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ORIGINAL ARTICLE

Glucosamine and Chondroitin Use and Mortality Among Adults in the United States from 1999 to 2014

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Abstract

Introduction: Glucosamine and chondroitin are supplements that are often, but not always, used in combination for arthritis and joint pain. Multiple studies have suggested that glucosamine and chondroitin may be associated with reduced risk of several diseases, as well as all-cause, cancer- and respiratory disease-specific mortality.

Methods: Nationally representative data from the National Health and Nutrition Examination Survey (NHANES) were used to further evaluate the association between glucosamine and chondroitin with mortality. Participants include 38,021 adults, ages 20+ years and older, who completed the detailed NHANES between 1999 and 2014. Participants were followed for death through linkage with the National Death Index through the end of 2015, over which time 4905 deaths occurred. Adjusted hazard ratios (HRs) for overall and cause-specific mortality were estimated using Cox regression models.

Results: Despite glucosamine and chondroitin use appearing to be inversely associated with mortality in the minimally adjusted models, no association was observed in multivariable models (glucosamine: HR = 1.02; 95% confidence interval [CI]: 0.86–1.21, chondroitin: HR = 1.04, 95% CI: 0.87–1.25). No association with cancer mortality or other mortality rate was observed after multivariable adjustment. There was a suggestive, nonsignificant inverse association for cardiovascular-specific mortality (glucosamine HR = 0.72; 95% CI: 0.46–1.15, chondroitin: HR = 0.76; 95% CI: 0.47–1.21).

Conclusion: The lack of significant relationship between glucosamine and chondroitin use and all-cause or cause-specific mortality after adjusting extensively for multiple covariates in this nationally representative adult population was in contrast to prior literature. Given the limited power to explore the cause-specific mortality, future well-powered studies will be needed to better understand the potential association with cardiovascular-specific mortality.

Keywords: glucosamine, chondroitin, mortality, cohort

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Introduction

GLUCOSAMINE AND CHONDROITIN are dietary supplements that are available as over-the-counter products in the United States. These supplements are commonly used by older adults[1,2] to treat joint pain and arthritis, often as alternatives to nonsteroidal anti-inflammatory drugs (NSAIDs). Glucosamine and chondroitin have a favorable side effect profile,[3–5] compared with NSAIDs and equivalent drugs.[6–11] Glucosamine and chondroitin are often, but not always, combined (and are sometimes further combined with methylsulfonylmethane [MSM] in joint health supplements). Although often used for joint pain, existing studies show varied results of the effectiveness of glucosamine and chondroitin in relieving joint symptoms.[12–16]

Emerging evidence suggests that glucosamine may have a role in reducing risk of colorectal and lung cancer, and mortality from cancer, cardiovascular disease, and respiratory disease compared with those not taking glucosamine supplements.[17–28] In the VITamins And Lifestyle (VITAL) study, a cohort of 77,510 persons followed for a mean of 6.8 years over which time 5362 deaths occurred, the adjusted hazard ratio (HR) associated with current use of glucosamine was 0.82 (95% confidence interval [CI]: 0.75–0.9), and 0.86 (95% CI: 0.78–0.96) for current use of chondroitin.[19] The study found significant risk reductions in mortality due to cancer and other causes of death for those taking glucosamine/chondroitin compared with those who did not.

If glucosamine/chondroitin use reduces the risk of overall mortality, it may be due to their role in inflammation. *In vitro* and animal research has shown promising evidence of this.[29–34] Existing human studies (both observational and clinical trials), show the reduction of some inflammatory biomarkers, including high-sensitivity C-reactive protein (hsCRP) and prostaglandin E_2(PGE2).[35–38] hsCRP is correlated with both the all-cause and cancer-related mortality,[39] alongside other markers of inflammation.[40]

A recently published study looked at the impact of glucosamine/chondroitin on mortality using the data from the National Health and Nutrition Examination Survey (NHANES).[22] While this study observed glucosamine/chondroitin use to be significantly associated with reduced mortality, power and adjustment for covariates were limited. Therefore, this study will expand on the results using NHANES data by examining the association between glucosamine/chondroitin and both the all-cause and cause-specific mortality in a larger study with a broader range of covariates. Given some evidence of heterogeneity by follow-up time and calendar time[25,41] in prior analyses of glucosamine/chondroitin (in the context of inflammation and cancer), this study will conduct stratified analyses by these two time constructs.

