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Relationship between glucosamine use and the risk of lung cancer: data from a nationwide prospective cohort study

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Abstract

Background: Research on glucosamine shows anti-inflammatory and anti-cancer benefits with a minimal adverse effects. We aimed to explore the relationship between use of glucosamine and risk of lung cancer and lung cancer mortality based on data from the large-scale nationwide prospective UK Biobank cohort study.

Methods: Participants were enrolled between the year 2006 and 2010 and followed up to 2020. Cox proportion hazards model were used to assess the relationship between glucosamine use and risk of lung cancer and lung cancer mortality. Subgroup analyses and sensitivity analyses were performed to explore the potential effect modifications and the robustness of main findings.

Results: A total of 439,393 participants (mean age: 56 years; 53% females) with a mean follow-up of 11 years were included for analyses. There were 82,603 (18.80%) participants reporting regular use of glucosamine at baseline. During follow-up, there were 1,971 (0.45%) lung cancer events documented. Glucosamine use was significantly associated with a decreased risk of lung cancer (hazard ratio = 0.84, 95% CI: 0.75 - 0.92, $p < 0.001$) and lung cancer mortality (hazard ratio = 0.88, 95% CI: 0.81 - 0.96, $p = 0.002$) in fully-adjusted models. A stronger association between glucosamine use and decreased lung cancer risk was observed in participants with a family history of lung cancer when compared to those without a family history.

Conclusion: Regular use of glucosamine was significantly related with decreased risk of lung cancer and lung cancer mortality, based on data from this nationwide prospective cohort study.

Keywords: glucosamine; lung cancer; lung cancer mortality; cohort study

Introduction

Lung cancer remains the leading cause of deaths from cancer, with an estimated annual mortality of 2.5 million by 2030 [1, 2]. Inflammation has been consistently reported to accelerate the development and progression of lung cancer, while an inverse relationship between use of non-steroidal anti-inflammatory drug (NSAID) and risks of lung cancer and mortality was also observed in some studies [3, 4]. Nevertheless, NSAID was not recommended as a chemoprevention largely due to concerns about its adverse effects.

In contrast, glucosamine as a supplement mainly used for osteoarthritis and joint pain, shows anti-inflammatory and anti-cancer properties with a minimal risk of adverse effects [5, 6]. One study investigated the relationship between glucosamine and risk of lung cancer in adults, reporting a remarkably lower risk of lung adenocarcinoma observed in those taking glucosamine regularly (hazard ratio: 0.49, 95% confidence interval: 0.27 - 0.90) [7]. However, the relatively small sample size precluded extensive investigations of how the relationship would be modified by other risk factors. Furthermore, evidence on the association between glucosamine and risk of lung cancer remained largely limited, with no study on the lung cancer mortality related to glucosamine available in the literature. Therefore in this study, we aimed to assess the relationship between use of glucosamine and risk of lung cancer and lung cancer mortality based on data from the large-scale nationwide prospective UK Biobank cohort study. Second, we comprehensively explored the potential effect modifications by other risk factors for lung cancer on this relationship.

Methods

Participants and setting

Details on the UK Biobank study has been described on the website (www.ukbiobank.ac.uk) and elsewhere [8]. In brief, the UK Biobank study is a nationwide, population-based prospective cohort study aiming to enroll more than 500,000 participants in the UK aged 40-69 years between the year 2006 and 2010. Baseline data were collected through participants' self-reports, interview with nurses and physical measurements. We excluded participants who had a history or baseline diagnosis of cancer (n = 57,521) or did not have the information on glucosamine use (n = 5,578) from this study

(**Supplemental Figure 1** shows the participant selection process in this study). Written consent was obtained from all participants. The UK Biobank study was approved by the North West Multicenter Research Ethics Committee in the United Kingdom.

Use of glucosamine and outcome measurement

At baseline participants were asked about whether they regularly took a list of supplements including glucosamine. We defined the regular use of glucosamine if they selected the answer of "yes".

Data on incidence and survival time of lung cancer and death were obtained via linkage to national registries, in which lung cancer cases were defined according to the International Classification of Diseases, 10th Revision (ICD-10) codes (C33 and C34) and ICD-9 codes (162) [9, 10]. Lung cancer cases from participant self-report were also validated by interview with trained nurses. Detailed information on the verification of lung cancer incidence and lung cancer mortality could be found online at https://biobank.ctsu.ox.ac.uk/showcase/label.cgi?id=2000. Participants were followed up from baseline until the date of a lung cancer diagnosis, death, or May 21st, 2020, whichever came first.

Other variables

Based on clinical expertise and consensus among the authors, a list of independent variables was chosen a priori in this study. Variables of interest included age (in years), ethnicity, sex, family history of lung cancer, education, annual household income, Townsend Deprivation Index (a composite measure of deprivation integrating non-car and non-home ownership, unemployment and household overcrowding; a higher index indicating a greater degree of deprivation), smoking, alcohol intake, body mass index (BMI), physical activity (< 600, ≥ 600 MET min/week), consumption of fruit and vegetable, personal medical condition (including arthritis, hypertension, non-hypertensive cardiovascular disease, emphysema or chronic bronchitis, diabetes, high cholesterol, digestive disease and depression), use of aspirin and non-aspirin NSAIDs, chondroitin intake, supplementation of nutrients (vitamins, minerals and other dietary supplementation including fish oil, zinc, calcium, iron and selenium), and lung function evaluated by spirometry (forced expiratory volume in 1 second [FEV1], in liters).

