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Original Contribution

Association Between Use of Specialty Dietary Supplements and C-Reactive Protein Concentrations

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Laboratory evidence suggests that certain specialty dietary supplements have antiinflammatory properties, though evidence in humans remains limited. Data on a nationally representative sample of 9,947 adults from the 1999–2004 cycles of the National Health and Nutrition Examination Survey were used to assess the associations between specialty supplement use and inflammation, as measured by serum high-sensitivity C-reactive protein (hs-CRP) concentration. Using survey-weighted multivariate linear regression, significant reductions in hs-CRP concentrations were associated with regular use of glucosamine (17%, 95% confidence interval (CI): 7, 26), chondroitin (22%, 95% CI: 8, 33), and fish oil (16%, 95% CI: 0.3, 29). No associations were observed between hs-CRP concentration and regular use of supplements containing methylsulfonylmethane, garlic, ginkgo biloba, saw palmetto, or pycnogenol. These results suggest that glucosamine and chondroitin supplements are associated with reduced inflammation in humans and provide further evidence to support an inverse association between use of fish oil supplements and inflammation. It is important to further investigate the potential antiinflammatory role of these supplements, as there is a need to identify safe and effective ways to reduce inflammation and the burden of inflammation-related diseases such as cancer and cardiovascular disease.

anti-inflammatory agents; chondroitin; C-reactive protein; dietary supplements; fish oils; glucosamine; inflammation; nutrition surveys

Abbreviations: CI, confidence interval; CRP, C-reactive protein; hs-CRP, high-sensitivity C-reactive protein; MET, metabolic equivalent of task; MSM, methylsulfonylmethane; NHANES, National Health and Nutrition Examination Survey; NSAID, nonsteroidal antiinflammatory drug; PUFA, polyunsaturated fatty acid; VITAL, VITamins And Lifestyle.

Inflammation has been implicated in the etiology of several chronic diseases, including cardiovascular disease and several types of cancer (1–4). Consistent with these observations, the antiinflammatory drug aspirin has been found to reduce the risk of cardiovascular disease (5, 6) and colorectal cancer (7) in randomized controlled trials and has been associated with reduced risk of other cancers in observational studies (8–10). Concerns remain about the adverse effects of long-term use of aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs) (6, 11–13); consequently, there is a need to identify other safe and effective measures for reducing inflammation and inflammation-related diseases.

Laboratory studies suggest that certain nonvitamin, nonmineral "specialty" supplements may act to reduce inflammation. These include glucosamine (14–19), chondroitin (20, 21), methylsulfonylmethane (MSM) (22), fish oil supplements containing omega-3 polyunsaturated fatty acids (PUFAs) (23, 24), garlic (25–27), ginseng (28, 29), ginkgo biloba (30), saw palmetto (31), and pycnogenol-containing supplements (32, 33). Despite the suggested antiinflammatory properties of these supplements, evidence in humans remains limited. Of these supplements, omega-3 PUFA supplementation has been the best studied, with recent randomized controlled trial evidence suggesting that omega-3 supplements reduce inflammation (34, 35).

Given the current gap in our knowledge about the biologic effects of these supplements and the need for safe and effective measures to reduce inflammation, study of these supplements is warranted. We used data collected in the National Health and Nutrition Examination Survey (NHANES) to assess whether the aforementioned supplements are associated with inflammation in US adults, with inflammation being measured by serum high-sensitivity C-reactive protein (hs-CRP) concentration.

MATERIALS AND METHODS

Data source/study population

The analyses were based on data collected as part of the 1999–2000, 2001–2002, and 2003–2004 cycles of NHANES, a nationally representative cross-sectional survey of civilian, noninstitutionalized persons living in the United States (National Center for Health Statistics, online data (http://www.cdc.gov/nchs/nhanes.htm); 36). These cycles were selected because they included data on the exposures (supplements), the outcome (hs-CRP), and covariates of interest.

Information on health and health behaviors was collected during an at-home interview, with further data collection, physical examination, and laboratory testing conducted in a subset of participants at NHANES mobile examination centers. NHANES, a stratified, complex, multistage probability-based survey, oversamples persons aged ≥60 years, persons with low incomes, and persons in certain racial/ethnic groups. All participants are assigned weights to account for the unequal sampling probability.