Methods

Population

The study used data from NHANES, a nationally representative survey that assesses the health and nutritional status of civilian, noninstitutionalized adults and children in the United States. NHANES collected information on the demographic characteristics of the study population, as well lifestyle factors, health history, use of prescription medications, dietary supplements, and diet.

This analysis used data from NHANES from 1999 to 2014. Of the persons identified within the NHANES who were ages 20+ and who participated in surveys between 1999 and 2014 ($N=41{,}659$), participants with missing information on any supplement use ($N=42$), those who were pregnant ($N=1344$), those with a history of rheumatoid arthritis ($N=2194$), and those who were ineligible for mortality follow-up ($n=58$) were excluded, resulting in a final sample size of 38,021 persons.

Participants in the study provided written informed consent. Study procedures were approved by the NCHS Research Ethics Review Board. The Memorial Sloan Kettering Cancer Center Institutional Review Board concluded that the analysis did not constitute human subjects research and subsequently did not require human subjects' approval.

Exposure

The use of glucosamine/chondroitin was assessed through interview and inventory. Participants reported supplement use in the prior 30 days, including any use and number of days of use. They provided physical evidence of each supplement, or if unavailable, recalled each product taken. Supplement products included could be capsules, tablets, et cetera, and be produced as single or combined products. Then, the ingredients' database from NHANES was used to identify specific supplements containing either glucosamine or chondroitin as an ingredient, which was used to define exposure variables.

There were two primary exposures in this study: regular use of glucosamine and regular use of chondroitin (defined by use on 20 or more of the prior 30 days for both), compared with those who report neither. Regular users were defined as such, so that persons in the exposed group would have used the exposure frequently enough to have a potential biologic effect.[17] Those who used glucosamine or chondroitin for <20 days in the prior 30 days were classified with nonusers as no regular glucosamine use.

The secondary exposures examined were associations for glucosamine/chondroitin, defined as a three-level variable: regular use of glucosamine/chondroitin, regular use of glucosamine alone, or regular use of neither glucosamine nor chondroitin. Associations for the combined products were examined, as they are commonly prepared and used in combination, although sometimes glucosamine alone is used (it was not possible to examine chondroitin alone as it is rarely used in the absence of glucosamine). MSM was also examined in secondary analyses due to the frequency with which it is combined with glucosamine/chondroitin supplements.

Outcome

The primary outcome in this study was the all-cause mortality, as defined by any deaths occurring from the time of baseline questionnaire through the end of 2015. All deaths were identified by linkage with the National Death Index (NDI) data.[42]

In secondary analyses, cause of death was classified based on the International Classification of Diseases (ICD-10th revision) as cardiovascular-, cancer-, or other mortality.

Statistical analyses

Survival analyses were conducted using Cox proportional hazard models to estimate HRs and the corresponding 95% CIs, comparing users with nonusers. Both minimally adjusted models adjusting for age and sex, and multivariable models, were conducted, both with age as the time-axis of analysis. Covariates in multivariable models were selected *a priori* to include factors associated with glucosamine use and/or the overall or disease-specific mortality.

Multivariable models adjust for age and sex as well as race/ethnicity (non-Hispanic white; non-Hispanic black; Mexican American; other Hispanic; other race/mixed-race), educational status (<high school; high school graduate or equivalent; some college or associate degree; college graduate or above), marital status (married/living with partner; widowed; divorced/separated; never married), poverty–income ratio (<1 [lowest income]; 1 to <2; 2 to <4; >4 [highest income]), and health insurance (insured; noninsured). Lifestyle factors, including body mass index (BMI; <18.5; 18.5 to 25, 25 to 27.5; 27.5 to <30; >30), alcohol use (<1 drink/month; >1 drink/month to 4 drinks/week; >4 drinks/week to 2 drinks/day; >2 drinks/day), smoking (never; former; current with pack-year data computed from the survey), medication use (aspirin: never; low; high; non-aspirin NSAID use: never; low; high), and physical activity (none; moderate; vigorous), were also incorporated.