Data on aspirin and non-aspirin NSAIDs were obtained from participant self-reports in combination with the information on treatment/medication received at baseline from the interview. Likewise, to

minimize the under-recognition of data on personal medical condition at baseline, we used the information from participant self-reports, baseline ICD-9/ICD-10 codes and the data on treatment/medication received during the interview with nurses. To support the accuracy of self-reported data, we cross-checked the information from self-reports with ICD codes for identification of personal medical condition at baseline. Dara from self-reports were largely consistent with those from ICD codes, with a Kappa statistic ranging from 0.43 (for digestive disease) to 0.72 (emphysema or chronic bronchitis).

Statistical analysis

Continuous variables were shown as mean and standard deviation (SD), and categorical variables as counts and percentages. We used Kaplan-Meier method to graph survival curves for lung cancer and compared survival between glucosamine users and non-users by the log-rank test. Cox proportion hazards model were employed to quantify the association between glucosamine and risk of lung cancer, where the assumption of proportional hazards was evaluated by both a statistical test and the Schoenfeld residuals.

We first performed a basic model adjusted for age, sex and smoking to explore the relationship between glucosamine and lung cancer risk. A fully-adjusted model was then conducted by adjusting for age, ethnicity, sex, family history of lung cancer, education, annual income, Townsend Deprivation Index, smoking and drinking, BMI, physical activity, fruit and vegetable intake, health condition, use of NSAID, use of chondroitin, FEV1, and nutrient supplementation. Covariates with a variance inflation factor of ≥ 4 were removed from the fully-adjusted model to avoid the effect of multicollinearity between the risk factors. Results were demonstrated as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). Similar analyses were performed to evaluate the association between glucosamine and risk of lung cancer mortality.

To investigate potential effect modifications on the relationship between glucosamine and risk of lung cancer, several a priori subgroup analyses were carried out by sex (males vs females), ethnicity (white vs others), age (< 55 vs ≥ 55 years), family history of lung cancer (no vs yes), physical activity (≥ 600 vs < 600 MET min/week), obesity (no vs yes), smoking (never vs former vs current), drinking (never vs former vs current), use of aspirin (no vs yes), use of non-aspirin NSAIDs (no vs yes), arthritis (no vs yes), hypertension (no vs yes), diabetes (no vs yes), emphysema or chronic bronchitis (no vs yes),

vitamin supplementation (no vs yes), and nutrient supplementation for non-vitamins (no vs yes). The potential effect modifications were assessed by modeling the cross-product term of the stratifying covariate with use of glucosamine in the fully-adjusted model. Moreover, we evaluated whether there was a dose-response relationship between glucosamine use and lung cancer risk in quartiles of FEV1 in the fully-adjusted model, taking the lowest quartile as reference.

To explore the robustness of main findings, we performed a sensitivity analysis by performing a competing risk analysis that took all-cause death as a competing event for lung cancer, where the cumulative incidence curves were used to display the marginal probability of lung cancer in the presence of competing events. Another three sensitivity analyses were also conducted by 1) excluding participants taking chondroitin from analysis because those using glucosamine also tended to consume chondroitin simultaneously, 2) using ten multiple imputation technique to impute the missing data, and 3) calculating a propensity score for each participant and running the fully-adjusted model after further adjusting for the individual propensity score.

Unless otherwise specified, all tests were two-sided with a significance level of 0.05. We used the STATA Version 17 (StataCorp., College Station, TX, USA) and R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) for analyses in this study.

Results

A total of 439,393 participants were included in this study with 4,874,665 person-years for analyses. Among the overall participants, the average age was 56.18 years (SD = 8.10), and 53% were females (**Table 1**). Baseline characteristics according to the use of glucosamine are also displayed in **Table 1**. There were 82,603 (18.80%) participants reporting regular use of glucosamine at baseline. Compared with non-glucosamine users, glucosamine users were older, had a higher proportion of females and a lower degree of deprivation. They tended to be more physically active, were more likely to have a family history of lung cancer, and less likely to be current smokers compared with non-glucosamine users. Glucosamine users also tended to consume fruits, vegetables, non-aspirin NSAIDs and nutrient supplementation. A lower prevalence of emphysema or chronic bronchitis, diabetes and high cholesterol was found in glucosamine users. Glucosamine users had a lower FEV1 than non-users.

During a mean follow-up of 11.09 years (11.12 and 11.08 years for glucosamine users and non-users respectively), there were 1,971 (0.45%) lung cancer events documented. A significantly lower lung cancer incidence was observed in glucosamine users compared with non-users (0.37% vs 0.47%, $p < 0.001$). **Figure 1** shows the Kaplan-Meier curves for the probability of lung cancer between glucosamine users and non-users ($p < 0.001$ for log-rank test).

