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Use of Glucosamine and Chondroitin in Relation to Mortality

Griffith A. Bell[1,2], **Elizabeth D. Kantor**[1,2], **Johanna W. Lampe**[1,3], **Danny D. Shen**[4,5], and **Emily White**[1,2]

[1]The Fred Hutchinson Cancer Research Center, Cancer Prevention Program, 1100 Fairview Ave. N., Seattle, WA 98109, USA

[2]Department of Epidemiology, University of Washington, Seattle, WA 98195, USA

[3]Department of Epidemiology and Interdisciplinary Program in Nutritional Sciences, University of Washington, Seattle, WA 98109, USA

[4]Department of Pharmacy and Pharmaceutics, School of Pharmacy, University of Washington, Seattle, WA 98109, USA

[5]The Fred Hutchinson Cancer Research Center, Clinical Research Division, 1100 Fairview Ave. N., Seattle, WA 98109, USA

Abstract

Background—Glucosamine and chondroitin are products commonly used by older adults in the US and Europe. There is limited evidence that they have anti-inflammatory properties, which could provide risk reduction of several diseases. However, data on their long-term health effects is lacking.

Objective—To evaluate whether use of glucosamine and chondroitin are associated with cause-specific and total mortality.

Design—Participants (n = 77 510) were members of a cohort study of Washington State (US) residents aged 50–76 y who entered the cohort in 2000–2002 by completing a baseline questionnaire that included questions on glucosamine and chondroitin use. Participants were followed for mortality through 2008 (n = 5362 deaths). Hazard ratios for death adjusted for multiple covariates were estimated using Cox models.

Results—Current (baseline) glucosamine and chondroitin use were associated with a decreased risk of total mortality compared to never use. The adjusted hazard ratio (HR) associated with current use of glucosamine (with or without chondroitin) was 0.82 (95% CI 0.75–0.90) and 0.86 (95% CI 0.78–0.96) for chondroitin (included in two-thirds of glucosamine supplements). Current use of glucosamine was associated with a significant decreased risk of death from cancer (HR 0.87 95% CI 0.76–0.98) and with a large risk reduction for death from respiratory diseases (HR 0.59 95% CI 0.41–0.83).

Conclusions—Use of glucosamine with or without chondroitin was associated with reduced total mortality and with reductions of several broad causes of death. Although bias cannot be ruled out, these results suggest that glucosamine may provide some mortality benefit.

Keywords

glucosamine; chondroitin; supplements; mortality; cohort; cancer

Corresponding Author: Griffith Bell, phone: 1.206.667.4068, gabell@fhcrc.org.

Glucosamine and chondroitin are commonly used preparations typically taken for osteoarthritis and joint pain. While in many European countries glucosamine and chondroitin are approved prescription drugs, in the United States, they are sold over-the-counter as dietary supplements. In the United Sates, glucosamine and chondroitin supplements are often taken together in one pill, and are among the most frequently used drugs by older adults (1). An estimated 7.4% of Americans age 57–85 used these supplements in 2005–06 (1), comparable in prevalence to use of acetaminophen and metformin (1).

Despite the popularity of these drugs, studies of their efficacy have yielded inconsistent results, with the most recent and best designed trials reporting no benefit for treatment of osteoarthritis (2–6). Furthermore, even though the European League Against Rheumatism rated glucosamine and chondroitin as two of the safest drugs for osteoarthritis(3), there are no large follow-up studies of the long-term adverse or beneficial effects of these supplements on conditions other than osteoarthritis. Nonetheless, evidence from laboratory, animal and a few human studies suggest that glucosamine and chondroitin have anti-inflammatory properties (7–10) which could reduce the risk of multiple diseases. Specifically, chronic inflammation has been linked to cancer (11), chronic obstructive pulmonary disease (12), and cardiovascular disease (13, 14).

Recently, we reported results of an exploratory study of total mortality in relation to use of 20 less commonly used vitamin, mineral and non-vitamin, non-mineral supplements among participants in the VITamins And Lifestyle (VITAL) cohort study (15). Glucosamine and chondroitin were two of only three supplements that were associated with decreased mortality after controlling for a large number of health and lifestyle factors, including osteoarthritis or joint pain. The hazard ratio (HR) for death comparing persons with high intake (≥4 days/week for ≥3 years) to non-users was 0.83 (95% CI: 0.72, 0.97) (P for trend = 0.01) for glucosamine and 0.83 (95% CI: 0.69, 1.00) (P for trend = 0.01) for chondroitin (15). These findings are intriguing because use of the anti-inflammatory drug aspirin has been found to be associated with reduced risk of total mortality and cancer mortality (16, 17). Therefore, we have expanded our previous report on the relation of glucosamine and chondroitin use and mortality to include associations by formulation (e.g., glucosamine alone), effect modification by factors associated with inflammation, and cause-specific mortality in the VITAL cohort, with two additional years of follow-up.