In addition, self-reported health status (excellent/very good; good/fair; poor), a morbidity score (none; low; high), and history of arthritis (no; yes) were included. The morbidity score was calculated using beta-coefficients of age-adjusted, sex-specific proportional hazard models of death based on models with specific health conditions (listed in the footnote of Table 1). A risk score per participant was created, using the natural log of the coefficients for the HR for death based on the subject's own group of health conditions compared with a subject with no conditions. A missing indicator was added for each variable where data were unavailable to maximize the number of individuals in the analysis. As aspirin and non-aspirin NSAID use were only available from 1999 to 2004, sensitivity analyses were restricted to these cycles, with and without adjustment for both.

As effect estimates were comparable in the two models and their inclusion reduced the sample size (due to the limited cycle availability), these variables were excluded from the final models. All data on the above covariates were collected at baseline.

Given prior observation of a stronger association for colorectal cancer in the early years of follow-up,[17,20,26] separate secondary analyses were conducted in early and late follow-up (defined as before and after median follow-up, respectively). Specifically, in models of early follow-up, all results are censored at 8.1 years; in models of late follow-up, follow-up starts at 8.1 years, with anyone censored in the first half of follow-up not contributing to this analysis. To further disaggregate this from calendar time (and given evidence that the association for CRP may be stronger in the earlier years[21,22,24,26]), analyses stratified on baseline year of exposure assessment and cohort entry (1999–2006 vs. 2007–2014) were also conducted.

Secondary analyses were conducted to examine associations with cause-specific mortality, including cancer-specific, cardiovascular-specific, and other mortality. In these analyses, those who died from causes other than the cause under study were censored at date of death. Lastly, to facilitate comparisons with prior cohorts, a sensitivity analysis was conducted restricted to persons ages 50+ years at the time of baseline survey. All secondary/sensitivity analyses were conducted for the two primary exposures: regular glucosamine use and regular chondroitin use.

All analyses were weighted to account for unequal sampling probability and nonresponse and were conducted using Stata version 15.1.[43]

Results

Of the 38,021 adults included in this study, 1181 (3.5%) reported regular glucosamine use (Table 1) and 2.4% reported regular chondroitin use. Glucosamine use was most prevalent in the age categories of 60–69 and 70–79, with a prevalence of 8.2% in both, compared with 0.5% and 0.9% in the 20–29 and 30–39 age categories, respectively. Glucosamine use was also correlated with income: among those with a poverty-to-income ratio of greater than or equal to 4 (highest income), 5.3% of people were regular glucosamine users compared with those with a poverty-to-income ratio of <1 (lowest income), where only 1.1% of people were regular glucosamine users. Regular glucosamine use is more prevalent in non-Hispanic white, married, and higher educated adults. Glucosamine users were also more likely than nonusers to have some or high use of aspirin and other NSAIDs.

In this study, 4908 persons died over a median of 8.1 years of follow-up (max: 16.75 years), including 1086 deaths due to cancer, 840 deaths due to cardiovascular disease, and 2969 deaths due to other causes. Of these deaths, 12.2% were among those who regularly used any glucosamine, and 8.8% in those who did not (Table 2).

Despite glucosamine use seemingly inversely associated with mortality in minimally adjusted models (HR: 0.70; 95% CI: 0.59–0.84), following multivariable adjustment, no association was observed (HR: 1.02; 95% CI: 0.85–1.23) (Table 2). Similar results were observed for chondroitin and joint use of glucosamine and chondroitin, with no association observed after multivariable adjustment (chondroitin: HR: 1.05; 95% CI: 0.87–1.27; glucosamine chondroitin: HR: 1.05; 95% CI: 0.86–1.28; or MSM: HR: 1.02; 95% CI: 0.74–1.40).