Table 2 displays the association between glucosamine use and risk of lung cancer. The use of glucosamine was significantly related with decreased risk of lung cancer: HR = 0.73 (95% CI: 0.65 - 0.83, $p < 0.001$) from the basic model, and HR = 0.84 (95% CI: 0.75 - 0.92, $p < 0.001$) from the fully-adjusted model. Among the lung cancer events, there were 1,539 deaths (78.08%) occurred during the follow-up, in which a significantly smaller lung cancer mortality incidence was reported in glucosamine users than non-users (0.28% vs 0.37%, $p < 0.001$). Significantly decreased risk of lung cancer mortality was observed to be associated with use of glucosamine, with a HR of 0.88 (95% CI: 0.81 - 0.96, $p = 0.002$) found from the fully-adjusted model.

We performed several predefined subgroup analyses to explore the potential subgroup effect (**Figure 2**). Stronger relationship between glucosamine use and decreased risk of lung cancer was found in participants with a family history of lung cancer when compared to those without a family history ($p = 0.02$ for interaction). A lower HR between glucosamine use and risk of lung cancer was observed in participants reporting use of aspirin; however the effect modification was not statistically significant ($p = 0.07$ for interaction). The association between glucosamine use and risk of lung cancer mortality was not modified by the stratifying risk factors, with all p-values for interaction of > 0.05.

A similar relationship between glucosamine use and risk of lung cancer was observed based on the quartiles of FEV1, with HRs ranging from 0.84 to 0.88 (**Supplemental Table 1; Figure 3**). There was no significant dose-response relationship for quartiles of FEV1 regarding the association between glucosamine use and lung cancer risk ($p = 0.39$).

There were 13,592 deaths as competing events documented during follow-up in participants without a lung cancer. **Supplemental Figure 2** depicts the cumulative incidence curves according to the use of glucosamine, which shows a similar pattern to the Kaplan-Meier curves. The competing risk analysis yielded consistent findings with those from Cox proportion hazards model (**Supplemental Table 2**). Similar findings to the main results were also found in the other sensitivity analyses by excluding

participants taking chondroitin, performing multiple imputation for missing data, and further adjusting for propensity scores in the fully-adjusted model.

Discussion

In this study based on data from the prospective UK Biobank study, we found that regular use of glucosamine was significantly related with a 16% lower risk of lung cancer and a 12% decreased risk of lung cancer mortality. Second, the relationship between glucosamine use and risk of lung cancer was modified by participants' status regarding family history of lung cancer. No significant dose-response relationship for quartiles of FEV1 was observed. Results from sensitivity analyses supported the robustness of the main findings.

Consistent with the previous VITAL (VITamins And Lifestyle) study showing an inverse relationship between glucosamine use and risk of lung cancer [7], our current study used the data from 439,393 participants with a follow-up of 11 years to further support the decreased risk of lung cancer and lung cancer mortality in glucosamine users. Glucosamine was well-known to have the anti-inflammatory properties that were expected to prevent the development of lung cancer, in which the use of anti-inflammatory agents had been linked to 20-40% reductions in risk of lung cancer [3, 11, 12]. More specifically, a significant reduction of circulating C-reactive protein concentration as a biomarker of systematic inflammation had been reported in glucosamine users [5, 13], thereby yielding an anti-cancer potential for pulmonary inflammation in lung carcinogenesis [14]. Other biological plausibility for the potential protective effect of glucosamine on lung cancer included its anti-cancer activities by influencing pathways involved in cell proliferation, apoptosis, angiogenesis, migration and invasion [15]. For instance, glucosamine was found to inhibit phosphorylation of FOXO (forkhead transcription factors of the O class) *in vitro* and therefore suppress the translocation of FOXO from nucleus to cytoplasm, potentially reducing the risk of developing lung cancer [6]. Moreover, glucosamine was involved into antioxidant activities by scavenging the superoxide and hydroxyl radicals and protecting the macromolecules. While oxidative stress had been consistently identified to associate with increased lung cancer risk [16, 17], the antioxidant properties of glucosamine may thus help with interpreting its potential anti-lung cancer mechanism. Furthermore, a previous animal study reported that glucosamine could mimic a low carbohydrate diet featured with reduced glycolysis and

improved amino acid catabolism [18]. This may also partly explain the anti-lung cancer effect of glucosamine because low carbohydrate diets were significantly related with a decreased lung cancer risk as reported from a recent large prospective cohort study [19].