MATERIALS AND METHODS

Study population and study overview

The VITAL cohort study is a prospective study of men and women aged 50–76, and has been described in detail elsewhere (18). The study population was recruited from Washington State residents who lived in a 13-county area covered by a Surveillance, Epidemiology and End Results (SEER) cancer registry. A 24-page questionnaire was mailed with a cover letter targeting dietary supplement users to 364 418 potential participants from October 2000 to December 2002. 77 718 questionnaires were returned and passed eligibility and quality control checks. 45 patients who reported a condition that affected their absorption of supplements (e.g., gastric bypass surgery) were excluded. An additional 163 participants had missing information on use of both glucosamine and chondroitin, leaving 77 510 participants included in the analysis.

Ascertainment of glucosamine and chondroitin use

Information about use of glucosamine and chondroitin was ascertained by questions on current/former/never use, number of years taken and number of days per week each

supplement was used, over the 10 years prior to baseline. A separate study showed good reliability/validity when comparing our questionnaire information on supplement use with a second questionnaire given 3 months after baseline, with an in-home supplement inventory and with nutrient biomarkers (19); however, we did not specifically evaluate glucosamine and chondroitin supplement use.

Information about use of glucosamine and chondroitin was reported on the baseline questionnaire. Detailed information about glucosamine and chondroitin use was ascertained by questions on current/former/never use, number of years taken and number of days per week each supplement was used, over the 10 years prior to baseline. A separate study conducted in a sample of the cohort showed good reliability/validity when comparing baseline questionnaire information on other supplement use with a second questionnaire given 3 months after baseline, with an in-home supplement inventory, and with nutrient biomarkers (19). While several other common supplements were evaluated in this substudy, the reliability/validity of glucosamine and chondroitin use was not specifically examined.

Ascertainment of potential confounders

Potential confounders, measured on the baseline questionnaire, were selected *a priori* as factors associated with total mortality or with the diseases for which we analyzed disease-specific mortality. These included demographic factors, body mass index (BMI) at age 45 and baseline, alcohol intake at age 45 and baseline, cigarette smoking (from which we computed pack-years), average physical activity across the 10 years before baseline, aspirin and other non-steroidal anti-inflammatory drug (NSAID) use over the past 10 years, current use of cholesterol-lowering medication, years of hormone therapy and formulation, and reproductive factors. Screening information included PSA screening in the last 2 years, mammogram in the last 2 years, and sigmoidoscopy/colonoscopy in the last 10 years. Physical activity across the 10 years before baseline was measured in metabolic equivalent tasks (MET) hours per week, based on a one-page questionnaire that included 13 types of recreational physical activity (20). Participants' recall of BMI and alcohol intake at 45 years of age rather than baseline used as covariates because these estimates at 45 years of age had a stronger association with mortality than the baseline measures.

We also collected age at death of mother, age at death of father, self-rated health, and an extensive medical history. A morbidity score was created as a measure of each participant's overall risk of death at baseline. The score was created from the beta coefficients of age-adjusted, sex-specific proportional hazards models of death based on a model with 23 health conditions for men and 27 health conditions for women (listed in footnote c of Table 2). We then created a risk score for each participant, using the natural log of the coefficients for the hazard ratio for death based on the subject's own group of health conditions compared with a subject with no conditions.

Diet in the year before baseline was measured using a validated food frequency questionnaire (FFQ) modified from one developed for the Women's Health Initiative (21). To reduce the large number of possible dietary contributors to death, we evaluated the dietary factors in the US Dietary Guidelines Advisory Committee recommendations (22), and only included as adjustment factors those which were associated with total mortality in this study: daily servings of fruits, daily servings of vegetables (excluding potatoes), percent of energy from *trans* fat, and percent of energy from saturated fat.

A different set of covariates was used in each cause-specific mortality analysis, as indicated in the Table 3 footnotes. Generally, the overall morbidity score was replaced with personal history of the disease of interest (defined by participant's self-report of physician diagnosis of disease) as a better predictor of death from that cause. Age of death of mother and father

was replaced with family history of the specific disease of interest (coded as 0, 1, or 2+ first degree relatives). In addition, specific dietary, reproductive and smoking risk factors were added for some diseases, including additional reproductive (women's age at birth of first child, age at menarche), dietary (number of servings per week of red or processed meat) or smoking variables (pack-years squared, number of years smoked). Further adjustment for total energy (kcals) did not meaningfully change the results.

Finally, to control for confounding by indication, all analyses were controlled for the primary reason for use of glucosamine and chondroitin. This variable was defined as self–reported doctor diagnosis of osteoarthritis or self-report of joint pain at least half the days of the last year and was modeled as a yes/no binary variable.