For cause-specific mortality, a significant inverse association was found after regular use of glucosamine/chondroitin for both cardiovascular mortality and other cause mortality rate in the minimally adjusted model (Table 3). However, after multivariable adjustment, the association did not remain statistically significant for the cardiovascular mortality (glucosamine: HR 0.72; 95% CI: 0.45–1.14, chondroitin: HR: 0.75; 95% CI: 0.46–1.21) and was null for other cause mortality rate (glucosamine: HR: 1.00; 95% CI: 0.79–1.25, chondroitin: HR: 0.98; 95% CI: 0.78–1.23). There was no significant association between use of either glucosamine or chondroitin and cancer mortality (Table 3).

In follow-up time stratified models, there appeared to be some difference in early and late years. Specifically, an HR of 1.08 (95% CI: 0.90–1.31) was observed in the early years of follow-up for glucosamine, compared with 0.86 (95% CI: 0.57–1.29) in the later years of follow-up (Supplementary

Table 1. Population Characteristics, by Glucosamine Use

Population characteristics	*Cohort,* N *(weighted %), 38,021 (100)*	*Regular*[a] *glucosamine users,* N *(weighted %), 1181 (3.5)*	*Not regular glucosamine users,* N *(weighted %), 36,816 (96.5)*
Sociodemographic			
Age			
20–29	6510 (18.9)	28 (0.5)	6480 (99.5)
30–39	6503 (19.1)	48 (0.9)	6454 (99.1)
40–49	6774 (20.9)	111 (2.1)	6660 (97.9)
50–59	5587 (17.5)	222 (5.3)	5362 (94.7)
60–69	5911 (11.8)	341 (8.2)	5565 (91.8)
70–79	4036 (7.5)	268 (8.2)	3759 (91.8)
80+	2700 (4.2)	163 (6.3)	2563 (93.7)
Sex			
Male	19,104 (49.2)	558 (3.3)	18,535 (96.7)
Female	18,917 (50.8)	623 (3.6)	18,281 (96.4)
Race/ethnicity			
Non-Hispanic white	17,818 (69.6)	840 (4.3)	16,963 (95.7)
Non-Hispanic black	7789 (10.9)	73 (0.7)	7713 (99.3)
Mexican American	6784 (8.0)	95 (1.1)	6684 (98.9)
Other Hispanic	2847 (5.4)	72 (1.8)	2774 (98.2)
Other race/mixed race	2783 (6.1)	101 (3.3)	2682 (96.7)
Missing			
Educational status			
<High school	10,684 (18.4)	171 (1.6)	10,509 (98.4)
High school graduate/GED or equivalent	8853 (24.0)	239 (2.8)	8605 (97.2)
Some college or associate degree	10,457 (30.5)	362 (3.6)	10,088 (96.4)
College graduate or above	7974 (27.0)	409 (5.1)	7561 (94.9)
Missing	53 (0.1)	0 (0.0)	53 (100.0)
Marital status			
Married/living with partner	22,515 (62.6)	839 (4.3)	21,667 (95.7)
Widowed	3285 (5.8)	147 (5.1)	3133 (94.9)
Divorced/separated	5032 (12.3)	124 (2.7)	4903 (97.3)
Never married	6766 (18.0)	65 (0.9)	6697 (99.1)
Missing	423 (1.3)	6 (1.2)	416 (98.8)
Poverty-to-income ratio			
<1 (Lowest income)	7050 (13.1)	83 (1.1)	6964 (98.9)
1 to <2	9138 (19.1)	220 (2.5)	8913 (97.5)
2 to <4	9432 (27.3)	309 (3.2)	9118 (96.8)
≥4 (Highest income)	9212 (33.7)	490 (5.3)	8715 (94.7)
Missing	3189 (6.9)	79 (3.0)	3106 (97.0)
Health insurance			
Insured	29,234 (80.5)	1076 (4.1)	28,137 (95.9)
not insured	8602 (19.0)	105 (1.1)	8494 (98.9)
Missing	185 (0.5)	0 (0.0)	185 (100.0)
Lifestyle factors			
Body mass index (kg/m^2)			
Underweight (<18.5)	631 (1.7)	10 (1.8)	621 (97.2)
Normal weight (18.5 to <25)	10,922 (30.5)	303 (3.0)	10,610 (97.0)
Lower overweight (25 to <27.5)	6759 (17.8)	241 (3.8)	6514 (96.2)
Upper overweight (27.5 to <30)	6047 (15.6)	211 (4.0)	5832 (96.0)
Obese (≥30)	12,861 (32.7)	401 (3.6)	12,453 (96.4)
Missing	801 (1.7)	15 (2.3)	786 (96.4)
Alcohol use			
<1 Drink/month	16,673 (38.5)	530 (3.5)	16,131 (96.5)
≥1 Drink/month to <4 drinks/week	9832 (28.8)	320 (3.6)	9504 (96.4)
≥4 Drinks/week to <2 drinks/day	6002 (18.6)	223 (4.0)	5778 (96.0)
≥2 Drinks/day	1887 (5.6)	47 (2.8)	1839 (97.2)
Missing	3627 (8.4)	61 (2.2)	3564 (97.8)
Smoking			
Never	20,315 (53.2)	650 (3.7)	19,658 (96.3)
Former (pack-years Tertile 1)	2580 (6.9)	113 (4.6)	2465 (95.4)
Former (pack-years Tertile 2)	2625 (6.9)	125 (5.4)	2496 (94.6)