The relationship between glucosamine use and lung cancer risk was statistically stronger in participants with a family history of lung cancer than those without (HRs: 0.59 vs 0.90). Based on findings from a systematic review, family history of lung cancer as a significant risk factor for lung cancer was associated with a 15% higher risk approximately when compared with no family history, with a pooled odds ratio of 1.87 from case-control studies and a pooled relative risk of 1.82 from cohort studies respectively [20]. The propensity towards an elevated lung cancer risk in participants with a family history may be largely due to genetic and environmental factors that led to a consistently increased status of inflammation and oxidative stress [21, 22]; therefore glucosamine with its anti-inflammatory and antioxidant properties may be linked to a higher magnitude of the inverse association between glucosamine use and lung cancer risk in participants with a family history. However, our observational study was of exploratory nature and primarily hypothesis generating; therefore results should be interpreted with caution. More prospective studies and intervention trials are required to investigate the favorable effect of glucosamine in lung cancer prevention especially among those with a family history of cancer.

Use of NSAIDs or smoking status was not found to significantly modify the relationship between glucosamine use and lung cancer risk. However, it was difficult to identify the true absence of subgroup effect in an observational study because potential information bias or residual confounding effect could not be fully precluded even though we had carefully adjusted for potential confounding factors in the models [23, 24]. A previous study based on the data from UK Biobank study reported that adding FEV1 could modestly enhance discriminatory accuracy of the prediction model for the 2-year lung cancer risk, suggesting the important predictive value of FEV1 in lung cancer risk assessment [9]. Nevertheless, glucosamine users were found to have a lower FEV1 than non-users at baseline. Furthermore, no dose-response relationship of FEV1 was observed in the measures of association between glucosamine use and lung cancer risk. Likewise, we could not fully exclude the moderating effect of FEV1 on the relationship between glucosamine use and lung cancer risk, given the potential residual confounding and unmeasured variances in an observational study. However, the consistent inverse association between glucosamine use and lung cancer risk throughout the quartiles

of FEV1 further supported the favorable effect of glucosamine, regardless of participants' measures of lung function.

Comparison with other studies

While glucosamine use had been found to be significantly associated with decreased risk of colorectal cancer [25, 26], CVD [27, 28], diabetes [29], and all-cause death [27, 30], evidence on the relationship between glucosamine use and risk of lung cancer remained sparse and limited. The VITAL study as the only clinical investigation, collected dietary supplement data via mailed questionnaires from 76,904 USA participants and reported a significant association between glucosamine and decreased lung cancer risk. In our study, data on glucosamine were collected from participants' self-reports and interview with nurses in assessment centers based on a nationwide and multi-centered cohort [8]. Our results from a large sample size and a wealth of covariates were in agreement with the VITAL study. Unlike the VITAL study, we further explored the relationship between glucosamine use and lung cancer mortality, and performed a competing risk analysis taking all-cause death as competing events for lung cancer. These analyses strengthened the inverse association between glucosamine use and lung cancer risk. Nevertheless, given the non-randomized design in observational studies, well-designed clinical trials would be required to evaluate the efficacy of glucosamine in lung cancer.

Strengths and Limitations

Strengths of this study include the use of data from one of the largest prospective cohorts worldwide, the amount of information available in the cohort, and rigorous and comprehensive statistical analyses performed. The possibility of differential reporting bias for glucosamine use was minimal because we excluded participants with a baseline cancer diagnosis for analyses and all included participants finished the baseline assessment before a diagnosis of lung cancer. Nonetheless, our study has several limitations. First, no detailed information on the glucosamine consumption pattern including the forms, dosages and duration of use was collected in the cohort. This may weaken the study findings because for instance, in many epidemiological studies the duration of nutrient consumption would yield substantially different or even contradictory results. Likewise, data on glucosamine use were from self-reports without linkage to other sources for verification. Therefore more evidence that incorporates the glucosamine intake pattern and cross-validates the data on glucosamine for accuracy

is needed to further investigate the relationship between glucosamine use and lung cancer risk. In addition, regular glucosamine use might be a surrogate for a healthy lifestyle [28]; however it is difficult to isolate the effect of a healthy lifestyle from the effect of glucosamine in our study even though we had adjusted for physical activity, fruit and vegetable intake, and nutrient supplementation in the models. The observed inverse relationship between glucosamine use and lung cancer risk may be driven by some unmeasured factors related to a healthy lifestyle, which would provide glucosamine users with an artificial benefit compared with glucosamine non-users and therefore overestimate the inverse association between glucosamine use and lung cancer risk. Likewise, potential residual confounding and biases could not be fully precluded in an observational study design. Furthermore, there has been a debate on whether the UK Biobank participants are representative of the general population taking into consideration the low response rate to its baseline survey (5.5% baseline response rate), thereby potentially compromising the generalizability of study findings. Thus our results should be interpreted with caution and are hypothesis generating, requiring more evidence to further clarify the relationship between glucosamine use and decreased lung cancer risk.

Conclusions

Regular use of glucosamine was significantly related with decreased risk of lung cancer and lung cancer mortality, based on data from the large nationwide prospective cohort study.

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Disclosure:

GYHL has served as a consultant for Novartis, Bayer/Janssen, Biotronik, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Verseon, and Daiichi-Sankyo and as a speaker for Medtronic, Bayer, BMS/Pfizer, Boehringer Ingelheim, and Daiichi-Sankyo. No fees have been received directly or personally. All other authors have declared no conflicts of interest.