Ascertainment of deaths and censoring

Deaths were ascertained by linking participant identifiers data to the Washington State death files (n = 5313), with some additional deaths identified through the Social Security Death Index (n = 42), the western Washington SEER cancer registry for those diagnosed with cancer (n = 4), or by next of kin (n = 3), for a total of 5362 deaths. In addition to the 6.9% of subjects who died, subjects were censored if they moved out of Washington state (n = 4087, 5.3%) or withdrew from the study (n = 22, 0.03%). Moves out of state were identified through the National Change of Address system, and for uncertain moves, were followed up by phone calls and mailings.

Deaths were classified according to underlying cause of death information from ICD-10 codes (23) (available only for deaths on Washington State death files). Deaths were categorized as being due to cardiovascular disease (I00-I99), cancer (C00-D48) or other causes (all other codes). Within cardiovascular disease, we also examined deaths due to ischemic heart disease (I20-I25). Within cancer deaths we examined deaths from colorectal cancer (C18-C20 and C26.0), pancreatic cancer (C25), bronchus and lung cancer (C34), breast cancer (C50), lymphoid, haematopoietic and related tissue (C81-C96), and all other cancers (C00-D48 excluding those already listed). Within the "other" causes of death, we examined diseases of the respiratory system (J00-J99).

Statistical Analysis

We used Cox proportional hazard regression with covariates to adjust for confounding to estimate hazard ratios (HR) of death comparing those who were former or current users of glucosamine and chondroitin with those who never took the supplements. Hazard ratios were calculated for death from all causes and for specific causes of death listed in Table 3, with adjustments for the factors listed in footnotes of Tables 2 and 3. Results for cause-specific mortality were stratified by history of the disease. In order to prevent many participants from being dropped from the analyses due to "missing" data on covariates, we included missing categories for confounders which had more than 5% of participants with missing data.

RESULTS

Table 1 gives the association of participant characteristics with current use of glucosamine supplements (with or without chondroitin) as reported at baseline. Current use of glucosamine was higher among older individuals, women, whites, and those with greater education. The likelihood of current use of glucosamine decreased with increasing smoking and increasing fat intake, and increased with greater body mass index (BMI), physical activity, and vegetable intake. Current users of glucosamine and chondroitin rated their health as better than non-users on average, although use of NSAIDs and report of

osteoarthritis or joint pain were higher in the users. Results were very similar when participant characteristics of current chondroitin users were examined (data not shown).

After a mean of 6.8 years of follow-up (526 403 person-years), 5362 deaths were recorded, for a death rate of 10.2 deaths per 1000 person-years. 20.2% of participants ever used glucosamine, and about two-thirds of glucosamine supplements used by participants included chondroitin and about 10% contained methylsulfonylmethane (MSM). After multivariate adjustment, current (baseline) glucosamine supplement use of any formulation was associated with a decreased risk of total mortality compared to never use (HR 0.82, 95% CI 0.75–0.90). The adjusted hazard ratios were HR 0.86 (95% CI 0.78–0.96) for chondroitin, 0.78 (95% CI 0.67–0.91) for glucosamine without chondroitin, and non-significant for MSM.

We examined whether the risk of total mortality associated with current glucosamine use was modified by sex, BMI, or smoking status. Only the interaction by sex was statistically significant (P=0.01), with the risk reduction stronger in women (HR 0.75 95%CI 0.65–0.87) than in men (HR 0.90 95% CI 0.79–1.03). When interaction by sex was further examined for cause-specific mortality, the interaction by gender was statistically significant for cardiovascular disease death (p = 0.02), with a significantly lower risk of CVD death associated with current glucosamine use among women (HR 0.71 95%CI 0.53–0.96) and no association among men (HR 1.03 95% CI 0.82–1.29). We found no significant interaction by sex for cancer mortality (p=0.24) or all other causes of mortality (p=0.15).

The risk of death associated with glucosamine supplement use was further examined for specific causes of death (Table 3). We observed a non-significant reduced risk of mortality from total cardiovascular disease (HR 0.88 95% CI 0.74–1.06), with similar results for the subcategory of ischemic heart disease. There was a significant 13% decreased risk of death from cancer among current users of glucosamine (HR 0.87 95% CI 0.76–0.98). Among the five types of cancer with the most deaths, there was a non-significant reduction in death associated with current glucosamine use for lung cancer and haematopoietic cancers, but not for colorectal, breast or pancreatic cancer. For all other cancer deaths, current use of glucosamine was associated with reduced risk (HR 0.67 95% CI 0.54–0.87). We also observed a risk reduction for current use of glucosamine and all other causes of death other than cardiovascular disease and cancer (HR 0.74 95% CI 0.56–0.81), and within those other causes, a strong specific reduction in mortality due to respiratory disease (HR 0.59 95% CI 0.41–0.83), the subcategory with the most deaths. There were no clear differences when risks of mortality for the specific causes of death were stratified by whether the participant had the disease at baseline (Table 3).