Of the 12,063 persons aged 25 years or more for whom hs-CRP was measured, we further excluded 198 persons with outlying C-reactive protein (CRP) values (those with CRP values in the top 2% for their age group, gender, and body mass index category). We did this in order to exclude persons with acute illness, since the definition of outlying values may vary across such factors as age, gender, and body mass index (37). For example, among underweight and normal-weight men aged 25–39 years, the 98th percentile was 10.7 mg/L, while the 98th percentile for severely obese men aged ≥60 years was 30.3 mg/L. Corresponding 98th percentiles were higher among women (18.5 mg/L and 38.3 mg/L, respectively). We further excluded women aged 25–59 years with positive or unknown pregnancy test results ($n = 524$), as well as participants who had missing dietary data or who failed dietary quality-control checks ($n = 963$; described below) or who had missing information on the other covariates or exposures of interest: educational status ($n = 25$), smoking status ($n = 19$), measured height/weight ($n = 356$), physical activity ($n = 11$), aspirin/NSAID use ($n = 28$), statin use ($n = 20$), diabetes history ($n = 4$), history of coronary heart disease, angina, or myocardial infarction ($n = 63$), joint pain or arthritis ($n = 117$), memory loss/confusion ($n = 10$), or use of any supplements in the last 30 days ($n = 18$). The above reasons were not mutually exclusive; some persons were eliminated for more than one reason. After making these exclusions, 9,947 participants remained for analysis.

All participants provided informed consent, and the survey was approved by the NHANES Institutional Review Board. NHANES data are publicly available and do not require University of Washington Institutional Review Board approval.

Supplement use

The NHANES interview included a series of questions related to use of dietary supplements. Participants who indicated that they had used supplements in the 30 days prior to interview were asked to list all of the supplements they had used during this period and to provide information on the use of each supplement, including usual frequency of use. Information on each reported supplement was then linked to a database containing information on the ingredients in each type of supplement, which was then used to identify individual supplements and supplement combinations containing the ingredients of interest. We abstracted information on use of specialty supplements hypothesized to reduce inflammation, including glucosamine, chondroitin, MSM, fish oil, garlic, ginseng, pycnogenol-containing supplements (grape-seed extract, pine bark), ginkgo, and saw palmetto. Regular use (yes/no) of a given supplement was defined as use of a supplement during the month prior to baseline as well as a usual frequency of at least 20 days/month. Persons reporting no use were considered nonusers, and those reporting usual use on fewer than 20 days/month were excluded from supplement-specific analyses, as were persons missing information on usual frequency of use.

Outcome (hs-CRP)

CRP, an acute-phase protein synthesized as a result of inflammation, was used as a measure of inflammation in this study. Serum hs-CRP was measured by means of latex-enhanced nephelometry (38), with reported values ranging from 0.1 mg/L to 50.5 mg/L. The lower detectable limit of this hs-CRP assay was 0.2 mg/L; values below this lower detectable limit were assigned a value of 0.1 mg/L in NHANES. To normalize the right-skewed data distribution, hs-CRP values were log-transformed, and all analyses used these log-transformed values as a continuous measure of inflammation. Values have been exponentiated for presentation.

Covariates

Covariates used for adjustment were selected a priori based on associations with CRP in prior studies (39–53). All adjusted models included age (25–29, 30–39, 40–49, 50–59, 60–69, or ≥70 years) and gender.

Multivariate analyses were additionally adjusted for race/ethnicity (non-Hispanic white, Mexican-American, other Hispanic, non-Hispanic black, or mixed race/other), education (less than high school, high school graduation or equivalent, some college/associate's degree, college graduation or above), cigarette smoking history (current, former, or never smoker), and body mass index (weight (kg)/height $(m)^2$), with weight and height measured at interview. Body

Table 1. Medical and Sociodemographic Characteristics of Participants and Their Associations With C-Reactive Protein Concentration, National Health and Nutrition Examination Survey, 1999–2004