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Author contributions:

GL, XZ, LT and GYHL: conceived and designed the study. GL, XZ, YL, LL, JZ and GYHL: acquired data, performed analyses and interpretation, and drafted the manuscript. GL, XH, LT, and GYHL: provided professional and statistical support, and made critical revisions. All authors read and approved the final manuscript. GL, LT and GYHL acted as the guarantors of this work.

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Table and figure legends：

Table 1. Baseline characteristics of the study participants by use of glucosamine

Figure 1. Kaplan-Meier curves for the probability of lung cancer between glucosamine users and non-users

Table 2. Relationship between glucosamine use and risk of lung cancer and lung cancer mortality

Figure 2. Relationship between glucosamine use and risk of lung cancer and lung cancer mortality stratified by potential risk factors. Findings were adjusted for age, ethnicity, sex, family history of lung cancer, education, annual income, Townsend Deprivation Index, smoking and drinking, BMI, physical activity, fruit and vegetable intake, health condition, NSAID use, chondroitin use, FEV1, and nutrient supplementation

Figure 3. Dose-response relationship in quartiles of FEV1 regarding the association between glucosamine use and lung cancer risk. The red color (on top of blue) represents the number of lung caner cases in glucosamine non-users, while the yellow color (on top of green) represents the number of lung cancer cases in glucosamine users. Findings were adjusted for age, ethnicity, sex, family history of lung cancer, education, annual income, Townsend Deprivation Index, smoking and drinking, BMI, physical activity, fruit and vegetable intake, health condition, NSAID use, chondroitin use, FEV1, and nutrient supplementation

Table 1. Baseline characteristics of the study participants by use of glucosamine

Characteristics	All participants (n = 439,393)	Use of glucosamine	
		Yes (n = 82,603)	No (n = 356,790)
Age (years), mean (SD)	56.18 (8.10)	58.78 (7.13)	55.58 (8.20)
Female sex, n (%)	232,946 (53.0)	50,646 (61.3)	18,2300 (51.1)
BMI (kg/m^2), mean (SD)	27.44 (4.79)	27.37 (4.65)	27.46 (4.82)
Townsend Deprivation Index, mean (SD)	-1.30 (3.09)	-1.79 (2.80)	-1.19 (3.14)
Annual household income*, n (%)			
< 18,000	83,318 (22.1)	14,540 (20.7)	68,778 (22.4)
18,000-30,999	94,757 (25.1)	19,887 (28.3)	74,870 (24.4)
31,000-51,999	99,352 (26.4)	18,809 (26.8)	80,543 (26.3)
52,000-100,000	78,661 (20.1)	13,632 (19.4)	65,029 (21.2)
>100,000	20,890 (5.5)	3,369 (4.8)	17,521 (5.7)
Physical activity (≥ 600 MET min/week), n (%)	289,690 (81.3)	57,688 (85.5)	232,002 (80.3)
Family history of lung cancer, n (%)	54,119 (12.3)	10,563 (12.8)	43,556 (12.2)
White ethnicity, n (%)	413,052 (94.3)	79,013 (95.9)	334,039 (94.0)
With college or university degree, n (%)	143,842 (33.1)	27,456 (33.5)	116,386 (33.0)
Smoking status, n (%)			
Never	242,274 (55.3)	45,742 (55.6)	196,532 (55.3)
Former	149,376 (34.1)	31,232 (37.9)	118,144 (33.2)
Current	46,143 (10.5)	5,356 (6.5)	40,787 (11.5)
Drinking status, n (%)			
Never	19,519 (4.5)	2,856 (3.5)	16,663 (4.7)
Former	15,476 (3.5)	2,323 (2.8)	13,153 (3.7)
Current	403,896 (92.0)	77,371 (93.7)	326,525 (91.6)
Fruit intake of ≥4.0 servings/day, n (%)	136,522 (31.5)	32,939 (40.3)	103,583 (29.5)
Vegetable intake of ≥4.0 servings/day, n (%)	135,295 (31.4)	28,784 (35.3)	106,511 (30.5)
Personal medical condition			
Hypertension, n (%)	249,111 (56.7)	47,979 (58.1)	201,132 (56.4)
Non-hypertensive CVD, n (%)	41,039 (9.3)	7,301 (8.8)	33,738 (9.5)
Arthritis, n (%)	27,545 (6.2)	7,992 (9.6)	19,553 (5.5)
Emphysema or chronic bronchitis, n (%)	8,495 (1.9)	1,438 (1.7)	7,057 (1.9)
Diabetes, n (%)	29,705 (6.8)	4,438 (5.4)	25,267 (7.1)
High cholesterol, n (%)	82,759 (18.8)	15,084 (18.3)	67,675 (19.0)
Digestive disease, n (%)	72,433 (16.5)	13,646 (16.5)	58,787 (16.5)
Depression, n (%)	67,320 (15.3)	12,881 (15.6)	54,439 (15.3)
Medication or supplementation			
Use of aspirin, n (%)	61,850 (14.1)	11,663 (14.2)	50,187 (14.1)
Use of non-aspirin NSAIDs, n (%)	65,020 (14.8)	15,517 (18.8)	49,503 (13.9)
Use of chondroitin, n (%)	5,530 (1.3)	5,157 (6.2)	373 (0.1)
Use of vitamin supplementation, n (%)	138,045 (31.5)	45,748 (55.6)	92,297 (26.0)
Use of minerals and other dietary supplementation, n (%)	161,491 (36.8)	57,049 (69.1)	104,445 (29.3)
FEV1 (liters), mean (SD)	2.84 (0.80)	2.75 (0.77)	2.86 (0.82)