Results for current use of chondroitin with mortality were similar to those for current use of glucosamine, except that there was no association between current chondroitin use and total cancer mortality (HR 0.94 95% CI 0.81–1.10) (data not shown). When glucosamine and chondroitin were categorized by the amount of use over the 10 years prior to baseline (based on years of use and days per week), the results did not differ greatly from the never/former/current categorization (data not shown). We also conducted a sensitivity analysis, removing the first two years of follow-up for each participant. The fully-adjusted results were very similar to those presented in Tables 2 and 3. Specifically the hazard ratio for current glucosamine use with total mortality was 0.80 (95% CI 0.72–0.89), with CVD mortality was 0.84 (95% CI 0.6–1.03), with cancer mortality was 0.83 (95% CI 0.72–0.96) and with other causes of mortality was 0.75 (95% CI 0.57–0.96).

DISCUSSION

Current use of glucosamine supplements at baseline was associated with a statistically significant 18% reduced risk of total mortality compared with never users. In terms of formulation, the risk reduction was somewhat less for current users of chondroitin (included in about two-thirds of glucosamine supplements), somewhat greater for current users of glucosamine alone, with no benefit for supplements containing MSM, suggesting that there is no benefit in terms of mortality from the combinations. When specific causes of death were examined, current use of glucosamine was associated with a non-significant 12% reduced risk of death from cardiovascular disease, a significant 13% risk reduction for death from cancer and a significant 33% risk reduction for deaths from all other causes. Within the cancer deaths, there were no significant associations with the cancer sites with the highest death rates, while within the other causes of death category, current use of glucosamine was associated with a large risk reduction for death from respiratory diseases.

To our knowledge, the only human studies of glucosamine and/or chondroitin supplement use and disease outcomes other than arthritis have been conducted within the VITAL cohort. In prior studies, we found that glucosamine and chondroitin use were associated with reduced incidence of lung and colorectal cancer (24, 25), but not breast or hematologic malignancies (26, 27). Results from the current study suggest that the overall reduction in cancer mortality associated with current use of glucosamine was driven mostly by a reduced risk of death from the less common cancers, so our current findings on mortality are not consistent with our prior findings on incidence. There have been no human studies on glucosamine and chondroitin use and incidence or mortality from other major diseases. However, there is some experimental evidence that glucosamine and/or chondroitin have the capacity to modulate disease pathways *in vivo*. In several animal studies, both glucosamine and chondroitin impeded the pathogenesis of cardiovascular disease (28–32), and one small human trial found that glucosamine inhibited platelet aggregation in some subjects, similar to the effects of aspirin (33).

Because there have been no prior studies of glucosamine and chondroitin and mortality, we can compare our results to observational and randomized studies of another anti-inflammatory drug, aspirin, and risk of death from cardiovascular disease, cancer and all-cause mortality. The Iowa Women's Study reported that any use of aspirin was associated with a statistically significant 16% lower risk of cancer mortality, 25% lower risk of coronary heart disease mortality and 18% lower all-cause mortality (34). In NHANES II, aspirin users had a significant 12% reduction in all-cause mortality (35). Meta-analyses of the data from trials of aspirin in relation to cardiovascular events found that aspirin use led to a borderline significant reduced risk of all-cause mortality (OR 0.94 95% CI 0.87 – 1.00), (17) but not of cardiovascular mortality (17). In a 2011 pooled meta-analysis of eight randomized trials of aspirin, aspirin significantly reduced death due to cancer (OR 0.79 95% CI 0.68–0.92) (16). Thus there is substantial evidence that aspirin reduces the risk of death from cancer and all-causes combined, and this provides some plausibility that glucosamine may offer similar protection. In contrast, there is little evidence to support our finding that current use of glucosamine is associated with reduced risk of death from respiratory disease; however, anti-inflammatory drugs have been proposed as an approach to improve the course of chronic obstructive pulmonary disease (36, 37).