Characteristic	No. of Subjects	Weighted %	Unadjusted Geometric Mean CRP Level, mg/L		Multivariate-Adjusted Geometric Mean CRP Level, mg/L[a]	
			Mean	95% CI	Mean	95% CI
Demographic factors						
Age group, years						
25–29	820	9.22	1.31	1.16, 1.48	1.47	1.30, 1.66
30–39	1,746	22.16	1.56	1.45, 1.68	1.59	1.49, 1.69
40–49	1,952	23.50	1.77	1.62, 1.94	1.72	1.60, 1.85
50–59	1,488	18.68	2.10	1.95, 2.27	2.04	1.92, 2.18
60–69	1,791	13.51	2.64	2.48, 3.21	2.44	2.28, 2.61
≥70	2,150	12.93	2.42	2.31, 2.55	2.58	2.42, 2.75
Gender						
Male	4,976	48.73	1.57	1.49, 1.65	1.58	1.51, 1.67
Female	4,971	51.27	2.28	2.16, 2.41	2.26	2.14, 2.38
Race/ethnicity						
Non-Hispanic white	5,259	74.84	1.86	1.77, 1.95	1.88	1.81, 1.97
Mexican-American	2,209	6.52	2.04	1.86, 2.23	2.07	1.92, 2.24
Other Hispanic	430	4.97	1.91	1.69, 2.15	1.94	1.73, 2.17
Non-Hispanic black	1,742	9.51	2.37	2.16, 2.60	1.93	1.77, 2.11
Other	307	4.15	1.56	1.30, 1.86	1.81	1.55, 2.12
Education						
Less than high school graduation	3,136	19.38	2.36	2.21, 2.52	2.00	1.88, 2.13
High school graduation/GED or equivalent	2,357	25.50	2.09	1.99, 2.21	1.95	1.84, 2.06
Some college or associate's degree	2,504	28.83	1.92	1.81, 2.03	1.88	1.78, 1.99
College graduation or above	1,950	26.30	1.46	1.35, 1.58	1.80	1.69, 1.93
Lifestyle factors						
Smoking history						
Never smoker	4,937	49.19	1.81	1.71, 1.91	1.80	1.72, 1.89
Former smoker	2,896	27.78	1.97	1.86, 2.09	1.83	1.72, 1.94
Current smoker	2,114	23.04	2.03	1.91, 2.15	2.23	2.09, 2.37
Body mass index[b] category						
Underweight (<18.5)	135	1.64	0.75	0.59, 0.96	0.73	0.57, 0.95
Normal-weight (18.5–<25)	2,855	31.17	1.08	1.01, 1.14	1.09	1.03, 1.15
Overweight (25–<30)	3,711	35.65	1.82	1.72, 1.91	1.86	1.77, 1.96
Obese (30–<35)	1,969	19.07	2.94	2.75, 3.13	2.88	2.70, 3.07
Severely obese (≥35)	1,277	12.47	5.22	4.83, 5.65	4.85	4.49, 5.23
Leisure-time physical activity level, MET-minutes/week						
None	4,450	36.34	2.41	2.26, 2.57	2.06	1.94, 2.19
Low (>0–<600)	2,167	24.48	1.91	1.79, 2.05	1.87	1.76, 1.99
High (≥600)	3,330	39.18	1.52	1.44, 1.61	1.78	1.70, 1.86
Dietary factors						
Vitamin E supplement use						
No	8,753	86.91	1.91	1.84, 1.99	1.91	1.84, 1.99
Yes	1,194	13.09	1.81	1.67, 1.97	1.82	1.68, 1.97

Table continues

Table 1. Continued

Characteristic	No. of Subjects	Weighted %	Unadjusted Geometric Mean CRP Level, mg/L		Multivariate-Adjusted Geometric Mean CRP Level, mg/L[a]	
			Mean	95% CI	Mean	95% CI
Quintile of dietary fiber intake, g/day						
Q1 (≤8.4)	1,990	19.05	2.25	2.08, 2.43	2.12	1.97, 2.28
Q2 (>8.4–≤12.1)	1,989	20.13	2.14	1.98, 2.32	2.01	1.87, 2.16
Q3 (>12.1–≤16.2)	2,004	20.67	2.02	1.87, 2.18	1.98	1.76, 2.10
Q4 (>16.2–≤22.1)	1,975	19.96	1.82	1.68, 1.97	1.84	1.72, 1.96
Q5 (>22.1)	1,989	20.18	1.41	1.30, 1.53	1.61	1.49, 1.74
Quintile of dietary fat intake, g/day						
Q1 (≤44)	1,990	16.79	1.99	1.83, 2.17	1.78	1.58, 2.01
Q2 (>44–≤60)	1,989	18.86	1.94	1.79, 2.11	1.81	1.67, 1.97
Q3 (>60–≤78)	1,990	19.65	2.00	1.87, 2.14	1.97	1.87, 2.08
Q4 (>78–≤105)	1,989	20.46	1.88	1.75, 2.01	1.93	1.81, 2.05
Q5 (>105)	1,989	24.24	1.75	1.60, 1.93	1.98	1.79, 2.18
Quintile of total energy intake, kcal/day						
Q1 (≤1,336)	1,992	16.77	2.28	2.11, 2.46	1.82	1.64, 2.04
Q2 (>1,336–≤1,708)	1,989	18.74	2.08	1.92, 2.26	1.88	1.71, 2.07
Q3 (>1,708–≤2,113)	1,989	19.76	1.92	1.80, 2.05	1.84	1.72, 1.97
Q4 (>2,113–≤2,693)	1,988	21.21	1.89	1.75, 2.04	2.00	1.86, 2.16
Q5 (>2,693)	1,989	23.51	1.55	1.43, 1.68	1.93	1.75, 2.13
Medical factors						
Medication use						
Aspirin use[c]						
No	8,632	87.58	1.85	1.77, 1.93	1.91	1.83, 1.98
Yes	1,315	12.42	2.33	2.15, 2.53	1.85	1.71, 2.00
Nonaspirin NSAID use[c]						
No	9,605	96.03	1.89	1.81, 1.96	1.90	1.83, 1.98
Yes	342	3.97	2.25	1.85, 2.74	1.81	1.54, 2.12
Statin use						
No	8,760	89.04	1.87	1.79, 1.95	1.93	1.86, 2.01
Yes	1,187	10.96	2.16	1.98, 2.36	1.68	1.53, 1.85
Medical history						
Diabetes mellitus						
No	8,734	91.11	1.82	1.75, 1.90	1.89	1.81, 1.98
Borderline	150	1.22	2.48	1.81, 3.39	1.81	1.39, 2.35
Yes	1,063	7.67	3.00	2.67, 3.36	2.02	1.84, 2.21
Heart disease[d]						
No	9,033	92.40	1.84	1.77, 1.92	1.88	1.81, 1.95
Yes	914	7.60	2.74	2.44, 3.08	2.20	2.00, 2.42
Arthritis or joint pain not due to injury						
No, neither	5,405	56.71	1.63	1.55, 1.71	1.87	1.78, 1.96
Yes, either	4,542	43.29	2.33	2.22, 2.44	1.95	1.85, 2.05