(*continued*)

Table 1. (Continued)

Population characteristics	*Cohort,* N *(weighted %), 38,021 (100)*	*Regular*[a] *glucosamine users,* N *(weighted %), 1181 (3.5)*	*Not regular glucosamine users,* N *(weighted %), 36,816 (96.5)*
Former (pack-years Tertile 3)	4204 (10.6)	204 (5.2)	3995 (94.8)
Current (pack-years Tertile 1)	1876 (5.0)	12 (0.6)	1864 (99.4)
Current (pack-years Tertile 2)	1759 (5.1)	15 (1.0)	1742 (99.0)
Current (pack-years Tertile 3)	4628 (12.4)	62 (1.6)	4562 (98.4)
Missing	34 (0.1)	0 (0.0)	34 (100.0)
Physical activity			
No	14,652 (32.1)	342 (2.7)	14,302 (97.3)
Moderate	11,276 (30.8)	472 (4.5)	10,799 (95.5)
Vigorous	12,083 (37.1)	367 (3.3)	11,705 (96.7)
Missing	10 (0.0)	0 (0.0)	10 (100.0)
Medication use			
Aspirin use (1999–2004)			
No use	10,718 (86.8)	245 (2.5)	10,457 (97.5)
Low use	904 (6.5)	67 (8.8)	835 (91.2)
High use	780 (5.4)	54 (7.4)	724 (92.6)
Missing	172 (1.3)	12 (7.6)	160 (92.4)
Non-aspirin NSAID use (1999–2004)			
No use	11,708 (91.8)	320 (2.9)	11,368 (97.1)
Low use	604 (5.9)	40 (6.1)	564 (93.9)
High use	173 (1.6)	11 (9.8)	162 (90.2)
Missing	89 (0.7)	7 (6.9)	82 (93.1)
Health status and other risk factors			
Self-reported health status			
Excellent/very good	15,970 (50.1)	632 (4.2)	15,329 (95.8)
Good/fair	20,365 (46.8)	523 (2.9)	19,830 (97.1)
Poor	1665 (3.1)	25 (1.3)	1637 (98.7)
Missing	21 (0.0)	1 (5.4)	20 (96.5)
Morbidity score[b]			
None	25,461 (70.6)	727 (3.3)	24,724 (96.7)
Low	5688 (15.4)	250 (4.5)	5430 (95.5)
High	6353 (12.9)	184 (3.3)	6163 (96.7)
Missing	519 (1.0)	20 (4.4)	499 (96.5)
History of arthritis			
No	8664 (21.1)	606 (7.7)	8047 (92.3)
Yes	29,276 (78.8)	573 (2.3)	28,690 (97.7)
Missing	81 (0.2)	2 (2.6)	79 (97.4)

[a]Regular use defined by use in the month before baseline and reported usual frequency of use 20+ days/month.
[b]Morbidity score is the linear predictor for each individual based on a Cox proportional hazards model modeling time to death as a function of comorbidities, including diabetes, kidney failure, asthma, congestive heart failure, myocardial infarction, stroke, emphysema, chronic bronchitis, liver condition, cancer, and osteoporosis.
GED, general educational development; NSAID, nonsteroidal anti-inflammatory drug.