If our results reflect a causal relationship for the observed effect of glucosamine supplements on total mortality and mortality from cancer and respiratory disease, the likely mechanism is through modulation of inflammation by glucosamine and/or chondroitin. Laboratory studies suggest that glucosamine and chondroitin may affect inflammation by inhibiting the transcription factor nuclear factor kappa B (NFkB) from translocating to the

nucleus (8, 38). NFkB lies upstream of many inflammatory processes and has been implicated in several diseases, including inflammation-related cancers (39). The proposed mechanism of NFkB inhibition is additionally supported by studies which have demonstrated that glucosamine and chondroitin also inhibit inflammatory factors downstream of NFkB signaling, including IL-1β, IL-6, TNF-α, and PGE_2, as well as COX-2 expression (8, 9, 38, 40–42). These results hold in studies of glucosamine alone (8, 41), chondroitin alone (7, 38), and in studies of both supplements combined (43). In addition, a few studies have reported on the association between glucosamine and chondroitin use and biomarkers of inflammation in humans. In a recent NHANES study of nearly 10 000 adults aged 25 and older, we observed that glucosamine use and chondroitin use were each associated with significantly reduced levels of the acute-phase reactant, c-reactive protein (CRP), with larger reductions in women (10). This finding supports a previous study in which glucosamine and chondroitin administration was associated with reduced levels of PGE_2 in persons with osteoarthritis (44), although another study among rheumatoid arthritis patients found no effect of glucosamine and chondroitin on CRP levels (45).

Strengths of this study include the large sample size, the prospectively collected data on a large number of covariates, and ascertainment of deaths by linkage to death records. Limitations include the possibility of bias from confounding because glucosamine and chondroitin use is associated with several positive health behaviors (although use of these supplements was also associated with some adverse health conditions such as osteoarthritis and higher BMI), bias due to reverse causality because ill health could have prompted participants to start or stop taking glucosamine, or selection bias if people who were taking supplements and were more (or less) healthy opted to join the study. To account for these biases, we controlled for numerous predictors of each cause of death and for the indications for glucosamine and chondroitin use (including joint pain), we presented results with the first two years of follow-up omitted, and we presented results stratified by whether subjects had the condition at baseline for cause--specific mortality analyses. Also, in our original study of 20 supplements and mortality, most supplements were associated with reduced risk of total mortality with control for only age and sex, but after full adjustment for confounders, only glucosamine, chondroitin and fish oil supplements remained associated with reduced risk (15). It is unlikely that biases would affect only these three supplements.

Another limitation of this study is the measurement error in our classification of supplement use, in part because we do not have information on use after baseline. In addition, we focused on current use as the main exposure because such use would likely reflect use after baseline. Although this is a very simple characterization of exposure, the amount of use among current users was substantial: 42% of current glucosamine users had used the supplement for at least 3 years prior to baseline, and 97% of current users took the supplement at least 4 days/week.

Overall, this study found that use of glucosamine supplements (with or without chondroitin) was associated with reduced total mortality and with reductions of several broad causes of death. Support for this association comes from studies of the anti-inflammatory effects of glucosamine and chondroitin, and the studies of aspirin which show reduction in total and cancer mortality. Nonetheless, bias in our results due to residual confounding cannot be ruled out. Given the adverse effects of NSAIDs, including ulcers and kidney damage for NSAIDs that target COX-1 and COX-2 pathways (46) and cardiovascular events for the COX-2 specific- inhibitors (46, 47), there is a need to continue to evaluate other anti-inflammatory drugs, such as glucosamine and chondroitin, that may have a more favorable safety profile and may provide risk reduction for the range of diseases associated with inflammation.

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Table 1

Association of Participant Characteristics with Use of Glucosamine Supplements at Baseline[a]

Characteristic	Never User (n=61769) %	Current User (n=12937) %
Demographic Factors		
Age at baseline (years)		
50 to <55	24	18
55 to <60	23	21
60 to <65	18	19
65 to <70	16	19
70 to <77	19	22
Sex		
Female	49	60
Male	51	40
Race		
White	91	93
Hispanic	1	1
Black	1	1
American Indian/Alaska Native	1	2
Asian or Pacific Islander	3	2
Other/missing	2	2
Education		
High school or less	21	17
Some college/technical school	37	38
College or advanced degree	40	43
Lifestyle Factors		
Smoking		
Never smoker	46	50
Ever smoker		
1 to 12.5 pack-years	16	17
12.6 to 35.0 pack-years	18	18
35.0+ pack-years	19	14
Alcohol use at age 45 years		
None	19	19
≤1 drink per day	53	55
1–2 drinks per day	12	12
≥2 drinks per day	11	10
Body mass index at age 45 years (kg/m^2)		
<18.5	1	1
18.5 to <25	51	54
25 to <30	32	30
30+	10	11