Table continues

Table 1. Continued

Characteristic	No. of Subjects	Weighted %	Unadjusted Geometric Mean CRP Level, mg/L		Multivariate-Adjusted Geometric Mean CRP Level, mg/L[a]	
			Mean	95% CI	Mean	95% CI
Memory loss/confusion						
No	9,114	93.23	1.86	1.79, 1.94	1.89	1.81, 1.97
Yes	833	6.77	2.53	2.26, 2.85	2.11	1.87, 2.37

Abbreviations: CI, confidence interval; CRP, C-reactive protein; GED, General Education Diploma; MET, metabolic equivalent of task; NSAID, nonsteroidal antiinflammatory drug; Q, quintile.

[a] Adjusted for all factors in the table except arthritis/joint pain not due to injury and memory loss/confusion.

[b] Weight (kg)/height $(m)^2$.

[c] Aspirin/nonaspirin NSAID use was defined as use of the product every day or nearly every day in the last 30 days among persons who report use of pain relievers taken nearly every day for 1 month or longer.

[d] Heart disease was defined by a report of physician-diagnosed coronary heart disease, angina, or myocardial infarction.

mass index was categorized as follows: <18.5 (underweight), 18.5–<25 (normal-weight), 25–<30 (overweight), 30–<35 (obese), and ≥35 (severely obese).

We also adjusted for leisure-time physical activity. Among participants who reported engaging in moderate or vigorous leisure-time physical activity in the last month, we calculated the metabolic equivalent of task (MET)-minutes for each reported activity, after which we summed the MET-minutes per person across all reported activities. This variable is presented as average MET-minutes of leisure-time physical activity per week and was categorized into 3 groups (no reported leisure-time physical activity, <600 MET-minutes/week, and ≥600 MET-minutes/week).

All fully adjusted models additionally included use of vitamin E supplements and 3 dietary variables (dietary fiber, fat, and total energy intake), with dietary intake determined by 1- or 2-day recall (a second recall was included where available). Each recall ascertained dietary intake in the 24-hour period prior to dietary interview (midnight to midnight), and information was collected at the time of examination or by telephone after examination. Approximately 32% of the study population had a second day's worth of reliable recall information collected. Information on this second day of recall was collected only for the 2003–2004 cycle, and the information was collected at least 3 days after the initial recall, with the number of days between recalls varying (36). For participants with a second reliable day of recall, we averaged intake over the two recalls to better estimate usual intake. If a given dietary recall was deemed unreliable according to NHANES criteria, data from the recall were unavailable and therefore excluded. We further excluded men reporting an average energy intake of <800 kcal/day or >5,000 kcal/day, as well as women reporting an average energy intake of <600 kcal/day or >4,000 kcal/day. Dietary factors were categorized into quintiles based on the distribution of raw numbers in the final data set.