SD = standard deviation; BMI = body mass index; CVD = cardiovascular disease; NSAID = non-steroidal anti-inflammatory drug; FEV1 = forced expiratory volume in 1 second

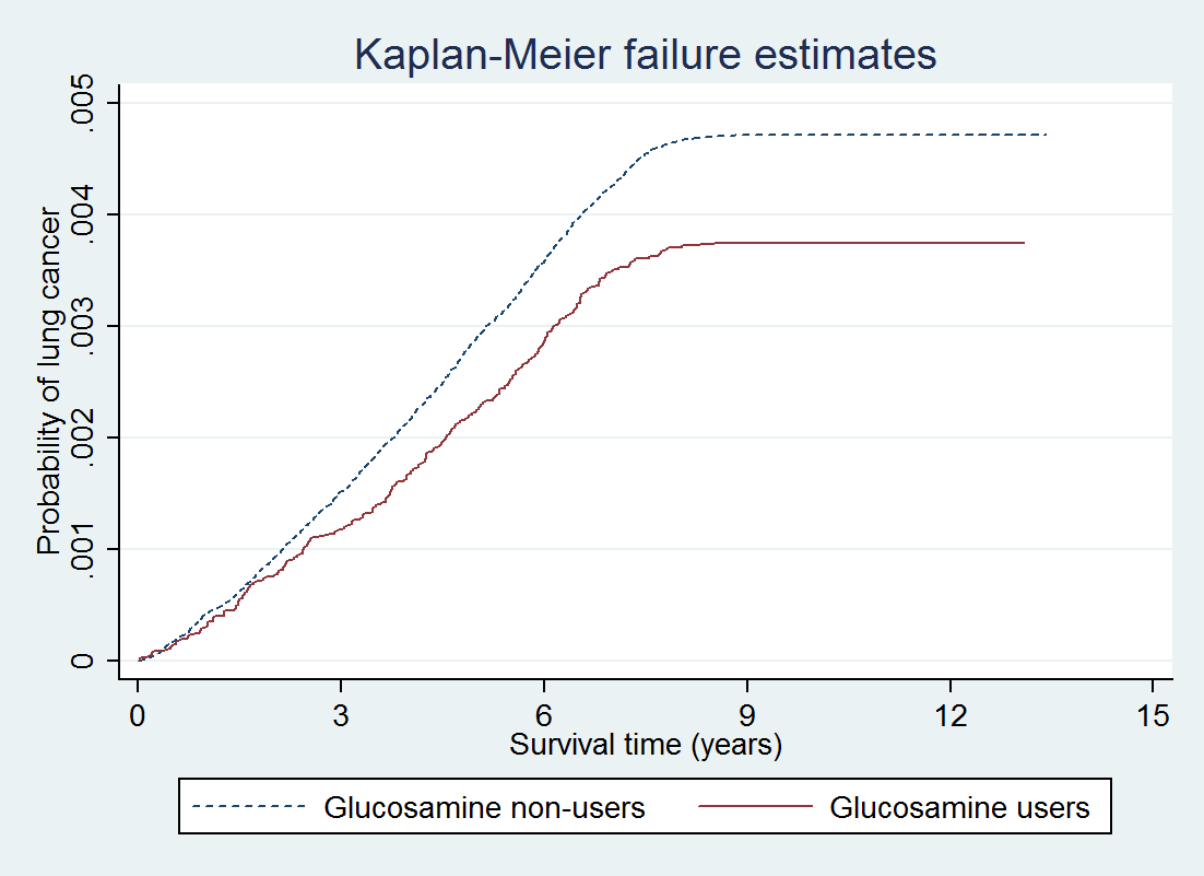
* in British Pound

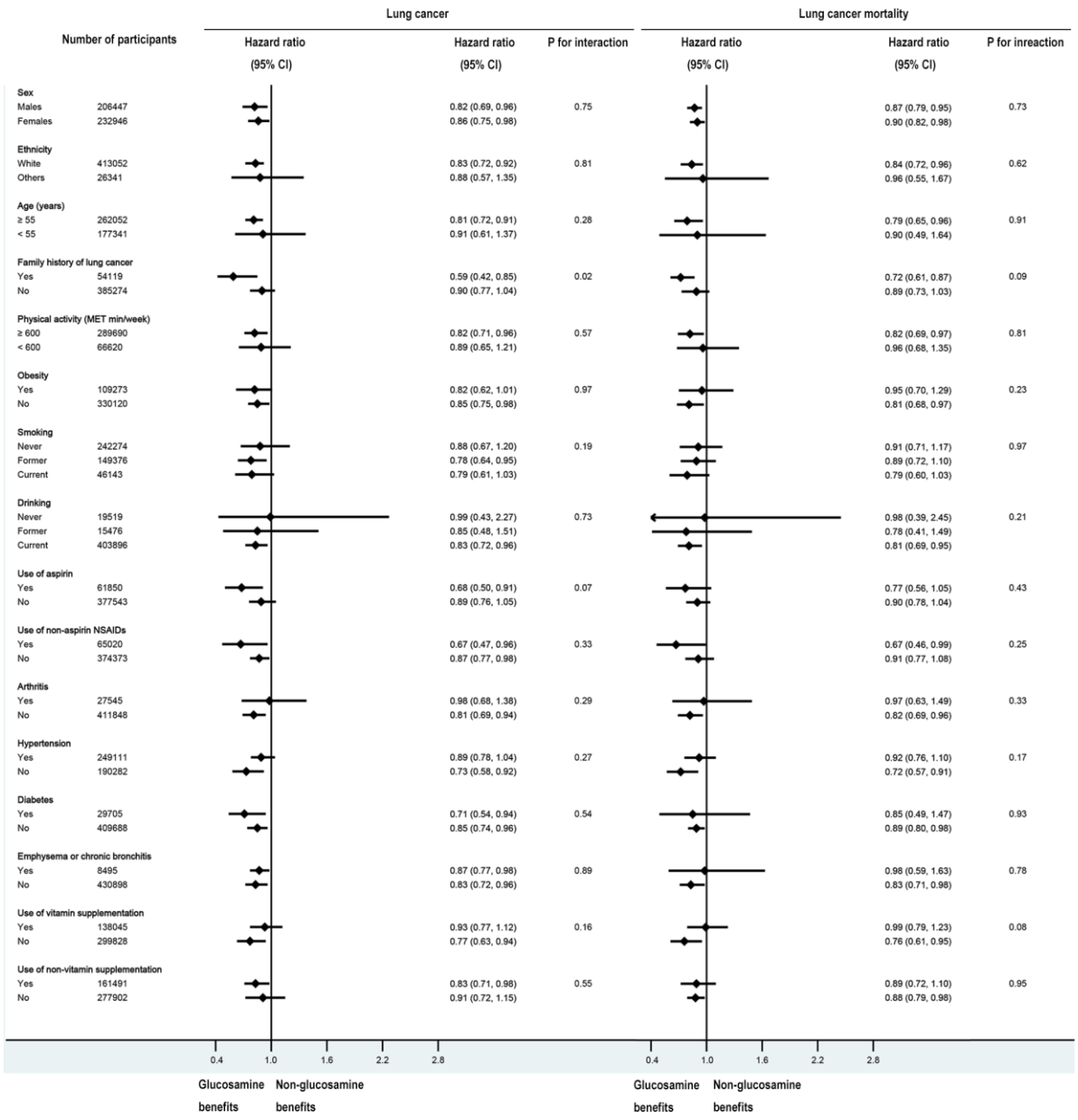
Table 2. Relationship between glucosamine use and risk of lung cancer and lung cancer mortality

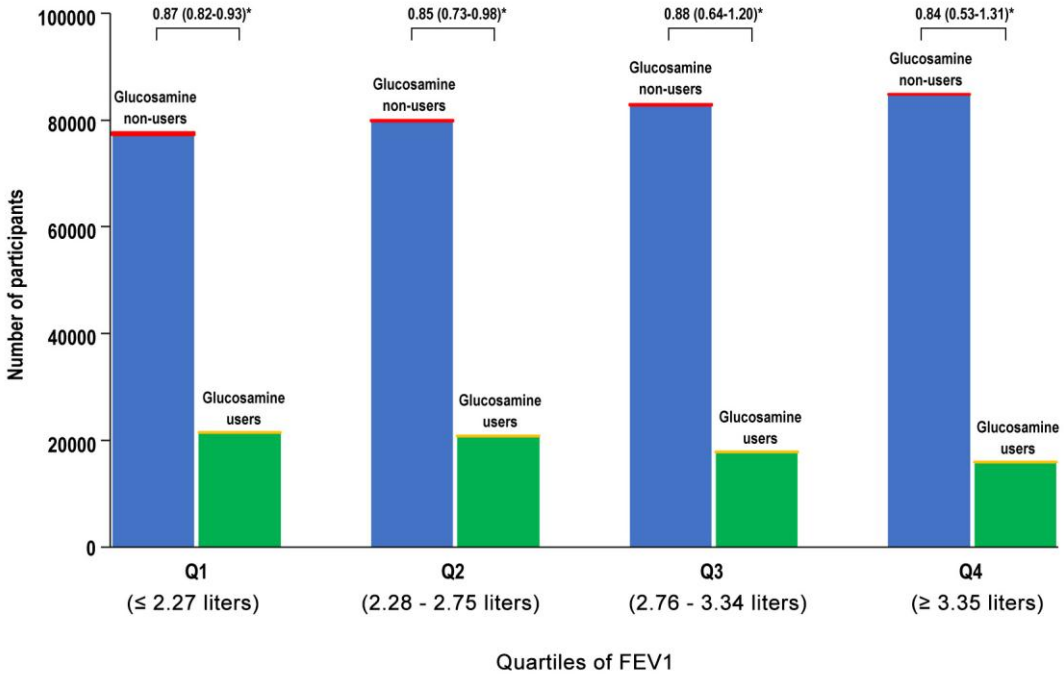
	Glucosamine non-user	Glucosamine user	P-value
Lung cancer			
Case, n (%)	1664 (0.47)	307 (0.37)	< 0.001
HRs (95% CI) from age-, sex- and smoking-adjusted model	Reference	0.73 (0.65 - 0.83)	< 0.001
HRs (95% CI) from fully-adjusted model*	Reference	0.84 (0.75 - 0.92)	< 0.001
Lung cancer mortality			
Case, n (%)	1304 (0.37)	235 (0.28)	< 0.001
HRs (95% CI) from age-, sex- and smoking-adjusted model	Reference	0.72 (0.63 - 0.84)	< 0.001
HRs (95% CI) from fully-adjusted model*	Reference	0.88 (0.81 - 0.96)	0.002