Table S3). Similarly, an HR of 1.15 (95% CI: 0.93–1.42) was observed for chondroitin in early follow-up, compared with 0.79 (95% CI: 0.53–1.19) in later follow-up (Supplementary Table S4). For both glucosamine and chondroitin, there was no evidence of interaction by year of study entry (p-interaction: 0.98 and p-interaction: 0.99, respectively) (Supplementary Tables S1 and S2).

In keeping with other studies, analyses were conducted restricted to those aged 50+. Results were comparable with those observed in overall models (Supplementary Table S5).

Discussion

In this nationally representative study, no significant association with all-cause mortality after multivariable adjustment was identified. Despite evidence of an association after adjustment for age and sex, the association attenuated to the null with incorporation of factors pertaining to lifestyle, demographics, and overall health measures. A similar pattern of association was observed for cause-specific mortality (mortality due to cancer, cardiovascular disease, and other causes). Further work in a larger study will be needed to better understand a potentially suggestive inverse (nonsignificant) association with cardiovascular mortality.

Our observation of no association between glucosamine and mortality contrasted with prior studies, where a significant inverse relationship was found.[19,20,22,24] It is likely that the difference in comparison with the prior NHANES study[22] reflects more complete adjustment for confounding factors, as this study included a less extensive panel of covariates (without inclusion of variables such as BMI, self-reported health status, or income); however, it seems unlikely

Table 2. Regular Use of Glucosamine, Chondroitin, and Methylsulfonylmethane Supplements in Relation to Mortality

Exposure	Cohort, N (weighted %)	Deaths, N (weighted %)	Age and sex-adjusted HR	Age and sex-adjusted 95% CI	Multivariable-adjusted[a] HR	Multivariable-adjusted[a] 95% CI
Primary exposures						
Regular use of any glucosamine[b]						
No regular use	36,816 (96.5)	4696 (8.8)	1.00	Ref.	1.00	Ref.
Regular use	1181 (3.5)	204 (12.2)	0.70	0.59–0.83	1.02	0.86–1.21
Regular use of any chondroitin[b]						
No regular use	37,178 (97.6)	4748 (8.8)	1.00	Ref.	1.00	Ref.
Regular use	826 (2.4)	156 (13.5)	0.74	0.61–0.89	1.04	0.87–1.25
Secondary exposures						
Regular use of glucosamine+chondroitin[b]						
No regular use of either	36,802 (96.5)	4693 (8.8)	1.00	Ref.	1.00	Ref.
Regular use of glucosamine only	369 (1.1)	51 (9.4)	0.63	0.46–0.85	0.95	0.69–1.31
Regular use of both	812 (2.3)	153 (13.5)	0.73	0.60–0.88	1.05	0.87–1.26
Regular use of any MSM[b]						
No use	37,559 (98.7)	4834 (8.9)	1.00	Ref.	1.00	Ref.
Use	457 (1.3)	71 (10.6)	0.77	0.59–0.99	0.99	0.74–1.33

[a]Adjusted for age, sex, race/ethnicity, educational status, marital status, poverty-to-income ratio, health insurance, body mass index, alcohol use, smoking, physical activity, aspirin use, nonaspirin NSAID use, self-reported heath status, morbidity score, history of arthritis, and survey cycle.
[b]Regular use defined by use in the month before baseline and reported usual frequency of use 20+ days/month.
95% CI, 95% confidence interval; HR, hazard ratio; MSM, methylsulfonylmethane; NSAID, nonsteroidal anti-inflammatory drug.