We also adjusted for current aspirin use and current nonaspirin NSAID use (yes/no, both defined as daily or nearly daily use in the last 30 days), as well as current statin use (yes/no, ascertained from a database of current medications). Adjustment was also made for history of medical conditions associated with CRP levels, including diagnosis of diabetes (yes, no, or borderline; gestational diabetes was excluded) and history of heart disease (diagnosis of coronary heart disease, angina, or myocardial infarction by a health professional). Finally, where available, we adjusted for the main indications of supplement use. For supplements for which joint pain/arthritis is considered an indication for use (glucosamine, chondroitin, MSM, fish oil), results were additionally adjusted for joint pain/arthritis, defined as a report of physician-diagnosed arthritis or a report of joint pain not caused by injury. Analyses of supplements indicated for memory loss (fish oil, ginkgo) were further adjusted for self-reported memory loss/confusion.

Statistical analysis

Linear regression was used to model the association between regular use of each supplement and log-transformed hs-CRP, adjusted for covariates:

$$\ln(\text{hs-CRP}) = \alpha + \beta 1 \times X1 + \beta 2 \times X2 + \ldots$$

where $X1$ and $X2$, etc., are indicator variables for each category of the independent variables. We present the results as e^{β}, which represents the ratio of geometric mean hs-CRP concentrations among persons in the category of interest to those in the reference category (e.g., the ratio of hs-CRP levels among regular glucosamine users to hs-CRP levels among nonusers). Analyses were adjusted for age group and gender in an initial model and multivariate-adjusted for the factors previously described in a fully adjusted model. We considered additional adjustment for alcohol consumption, as well as substitution of waist circumference for body mass index and saturated fat intake for total fat intake. Inclusion of these variables did not materially change the observed associations between specialty supplement use and hs-CRP; therefore, results from this alternative model are not presented. We also conducted stratified analyses to assess whether the associations between regular supplement use and hs-CRP varied by gender. Tests for multiplicative

interaction between supplement use and gender in an unstratified model were conducted, with statistical significance of the resulting 2-sided P values being assessed at the $\alpha = 0.05$ level.

Because of the stratified multistage sampling design of the NHANES data, analyses were weighted to reflect sampling probabilities, so as to allow for representation of the US population. All statistical analyses were conducted using Stata software, version 11 (StataCorp LP, College Station, Texas).

RESULTS

As Table 1 shows, hs-CRP was positively associated with increasing age and body mass index. In multivariate-adjusted models, persons with a body mass index over 35 had a geometric mean hs-CRP concentration of 4.85 mg/L, while persons with a body mass index less than 18.5 had a geometric mean hs-CRP concentration of 0.73 mg/L. Hs-CRP levels were inversely associated with education and physical activity. Furthermore, women had higher hs-CRP levels than men, current smokers had higher hs-CRP levels than nonsmokers, and persons with a history of heart disease had higher hs-CRP levels than those without heart disease. Increasing dietary fiber intake was associated with decreased hs-CRP levels, and statin use was associated with lower hs-CRP levels. However, vitamin E supplement use, dietary energy intake, dietary fat intake, diabetes, aspirin use, nonaspirin NSAID use, arthritis/joint pain, and memory loss did not appear to be associated with hs-CRP levels in the multivariate-adjusted estimates.

Table 2 presents the associations of regular use of specialty supplements (≥20 days/month) with CRP levels. The weighted percentage of regular use ranged from 1.2% for MSM use to 4.4% for ginseng use. In the fully adjusted model, regular use of glucosamine was associated with a statistically significant 17% reduction in hs-CRP levels (as compared with nonuse) (ratio = 0.83, 95% confidence interval (CI): 0.74, 0.93) and chondroitin was associated with a 22% reduction in hs-CRP (ratio = 0.78, 95% CI: 0.67, 0.92). Regular use of fish oil was also associated with a significant 16% reduction in hs-CRP levels (ratio = 0.84, 95% CI: 0.71, 0.997). Use of any of the remaining supplements (MSM, garlic, ginseng, ginkgo, saw palmetto, and pycnogenol-containing supplements) was not statistically significantly associated with hs-CRP.

Furthermore, we observed significant interactions by gender for the associations of glucosamine use with hs-CRP (P-interaction = 0.05) and chondroitin use with hs-CRP (P-interaction = 0.03). Among women, regular glucosamine use was associated with a 27% reduction in hs-CRP (ratio = 0.73, 95% CI: 0.61, 0.88), and regular chondroitin use was associated with a 33% reduction in hs-CRP (ratio = 0.67, 95% CI: 0.53, 0.84), while the associations among men were small and nonsignificant. Lastly, we observed a significant interaction between ginseng use and gender (P-interaction = 0.03), with the association being evident in men (ratio = 0.84; 95% CI: 0.72, 0.98) but not in women.