Characteristic	Never User (n=61769) %	Current User (n=12937) %
Missing	5	5
Average physical activity in the previous 10 years (MET-hours/week)		
None	16	11
Tertile 1 (>0–4.8)	29	27
Tertile 2 (4.39–13.59)	27	29
Tertile 3 (>13.59)	27	33
Percent calories from trans fat		
Quartile 1 (0.0–1.4)	23	31
Quartile 2 (1.5–1.9)	24	26
Quartile 3 (2.0–2.4)	20	18
Quartile 4 (2.5–10.4)	23	17
Missing	10	8
Percent calories from saturated fat		
Quartile 1 (0.0–8.56)	22	27
Quartile 2 (8.57–10.35)	22	24
Quartile 3 (10.36–12.51)	23	22
Quartile 4 (>12.52)	23	20
Missing	10	8
Fruit consumption (servings/day)		
Quartile 1 (0.0–0.72)	24	17
Quartile 2 (0.73–1.32)	23	22
Quartile 3 (1.33–2.28)	22	25
Quartile 4 (>2.29)	21	28
Missing	10	8
Vegetable consumption (servings/day)		
Quartile 1 (0.0–1.05)	24	17
Quartile 2 (1.06–1.66)	23	21
Quartile 3 (1.67–2.53)	22	24
Quartile 4 (>2.54)	21	30
Missing	10	8
Medical History		
Self-rated health		
Excellent	15	15
Very good	38	39
Good	35	36
Fair	11	9
Poor	2	1
Aspirin use past 10 years[c]		
None	72	70
Low	12	14
High	11	13

Characteristic	Never User (n=61769) %	Current User (n=12937) %
Missing	5	4
Non-aspirin NSAID use past 10 years[c]		
None	67	51
Low	21	31
High	6	12
Missing	6	6
History of cardiovascular disease[d]		
No	88	91
Yes	12	9
History of cancer[d]		
No	85	85
Yes	14	14
Osteoarthritis or chronic joint pain		
No	57	30
Yes	43	70

[a] Former users omitted

[b] OR = odds ratio of glucosamine use; CI = confidence interval

[c] Aspirin and non-aspirin NSAID use over 10 years before baseline: none, low = <4 days/week or <4 years, high=4+/days/week and 4+ years

[d] Self-report of doctor diagnosis

Table 2

Hazard Ratios for Total Mortality Associated with Glucosamine and Chondroitin Supplement Use

	Subjects		Deaths		Sex-and Age-Adjusted[a]		Multivariate-Adjusted[a,b]	
Supplement Use	**n**	**%**	**n**	**Crude rate per 1,000 person-years**	**HR**	**95% CI**	**HR**	**95% CI**
Glucosamine (any formulation)								
Never	61769	79.8	4529	10.8	1.00	Ref	1.00	Ref
Former	2692	3.5	168	9.2	0.87	0.75–1.02	1.03	0.88–1.22
Current	12937	16.7	631	7.1	0.62	0.57–0.67	0.82	0.75–0.90
Glucosamine (without chondroitin)								
Never	61613	92.1	4526	7.3	1.00	Ref	1.00	Ref
Former	1093	1.6	69	6.3	0.89	0.71–1.13	1.09	0.85–1.38
Current	4178	6.2	192	4.6	0.61	0.53–0.70	0.78	0.67–0.91
Chondroitin[d]								
Never	66976	86.5	4800	10.6	1.00	Ref	1.00	Ref
Former	1923	2.5	108	8.3	0.79	0.66–0.96	0.92	0.75–1.13
Current	8556	11.0	433	7.4	0.65	0.59–0.71	0.86	0.78–0.96
MSM[e]								
Never	73605	95.0	5141	10.3	1.00	Ref	1.00	Ref
Former	1997	2.6	95	7.0	0.86	0.70–1.05	0.96	0.78–1.18
Current	1855	2.4	110	8.7	0.92	0.76–1.11	0.96	0.79–1.17

[a] HR = hazard ratio; CI = confidence interval

[b] Adjusted for age, sex, race/ethnicity, marital status (married/living together, never married, separated/divorced, widowed), education (<high school graduate, some college, college/advanced degree), BMI at age 45 (<18.5, 18.5–<25.0 kg/m^2, 25.0–29.9 kg/m^2, ≥30.0 kg/m^2), average alcohol intake at age 45 (none, <1 drink/day, 1–2 drinks/day, ≥2 drinks/day), average physical activity in the 10 years before baseline (tertiles of MET hrs/wk), self-rated health (excellent, very good, good, fair, poor), mammogram in the last 2 years (yes/no), PSA test in the last 2 years (yes/no), sigmoidoscopy in the last 10 years (yes/no), current use of cholesterol-lowering medication (yes/no), aspirin use past 10 years (none, low, high, missing), non-aspirin NSAID use part 10 years (none, low, high, missing), smoking (never, 1–12.5 pack-years, 12.6–35.0 pack-years, 35.0+ pack-years), history of osteoarthritis or joint pain (yes/no), morbidity score[c], % calories from trans fat (quartiles), % calories from saturated fat (quartiles), number of servings per day of fruits (quartiles), number of servings per day of vegetables (quartiles), years of estrogen therapy (none, <5, 5–10, 10+), years of estrogen plus progestin therapy (none, <5, 5–10, 10+), age at menopause (39 or younger, 40–44, 45–49, 50–54, 55 or older), age at death of father (59 or younger, 60–69, 70–79, 80–89, 90 or older), and age at death of mother (59 or younger, 60–69, 70–79, 80–89, 90 or older)