Table 3. Association Between Glucosamine and Chondroitin Use and Mortality

	Cohort, N (%)	Case, N (%)	Age and sex-adjusted, HR (95% CI)	Multivariable-adjusted,[a] HR (95% CI)
Overall mortality				
Regular use of any glucosamine[b]				
No regular use	36,816 (96.5)	4696 (8.8)	1.00 (Ref.)	1.00 (Ref.)
Regular use	1181 (3.5)	204 (12.2)	0.70 (0.59–0.83)	1.02 (0.86–1.21)
Regular use of any chondroitin[b]				
No regular use	37,178 (97.6)	4748 (8.8)	1.00 (Ref.)	1.00 (Ref.)
Regular use	826 (2.4)	156 (13.5)	0.74 (0.61–0.89)	1.04 (0.87–1.25)
Cancer mortality				
Regular use of any glucosamine[b]				
No regular use	36,816 (96.5)	1028 (2.0)	1.00 (Ref.)	1.00 (Ref.)
Regular use	1181 (3.5)	55 (3.6)	0.90 (0.64–1.25)	1.19 (0.83–1.71)
Regular use of any chondroitin[b]				
No regular use	37,178 (97.6)	1040 (2.0)	1.00 (Ref.)	1.00 (Ref.)
Regular use	826 (2.4)	45 (4.2)	1.03 (0.74–1.45)	1.33 (0.92–1.90)
Cardiovascular mortality				
Regular use of any glucosamine[b]				
No regular use	36,816 (96.5)	815 (1.4)	1.00 (Ref.)	1.00 (Ref.)
Regular use	1181 (3.5)	24 (1.4)	0.47 (0.30–0.74)	0.72 (0.46–1.15)
Regular use of any chondroitin[b]				
No regular use	37,178 (97.6)	819 (1.4)	1.00 (Ref.)	1.00 (Ref.)
Regular use	826 (2.4)	20 (1.6)	0.51 (0.31–0.81)	0.76 (0.47–1.21)
Other mortality				
Regular use of any glucosamine[b]				
No regular use	36,816 (96.5)	2840 (5.4)	1.00 (Ref.)	1.00 (Ref.)
Regular use	1181 (3.5)	125 (7.2)	0.69 (0.56–0.85)	1.03 (0.83–1.28)
Regular use of any chondroitin[b]				
No regular use	37,178 (97.6)	2876 (5.4)	1.00 (Ref.)	1.00 (Ref.)
Regular use	826 (2.4)	91 (7.7)	0.70 (0.56–0.87)	1.01 (0.81–1.26)

[a]Adjusted for age, sex, race/ethnicity, educational status, marital status, poverty-to-income ratio, health insurance, body mass index, alcohol use, smoking, physical activity, aspirin use, nonaspirin NSAID use, self-reported heath status, morbidity score, history of arthritis, and survey cycle.
[b]Regular use defined by use in the month before baseline and reported usual frequency of use 20+ days/month.
95% CI, 95% confidence interval; HR, hazard ratio; NSAID, nonsteroidal anti-inflammatory drug.

that this explains the difference with the prior VITAL studies,[19,24] which also included a comprehensive panel of covariates. Notably, the population prevalence of use is much lower in this cohort (3.5%) versus 20.9% in VITAL. It is possible that this reflects differences in how use was captured and what it represents.

A difference in prevalence may also account for the difference between this study and the U.K. Biobank study, where 19.1% of the study population used glucosamine, which is regulated as a prescription drug in the United Kingdom.[20] Initial consideration suggested that this difference was due to age differences in the population (20+ here, vs. ages 50+ in VITAL and 40+ in the U.K. Biobank study), with younger adults having a lower risk of death due to cancer and cardiovascular disease and thus a lower potential immediate impact of an anti-inflammatory supplement. However, in *post hoc* sensitivity analyses, the overall effect estimates for glucosamine and chondroitin and the overall mortality were comparable in analyses of adults ages 50+ years.

In this study, no significant association between glucosamine/chondroitin and specific causes of mortality was found, in contrast to previous studies. In prior work, Bell et al. found a significant risk reduction for both death from cancer and respiratory disease.[19] This study was unable to evaluate respiratory-specific mortality rate, although no significant association with cancer mortality was observed, in contrast to the study by Bell et al. It is unlikely to be explained by difference in covariate adjustment, as both studies adjusted for a similar panel of covariates. One difference is that in the study by Bell et al., participants were aged 50–76 at baseline, in comparison with this study where adults older than 20 years were included.