DISCUSSION

In a representative sample of the US adult population, we observed use of glucosamine, chondroitin, and fish oil supplements to be associated with reduced inflammation, as measured by hs-CRP concentration. The magnitude of reduction in hs-CRP was 16%–22% for these supplements, comparable to what we and others have observed for the association between statin use and CRP (44, 50). Comparison with the effects of aspirin was not possible, since we and other investigators (54–57) have found no clear reduction in CRP levels with aspirin use, perhaps because aspirin may affect inflammation without affecting CRP (58, 59).

In our study, the percentages of persons reporting use of glucosamine, chondroitin, and fish oil were slightly lower than was reported in a recent study of US adults aged 57–85 years (60). These differences are largely a reflection of the age of the population included, as older adults are more likely to use these supplements. Differences in study years and exclusion of irregular users may also contribute to varying prevalence estimates across studies.

To our knowledge, this is the largest study that has investigated the association between use of glucosamine and chondroitin supplements and a marker of inflammation in humans. Our finding of lower hs-CRP levels among users of glucosamine and chondroitin supports laboratory studies which suggest that glucosamine and chondroitin supplementation may reduce inflammation via inhibition of nuclear factor kappa B activation (14, 61–63). Nuclear factor kappa B is a transcription factor which lies upstream of many inflammatory processes, including CRP. Laboratory studies have further shown that these compounds also affect factors downstream of nuclear factor kappa B, such as cyclooxygenase activity, as well as the proinflammatory cytokines interleukin-6 and tumor necrosis factor alpha (14–18, 64–66). Despite this suggestive laboratory evidence, we know of only 2 small studies on glucosamine or chondroitin supplement use and inflammation in humans. In a randomized controlled trial of rheumatoid arthritis patients, Nakamura et al. (67) randomized 25 persons to receive glucosamine and 26 to receive placebo for 12 weeks. In that study, Nakamura et al. reported no effect of glucosamine on CRP levels; however, persons with rheumatoid arthritis have higher levels of systemic inflammation than the general population, and therefore results from that study may not be generalizable to persons without chronic inflammatory conditions (67). A second randomized controlled trial was conducted in which 36 osteoarthritis patients were given a glucosamine hydrochloride and chondroitin sulfate compound and 17 were given placebo (19). After the 3-month intervention period, the investigators observed a significant decrease in serum prostaglandin E_2 concentrations among persons treated with glucosamine ($P < 0.01$) (19). We know of no other human studies on the association between use of these supplements and inflammation.

Our results suggest a biologic mechanism to substantiate the epidemiologic observation of an association between glucosamine and chondroitin use and reduced risk of chronic diseases. In observational studies carried out within

Table 2. Association of Regular Use[a] of Specialty Dietary Supplements With C-Reactive Protein Concentration, National Health and Nutrition Examination Survey, 1999–2004