[c] By using Cox regression, the following conditions, categorized as yes or no, were modeled simultaneously in sex-specific and age-adjusted models to obtain the morbidity score: current use of medication for depression or anxiety; current use of blood pressure medication; a history of lung cancer, colon cancer, bladder cancer, leukemia, non-Hodgkin's lymphoma, pancreatic cancer, melanoma, prostate cancer, breast cancer, cervical cancer, uterine cancer, ovarian cancer (as separate variables), and all other cancers except non-melanoma skin cancer combined; ischemic heart disease (defined as history of

heart attack, coronary bypass surgery, angioplasty, or diagnosis of angina); stroke; congestive heart failure; rheumatoid arthritis; diabetes; viral hepatitis; cirrhosis of the liver; other chronic liver disease; emphysema, chronic bronchitis, or chronic obstructive pulmonary disease; kidney disease; ulcerative colitis or Crohn's disease; Parkinson's disease; osteoporosis in women

[d] Chondroitin is included in about two-thirds of glucosamine supplements taken by VITAL participants and occasionally is taken alone

[e] MSM = methylsulfonylmethane; MSM is included in some supplements with glucosamine and chondroitin and is occasionally taken alone.

Table 3

Adjusted[a] Hazard Ratios for Cause-Specific Mortality Associated with Glucosamine Supplement Use

		Never Use	Former Use		Current Use	
Cause of Death	**No. of Deaths**	**HR[b]**	**HR[b]**	**95% CI[b]**	**HR[b]**	**95% CI[b]**
Death from Cardiovascular Disease						
Total[c]	1,365	1.00	1.12	0.82–1.52	0.88	0.74–1.06
No history at baseline	751	1.00	1.01	0.65–1.55	0.91	0.72–1.14
History at baseline	607	1.00	1.26	0.80–1.97	0.87	0.65–1.17
Death from ischemic heart disease[d]						
Total	755	1.00	1.22	0.81–1.83	0.85	0.66–1.09
No history at baseline	416	1.00	1.02	0.57–1.82	0.93	0.68–1.25
History at baseline	337	1.00	1.45	0.82–2.59	0.69	0.44–1.06
Death from Cancer						
Total[e]	2,436	1.00	1.12	0.89–1.41	0.87	0.76–0.98
No history at baseline	1,357	1.00	1.14	0.84–1.53	0.85	0.71–1.00
History at baseline	1,068	1.00	0.97	0.67–1.39	0.90	0.74–1.09
Death from lung cancer [f]						
Total	683	1.00	0.82	0.49–1.37	0.91	0.70–1.17
No history at baseline	563	1.00	0.69	0.37–1.30	0.92	0.70–1.21
History at baseline	117	1.00	1.27	0.40–4.02	0.84	0.38–1.83
Death from hematopoietic cancer[g]						
Total	274	1.00	1.24	0.64–2.37	0.81	0.53–1.22
No history at baseline	194	1.00	1.19	0.55–2.58	0.69	0.43–1.12
History at baseline	79	1.00	1.10	0.25–4.88	1.36	0.56–3.31
Death from colorectal cancer[h]						
Total	199	1.00	0.44	0.11–1.78	1.34	0.89–2.02
No history at baseline	121	1.00	0.68	0.08–5.48	1.26	0.60–2.65
History at baseline	77	1.00	0.33	0.05–2.39	1.25	0.75–2.07
Death from breast cancer[i]						
Total	168	1.00	0.30	0.07–1.23	1.09	0.73–1.62

		Never Use	Former Use		Current Use	
Cause of Death	**No. of Deaths**	**HR[b]**	**HR[b]**	**95% CI[b]**	**HR[b]**	**95% CI[b]**
No history at baseline	43	1.00	.	.	1.06	0.50–2.23
History at baseline	123	1.00	0.38	0.09–1.55	1.09	0.68–1.76
Death from pancreatic cancer[j]						
Total	168	1.00	1.32	0.61–2.84	1.13	0.72–1.78
No history at baseline	144	1.00	1.96	0.94–4.09	1.10	0.69–1.77
History at baseline	24	1.00	N/A		N/A	
Death from other cancers[e]	844	1.00	1.53	1.09–2.13	0.69	0.54–0.87
Death from Other Causes						
Total[k]	1,294	1.00	0.84	0.60–1.17	0.67	0.56–0.81
Death from respiratory disease[l]						
Total	472	1.00	0.98	0.53–1.81	0.59	0.41–0.83
No History at baseline	248	1.00	0.80	0.35–1.83	0.62	0.38–0.99
History at baseline	223	1.00	1.33	0.53–3.38	0.55	0.32–0.94

