of inflammatory markers by the frequency of soy consumption in the 24 hours before sample collection, the Shanghai Women's Health Study[a]

			Age-, Batch-, and Energy-Adjusted Model				Multivariable-Adjusted Model			
Marker	**n**	**Soy intake frequency**	**Geometric mean**	**SEE[b]**	**Difference[c] (%)**	***P* for trend**	**Geometric mean**	**SEE**	**Difference[c](%)**	***P* for trend**
Interleukin-6 (IL-6) (pg/mL)	547	0	3.94	1.05	Reference	0.03	3.92	1.05	Reference	0.04
	327	1	3.65	1.06	−7.36		3.64	1.06	−7.14	
	57	≥ 2	2.69	1.16	−31.73		2.78	1.16	−29.08	
Soluble GP130 (pg/mL)	551	0	179,425	1.01	Reference	0.57	179,476	1.01	Reference	0.55
	334	1	179,344	1.02	−0.05		179,413	1.02	−0.04	
	60	≥ 2	173,666	1.04	−3.21		173,216	1.04	−3.49	
Soluble IL-6 receptor (pg/mL)	553	0	21,977	1.02	Reference	0.14	21,923	1.02	Reference	0.23
	335	1	21,281	1.03	−3.16		21,365	1.03	−2.55	
	60	≥ 2	20,140	1.06	−8.36		20,366	1.07	−7.10	
Tumor necrosis factor-α (TNFα) (pg/mL)	581	0	6.24	1.03	Reference	0.003	6.25	1.03	Reference	0.003
	354	1	5.59	1.04	−10.42		5.55	1.04	−11.20	
	63	≥ 2	4.98	1.09	−20.19		5.08	1.09	−18.72	
Soluble TNF receptor 1 (pg/mL)	552	0	1,144.28	1.02	Reference	0.01	1,145.26	1.02	Reference	0.01
	337		1,121.25	1.02	−2.01		1,119.43	1.02	−2.26	
	62	≥ 2	961.22	1.05	−16.00		958.98	1.05	−16.27	
Soluble TNF receptor 2 (pg/mL)	555	0	4,369.81	1.01	Reference	0.01	4,367.76	1.01	Reference	0.02
	337	1	4,239.39	1.02	−2.98		4,249.58	1.02	−2.71	
	61	≥ 2	3,954.80	1.04	−9.50		3,957.87	1.04	−9.38	
IL-1β (pg/mL)	529	0	1.34	1.05	Reference	0.06	1.34	1.05	Reference	0.05
	319	1	1.14	1.07	−14.93		1.12	1.07	−16.42	
	52	≥ 2	1.16	1.17	−13.43		1.18	1.17	−11.94	
C-reactive protein (CRP) (mg/L)	463	0	1.25	1.05	Reference	0.20	1.24	1.05	Reference	0.25
	281	1	1.12	1.07	−10.40		1.13	1.07	−8.87	
	47	2	1.10	1.18	−12.00		1.13	1.17	−8.87	

[a]Adjusted for age, education, occupation, alcohol consumption, body mass index, menopausal status, season of interview, total intake of fruits and vegetables, total energy intake, physical activity, history of infectious and/or inflammation-related diseases and assay batch in general linear regression models, as well as factors collected for the preceding 24 hours, including cigarette smoking and use of antibiotics, vitamin supplements, and nonsteroidal anti-inflammatory drugs.

[b] SEE=standard error of estimate

[c] Difference (%)=(geometric mean of inflammatory marker in each group—geometric mean in the group with no consumption of soyfood)/geometric mean in the group with no consumption of soy food

Table 4

Multivariable-adjusted concentrations of inflammatory markers in women according to quintiles of daily intake of soy foods, including both detectable and undetectable measurements of the biomarkers studied, the Shanghai Women´s Health Study[ab]