Supplement	No. of Subjects[b]	Weighted %	Unadjusted Geometric Mean CRP Concentration, mg/L		Age- and Sex-Adjusted Ratio		Multivariate-Adjusted Ratio		Stratified Multivariate-Adjusted Ratio				*P* for Interaction[c]
									Men		Women		
			Mean	95% CI	Ratio[d]	95% CI	Ratio[d,e]	95% CI	Ratio[d,e]	95% CI	Ratio[d,e]	95% CI	
Glucosamine[f]													0.05
No	9,513	95.82	1.90	1.83, 1.98	1	Referent	1	Referent	1	Referent	1	Referent	
Yes	361	4.18	1.89	1.60, 2.22	0.83	0.71, 0.98	0.83	0.74, 0.93	0.95	0.83, 1.08	0.73	0.61, 0.88	
Chondroitin[f]													0.03
No	9,651	97.19	1.91	1.83, 1.98	1	Referent	1	Referent	1	Referent	1	Referent	
Yes	252	2.81	1.75	1.46, 2.10	0.76	0.62, 0.92	0.78	0.67, 0.92	0.93	0.78, 1.12	0.67	0.53, 0.84	
Methylsulfonylmethane[f]													0.08
No	9,807	98.79	1.90	1.83, 1.98		Referent	1	Referent	1	Referent	1	Referent	
Yes	116	1.21	1.96	1.53, 2.51	0.88	0.68, 1.15	0.87	0.66, 1.15	1.09	0.83, 1.43	0.69	0.46, 1.05	
Fish oil[g]													0.88
No	9,746	97.84	1.91	1.84, 1.99	1	Referent	1	Referent	1	Referent	1	Referent	
Yes	167	2.16	1.49	1.18, 1.89	0.69	0.56, 0.86	0.84	0.71, 1.00	0.86	0.64, 1.16	0.85	0.70, 1.03	
Garlic													1.00
No	9,595	96.78	1.90	1.83, 1.98	1	Referent	1	Referent	1	Referent	1	Referent	
Yes	296	3.22	1.90	1.58, 2.28	0.94	0.78, 1.13	0.97	0.83, 1.13	0.98	0.81, 1.20	0.96	0.79, 1.17	
Ginseng													0.03
No	9,478	95.57	1.92	1.85, 2.00	1	Referent	1	Referent	1	Referent	1	Referent	
Yes	370	4.43	1.58	1.36, 1.84	0.85	0.74- 0.99	0.92	0.81, 1.04	0.84	0.72, 0.98	1.06	0.87, 1.28	
Pycnogenol (grape seed/pine bark)													0.60
No	9,760	98.1	1.91	1.83, 1.99	1	Referent	1	Referent	1	Referent	1	Referent	
Yes	142	1.90	1.66	1.33, 2.06	0.84	0.67, 1.06	0.88	0.73, 1.06	0.88	0.71, 1.09	0.9	0.69, 1.19	
Ginkgo[h]													0.40
No	9,571	96.42	1.92	1.84, 2.00	1	Referent	1	Referent	1	Referent	1	Referent	
Yes	297	3.58	1.58	1.32, 1.89	0.79	0.67, 0.93	0.91	0.80, 1.03	0.88	0.76, 1.02	0.95	0.75, 1.19	

Table continues

Table 2. Continued

Supplement	No. of Subjects[b]	Weighted %	Unadjusted Geometric Mean CRP Concentration, mg/L		Age- and Sex-Adjusted Ratio		Multivariate-Adjusted Ratio		Stratified Multivariate-Adjusted Ratio				
									Men		Women		
			Mean	95% CI	Ratio[d]	95% CI	Ratio[d,e]	95% CI	Ratio[d,e]	95% CI	Ratio[d,e]	95% CI	*P* for Interaction[c]
Saw palmetto[i]													
No	4,803	97.09	1.59	1.51, 1.67	1	Referent	1	Referent	1	Referent			
Yes	137	2.91	1.27	1.03, 1.58	0.74	0.59, 0.93	0.85	0.69, 1.06	0.85	0.69, 1.06			

Abbreviations: CI, confidence interval; CRP, C-reactive protein.

[a] Regular use was defined as use in the past 30 days with a reported frequency of use of ≥20 days/month.

[b] Data do not total 9,947 for all supplements because some persons were excluded from supplement-specific analyses if they were missing information on frequency of use or if they reported usual use on fewer than 20 days/month.

[c] Two-sided *P* for interaction, tested at the $\alpha = 0.05$ level.

[d] Ratio of CRP levels among persons who reported regular use of a given supplement versus persons who reported no use/irregular use.

[e] Adjusted for age, gender, race/ethnicity, education, smoking history, body mass index, physical activity, vitamin E supplement use, dietary fiber intake, dietary fat intake, total energy intake, aspirin use, use of nonaspirin nonsteroidal antiinflammatory drugs, statin use, diabetes, and coronary heart disease.

[f] The multivariate model additionally adjusted for arthritis and/or joint pain not caused by injury.

[g] The multivariate model additionally adjusted for arthritis and/or joint pain not caused by injury, as well as memory loss/confusion.

[h] The multivariate model additionally adjusted for memory loss/confusion.

[i] Analyses were limited to men.

the VITamins And Lifestyle (VITAL) cohort, use of glucosamine and/or chondroitin was associated with reduced risk of colorectal cancer (68) and lung adenocarcinoma (69). Aspirin use follows a similar pattern: In combined analyses of randomized controlled trial results, aspirin use has been shown to reduce risk of both colorectal cancer (7) and death from lung adenocarcinoma (70). The VITAL study also found a reduction in total mortality associated with glucosamine and chondroitin use (71); similarly, aspirin use has been associated with reduced total mortality in some observational studies (72) and trials (73). Lastly, in the present study, the associations between glucosamine and chondroitin supplement use and CRP appear to have been largely driven by the associations in women, and in the VITAL study of lung cancer risk, Brasky et al. (69) also observed a greater protective effect of these supplements among women. While the biologic mechanism underlying this interaction is unclear, it is feasible that these observed gender differences may reflect differential bioavailability or metabolism by gender (74, 75).