[a] All models adjusted for age, sex, race/ethnicity, marital status (married/living together, never married, separated/divorced, widowed), education (≤high school graduate, some college, college/advanced degree), BMI at age 45 (<18.8, 18.5–<25.0 kg/m^2, 25.0–29.9 kg/m^2, ≥30.0 kg/m^2), number of servings per day of fruits (quartiles), number of servings per day of vegetables (quartiles), average alcohol intake at age 45 (none, <1 drink/day, 1–2 drinks/day, ≥2 drinks/day), self-rated health (excellent, very good, good, fair, poor), mammogram in the last 2 years (yes/no), PSA test in the last 2 years (yes/no), sigmoidoscopy in the last 10 years (yes/no), current use of cholesterol-lowering medication (yes/no), aspirin use past 10 years (none, low, high, missing), non-aspirin NSAID use part 10 years (none, low, high, missing), smoking (never, 1–12.5 pack-years, 12.6–35.0 pack-years, 35.0+ pack-years), history of osteoarthritis or joint pain (yes/no)

[b] HR = hazard ratio; CI = confidence interval

[c] Additionally adjusted for history of history of cardiovascular disease (yes/no, defined as history of heart attack, coronary bypass surgery, angioplasty, stroke, congestive heart failure, or diagnosis of angina), family history of heart attack (no. relatives 0,1,2+), current use of blood pressure medication (yes/no), % of calories from trans fat (quartiles), % calories from saturated fat (quartiles), years of estrogen therapy (none, <5, 5–10, 10+), and years of estrogen plus progestin therapy (none, <5, 5–10, 10+)

[d] Additionally adjusted for history of ischemic heart disease (yes/no, defined as history of heart attack, coronary bypass surgery, angioplasty, or diagnosis of angina), family history of heart attack (no. relatives 0,1,2+), current use of blood pressure medication (yes/no), % of calories from trans fat (quartiles), % calories from saturated fat (quartiles), years of estrogen therapy (none, <5, 5–10, 10+), and years of estrogen plus progestin therapy (none, <5, 5–10, 10+)

[e] Additionally adjusted for history of cancer other than non-melanoma skin cancer (yes/no), family history of cancer (no. relatives 0,1,2+), years of estrogen therapy (none, <5, 5–10, 10+), years of estrogen plus progestin therapy (none, <5, 5–10, 10+), age at menopause (39 or younger, 40–44, 45–49, 50–54, 55 or older), age at menarche (<=11, 12, 13, 14+), and servings per week of red/processed meat (quartiles)

[f] Additionally adjusted for history of lung cancer (yes/no), family history of lung cancer (no. relatives 0,1,2+), history of emphysema, chronic bronchitis or chronic obstructive pulmonary disease (yes/no), pack-years squared, and years smoked

[g] Additionally adjusted for history of leukemia/lymphoma (yes/no), family history of leukemia/lymphoma (no. relatives 0,1,2, history of any cancer (yes/no), history of rheumatoid arthritis (yes/no), history of fatigue/lack of energy (yes/no)

[h] Additionally adjusted for history of colorectal cancer (yes/no), family history of colorectal cancer (no. relatives 0,1,2+), years of estrogen therapy (none, <5, 5–10, 10+), years of estrogen plus progestin therapy (none, <5, 5–10, 10+), calcium intake from diet and calcium intake from supplements, and number of servings per week of red/processed meat (quartiles)

[i] Additionally adjusted for history of breast cancer (yes/no), family history of breast cancer (no. relatives 0,1,2+), years of estrogen therapy (none, <5, 5–10, 10+), years of estrogen plus progestin therapy (none, <5, 5–10, 10+) age at first birth, history of hysterectomy (none, simple, total), age at menopause (age 39 or younger, 40–44, 45–49, 50–54, 55 or older) and age at menarche (<=11, 12, 13, 14+)

[j] Additionally adjusted for history of pancreatic cancer (yes/no), family history of pancreatic cancer (no. relatives 0,1,2+), number of servings per week of red/processed meat (quartiles), and history of diabetes (yes/no)

[k] Additionally adjusted for morbidity score (see footnote c of Table 2), % calories from trans fat (quartiles), % calories from saturated fat (quartiles), years of estrogen therapy (none, <5, 5–10, 10+), years of estrogen plus progestin therapy (none, <5, 5–10, 10+), age at menopause (age 39 or younger, 40–44, 45–49, 50–54, 55 or older), age at death of father (59 or younger, 60–69, 70–79, 80–89, 90 or older), and age at death of mother (59 or younger, 60–69, 70–79, 80–89, 90 or older)

[l] Additionally adjusted for history of emphysema, chronic bronchitis or chronic obstructive pulmonary disease (yes/no), history of asthma (yes/no), and history of allergies (yes/no), pack-years squared, and years smoked