Given the limitations in power in the present study, it was not possible to examine cause-specific mortality alongside age restriction, to further evaluate this. It should also be noted that in other studies, glucosamine/chondroitin use has been observed to be associated with reduced risk of colorectal cancer and lung cancer, and thus, the finding of no association with cancer mortality in this study is surprising.[17,18,20,23,25,26] Several other studies examined the association between glucosamine use and cardiovascular disease and found a significant inverse relationship,[21,22] although both the King and Xiang and Ma et al. studies adjusted for far fewer potential confounders. A nonsignificant, inverse association was observed in this study. Further work in a well-powered study will be needed to better understand this association.

Results stratified by follow-up time suggested a nonsignificant association between glucosamine/chondroitin and decreased mortality in the later years of follow-up, with no association observed in early-follow-up. No difference in association was observed by calendar time of cohort entry. This suggests that these differences reflect the increased length of follow-up time, rather than any change in the exposure definition. Previous studies have noted an association between glucosamine and chondroitin and colorectal cancer, although they found decreased inflammatory biomarkers in the earlier years of follow-up.[26,41] There was no clear reason identified for this association.

There were several limitations in this study. NHANES excludes those residing in institutional settings. Given the data showing increased glucosamine use in the elderly and that as of 2017, there are 1.5 million senior citizens in America residing in institutionalized settings, this is an important limitation.[44] Although 3.5% of the population were regular users of glucosamine, only 2.4% used chondroitin regularly. Given the small numbers of those using glucosamine alone and chondroitin alone, it was not possible to compare glucosamine/chondroitin to glucosamine alone and chondroitin alone in the subsequent secondary/sensitivity analyses due to limited power.

In this study, regular use was defined by those who reported use of glucosamine on 20 or more days in the 30 days before survey administration, and thus, exposure is assessed by prevalent use, which could theoretically result in selection bias, although this is less likely in the context of a cancer outcome.[45] It is possible that these users may not have been consistent or long-term users through the etiologically relevant time-period, resulting in measurement error and possibly attenuating results toward the null. Similarly, it is possible that covariate status may have changed throughout follow-up, leading to measurement error in covariates and residual confounding. In the United States, where glucosamine is available over the counter, the confounding variables might vary in comparison with a population where glucosamine is used by prescription (as is the case in many European countries); that said, most prior work has been similarly conducted in U.S. populations.

There are several strengths in this study. It uniquely explores the impact of additional covariates (including demographics, physical health, medication use, a morbidity score, and self-reported health status) on the association between regular glucosamine use and mortality and found no significant association, suggesting that the association identified in existing studies may be secondary to residual unmeasured confounders. Extensive steps were taken to address confounding regarding healthy user bias, including adjusting for self-reported health status. The study also leveraged a nationally representative survey with a large sample size and subsequently highly powered analysis. Finally, the study was able to examine stratifications by study time and follow-up time to address questions about potential heterogeneity in association with time.

In this nationally representative study of U.S. adults, no significant associations between glucosamine/chondroitin and all-cause and cause-specific mortality were identified in contrast to prior studies, including a prior NHANES study. However, a suggestive, nonsignificant inverse association with cardiovascular mortality was seen; given the limited power to explore cause-specific mortality, future well-powered studies will be needed to better understand the potential association with cardiovascular-specific mortality.

Authors' Contributions

J.B.: writing—original draft and writing—reviewing and editing; K.O.: methodology, data curation, formal analysis, and writing—reviewing and editing; D.K.: investigation, methodology, data curation, formal analysis, and writing—reviewing and editing; M.D.: writing—reviewing and editing; S.L.N.: investigation and writing—reviewing and

editing; E.D.K.: conceptualization, supervision, project administration, data curation, methodology, funding acquisition, and writing—reviewing and editing.

Author Disclosure Statement

The authors have no conflict of interest to declare.

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Supplementary Material

Supplementary Table S1
Supplementary Table S2
Supplementary Table S3
Supplementary Table S4
Supplementary Table S5

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