Regular use of fish oil supplements was associated with lower CRP concentrations. Fish oil contains long-chain omega-3 PUFAs, such as eicosapentaenoic acid and docosahexaenoic acid. These omega-3 PUFAs are thought to reduce inflammation in several ways, including inhibition of nuclear factor kappa B activation and competitive inhibition of proinflammatory omega-6 PUFAs. Omega-3 PUFAs compete with omega-6 PUFAs for the cyclooxygenase 2 enzyme and displace omega-6 stores in cell membranes (24, 76, 77). There have been numerous human trials of omega-3 supplements and CRP or other markers of inflammation, primarily small trials of subjects at high risk of cardiovascular disease (78, 79). Two reviews published in 2006 concluded that the trials were inconsistent and inconclusive (78, 79). More recently, however, 2 larger randomized controlled trials of omega-3 supplementation found that the supplements reduced circulating CRP (34, 35) and tumor necrosis factor alpha (35) levels. These studies, plus our current study in a representative US population, provide evidence for the antiinflammatory effects of long-chain omega-3 PUFAs in humans, and they support one of several mechanisms (78, 80, 81) by which long-chain omega-3 PUFA intake may reduce the risk of cardiovascular disease (82), some cancers (68, 83–85), and total mortality (71, 82).

Despite the lack of a main effect for ginseng supplementation, we observed significant interaction between gender and ginseng use, with the association with CRP being evident among men but not women. Ginseng has been shown to be associated with reduced nuclear factor kappa B and cyclooxygenase expression in laboratory studies, though this hypothesis has not been widely tested, nor has it been studied in vivo among humans, to our knowledge (28, 29). It is interesting to note that in a cohort study, Yi et al. (86) reported an inverse association between ginseng use and total mortality—an association which was similarly limited to men.

We did not observe significant associations between CRP and any of the following supplements: MSM, pycnogenol-containing supplements, garlic, ginkgo, or saw palmetto. Power may have been limited to detect associations

in less commonly used supplements; it is also possible that these supplements may affect inflammation downstream of CRP or that these supplements may not be associated with inflammation in humans.

This study allowed us to address previously unexplored questions in a large, nationally representative population; however, it was not without limitations. First, glucosamine and chondroitin are often taken together in a single supplement, with about two-thirds of users taking a supplement containing both compounds and one-third taking glucosamine only (MSM is also included in some formulations). Thus, the observed associations between glucosamine and chondroitin and CRP in this study are not independent and may be due to the biologic activity of one or both of these supplements. In addition, we were unable to assess supplement use on the day of blood collection and did not explore the effect of cumulative dose on inflammation. We were, however, able to ascertain usual frequency of use and were able to limit the definition of use to regular use. While there may have been some measurement error in the classification of regular users versus nonusers, such misclassification would likely have been nondifferential across the population. The reliability of CRP measurements in short-term studies appears to be good (87), suggesting that 1 CRP measurement is sufficient to examine the relation between supplement use and CRP concentration at approximately the same point in time. Even so, we cannot exclude the possibility of measurement error. We were not able to adjust for strength of aspirin dose, as information on dose was not collected for all study cycles, nor were we able to adjust for the indications for use of all supplements. However, for those supplements with apparently significant associations (glucosamine, chondroitin, and fish oil), we were able to adjust for the primary indications for use. Further, adjustment for dietary factors was ascertained from 1- or 2-day recall, which may not be representative of true normal diet. Because these data were collected in an observational setting, we cannot discount the potential for residual confounding by lifestyle factors. While we might expect specialty supplement users to engage in healthier behaviors, it is important to note that the primary indications for glucosamine, chondroitin, and fish oil use are adverse health conditions (arthritis/joint pain, coronary artery disease). Furthermore, results were robust to multivariate adjustment, and the multivariate-adjusted predictors of inflammation in Table 1 correspond well with expectations based on the literature.

In summary, this study adds support to laboratory research and to some human studies which suggest that glucosamine, chondroitin, and fish oil may reduce systemic inflammation. In doing so, this study adds biologic plausibility to previous studies which have shown beneficial effects of these supplements on chronic diseases. Given the number of diseases with which inflammation is associated, such as cancer and cardiovascular disease, there is a need to find safe and effective ways to reduce inflammation. Research suggests that these 3 supplements have excellent safety profiles (88–92), supporting their potential role in disease prevention. It is therefore important that the potential antiinflammatory role of these supplements be further investigated.

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