	By Quintiles of Soy Food Intake[c]				By Quintiles of Soy Protein Intake[c]				By Quintiles of Isoflavone Intake[c]			
Marker	**n**	**Geometric mean±SEE[d]**	**Difference[e] (%)**	***P* for trend**	**n**	**Geometric mean± SEE**	**Difference[e] (%)**	***P* for trend**	**n**	**Geometric mean± SEE**	**Difference[e] (%)**	***P* for trend**
Interleukin-6 (IL-6) (pg/mL)	201	3.06±1.11	Reference	0.10	201	2.97±1.11	Reference	0.14	201	2.94±1.11	Reference	0.11
	201	3.07±1.11	0.33		201	3.09±1.11	4.04		201	3.34±1.11	13.61	
	201	2.73±1.11	−10.78		201	2.58±1.11	−13.13		201	2.53±1.11	−13.95	
	201	2.37±1.11	−22.55		201	2.79±1.11	−6.06		200	2.49±1.11	−15.31	
	197	2.60±1.11	−15.03		197	2.39±1.11	−19.53		198	2.55±1.11	−13.27	
Soluble GP130 (pg/ mL)	193	178,614±1.05	Reference	0.10	193	177,455 ±1.05	Reference	0.08	191	178,289 ±1.05	Reference	0.35
	189	175,758±1.05	−1.60		189	178,552±1.05	0.62		190	174,372±1.05	−2.20	
	189	178,277 ±1.05	−0.19		189	168,497 ±1.05	−5.05		189	169,803 ±1.05	−4.76	
	190	158,609 ±1.05	−11.20		191	176,964 ±1.05	−0.28		191	159,876±1.05	−10.33	
	195	164,563 ±1.05	−7.87		194	154,741 ±1.05	−12.80		195	172,932±1.05	−3.00	
Soluble IL-6 receptor (pg/mL)	193	21,711 ±1.06	Reference	0.20	193	21,090 ±1.06	Reference	0.16	191	21,895 ±1.06	Reference	0.50
	189	21,112±1.06	−2.76		189	22,142± 1.06	4.99		190	20,298 ±1.06	−7.30	
	189	21,386±1.06	−1.50		189	20,258 ±1.06	−3.94		189	21,110±1.06	−3.59	
	190	19,113±1.06	−11.97		191	21,324 ±1.06	1.11		191	18,875 ±1.06	−13.79	
	195	20,209 ±1.06	−6.92		194	18,801 ±1.06	−10.85		195	21,367 ±1.06	−2.41	
Tumor necrosis factor-α (TNFα) (pg/mL)	201	6.40±1.06	Reference	0.04	201	6.33 ±1.06	Reference	0.02	201	6.27 ±1.06	Reference	0.03
	201	5.98±1.06	−6.56		201	6.29±1.06	−0.63		201	6.22±1.06	−0.80	
	201	5.67 ±1.06	−11.41		201	5.30±1.06	−16.27		201	5.69±1.06	−9.25	
	201	5.49±1.06	−14.22		201	5.89±1.06	−6.95		200	5.25 ±1.06	−16.27	
	197	5.45 ±1.06	−14.84		197	5.22±1.06	−17.54		198	5.56±1.06	−11.32	
Soluble TNF receptor 1 (pg/mL)	193	1,073.42±1.05	Reference	0.70	193	1,072.69±1.05	Reference	0.56	191	1,085.90± 1.05	Reference	0.95
	189	1,130.10±1.04	5.28		189	1,146.93 ±1.04	6.92		190	1,110.69±1.04	2.28	
	189	1,080.03 ±1.04	0.62		189	1,063.62 ±1.04	−0.85		189	1,069.93 ±1.04	−1.47	
	190	1,100.16±1.04	2.49		191	1,117.95 ±1.04	4.22		191	1,048.08 ±1.04	−3.48	
	195	1,055.66±1.05	−1.65		194	1,040.14±1.05	−3.03		195	1,122.93 ±1.04	3.41	
Soluble TNF receptor 2 (pg/mL)	193	4,361.23 ±1.03	Reference	0.11	193	4,353.58± 1.03	Reference	0.04	191	4,349.28±1.03	Reference	0.21

Marker	By Quintiles of Soy Food Intake[c]				By Quintiles of Soy Protein Intake[c]				By Quintiles of Isoflavone Intake[c]			
	n	Geometric mean±SEE[d]	Difference[e] (%)	*P* for trend	n	Geometric mean± SEE	Difference[e] (%)	*P* for trend	n	Geometric mean± SEE	Difference[e] (%)	*P* for trend
	189	4,269.46 ±1.03	−2.10		189	4,347.65 ±1.03	−0.14		190	4,242.99±1.03	−2.44	
	189	4,307.56±1.03	−1.23		189	4,217.71 ±1.03	−3.12		189	4,273.97 ±1.03	−1.73	
	190	4,112.79± 1.03	−5.70		191	4,298.21 ±1.03	−1.27		191	4,150.09± 1.03	−4.58	
	195	4,093.58±1.03	−6.14		194	3,937.65 ±1.03	−9.55		195	4,126.07 ±1.03	−5.13	
IL-1β (pg/mL)	201	0.93±1.11	Reference	0.02	201	0.90±1.11	Reference	0.04	201	0.91 ±1.11	Reference	0.02
	201	1.02±1.11	9.68		201	1.03 ±1.11	14.44		201	1.12±1.11	23.08	
	201	0.89±1.11	−4.30		201	0.85 ±1.11	−5.56		201	0.80±1.11	−12.09	
	201	0.79±1.11	−15.05		201	0.85 ±1.11	−5.56		200	0.77±1.11	−15.38	
	197	0.68±1.12	−26.88		197	0.67 ±1.12	−25.56		198	0.72±1.11	−20.88	
C-reactive protein (CRP) (mg/L)	169	0.89±1.11	Reference	0.44	169	0.85 ±1.11	Reference	0.30	170	0.80±1.11	Reference	0.39
	179	0.96±1.11	7.87		179	1.02±1.10	20.00		177	1.13±1.10	41.25	
	163	0.99±1.10	11.24		167	0.96±1.10	12.94		164	0.92± 1.10	15.00	
	167	0.95±1.10	6.74		164	0.94±1.11	10.59		167	0.97± 1.10	21.25	
	170	1.02±1.11	14.61		169	1.05 ±1.11	23.53		170	1.01 ±1.11	26.25	

[a] Adjusted for age, education, occupation, cigarette smoking, alcohol consumption, body mass index, vitamin supplement use, menopausal status, aspirin and other nonsteroidal anti-inflammatory drug use, season of interview, total intake of fruits and vegetables, total energy intake, physical activity, history of infectious and/or inflammation-related diseases, and assay batch in general linear regression models.

[b] Assigned one half the detectable limits to undetectable measures.

[c] Quintile cutoffs for soy food intake assessed on a dry-weight basis: 0.01 —8.6,14.0,19.2, and 27.4—95.0 g/day; quintile cutoffs for soy protein intake: 0.01 —4.3,6.8,9.5, and 13.2—47.5 g/day; quintile cutoffs for isoflavone intake: 0.02—14.0, 23.0,33.1, and 46.4—147.2 mg/day.

[d] SEE=standard error of estimate.

[e] Difference (%)=(geometric mean of inflammatory marker in each quintile—geometric mean in the lowest quintile)/geometric mean in the lowest quintile of soy food, soy protein, or isoflavone intake.