HR = hazard ratio; CI = confidence interval

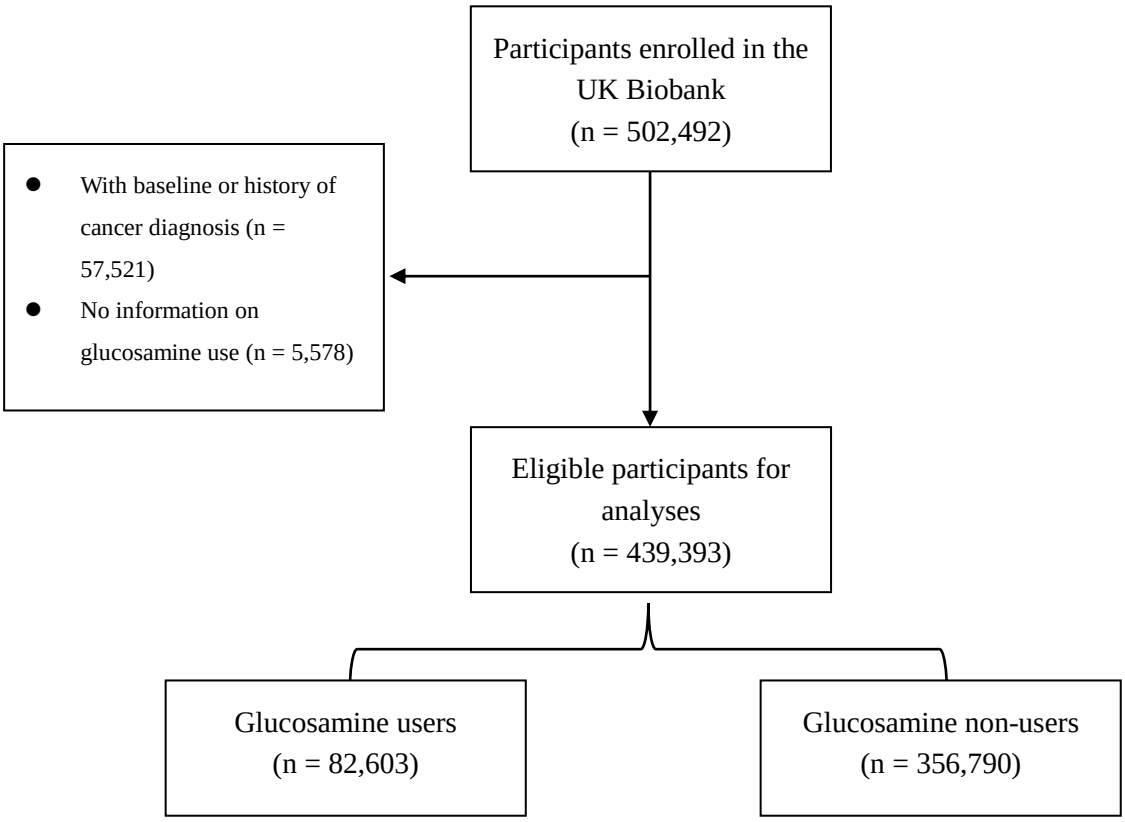
* model adjusted for age, ethnicity, sex, family history of lung cancer, education, annual income, Townsend Deprivation Index, smoking and drinking, BMI, physical activity, fruit and vegetable intake, health condition, NSAID use, chondroitin use, FEV1, and nutrient supplementation


Kaplan-Meier failure estimates
Probability of lung cancer
0
.001
.002
.003
.004
.005
0
3
6
9
12
15
Survival time (years)
Glucosamine non-users
Glucosamine users

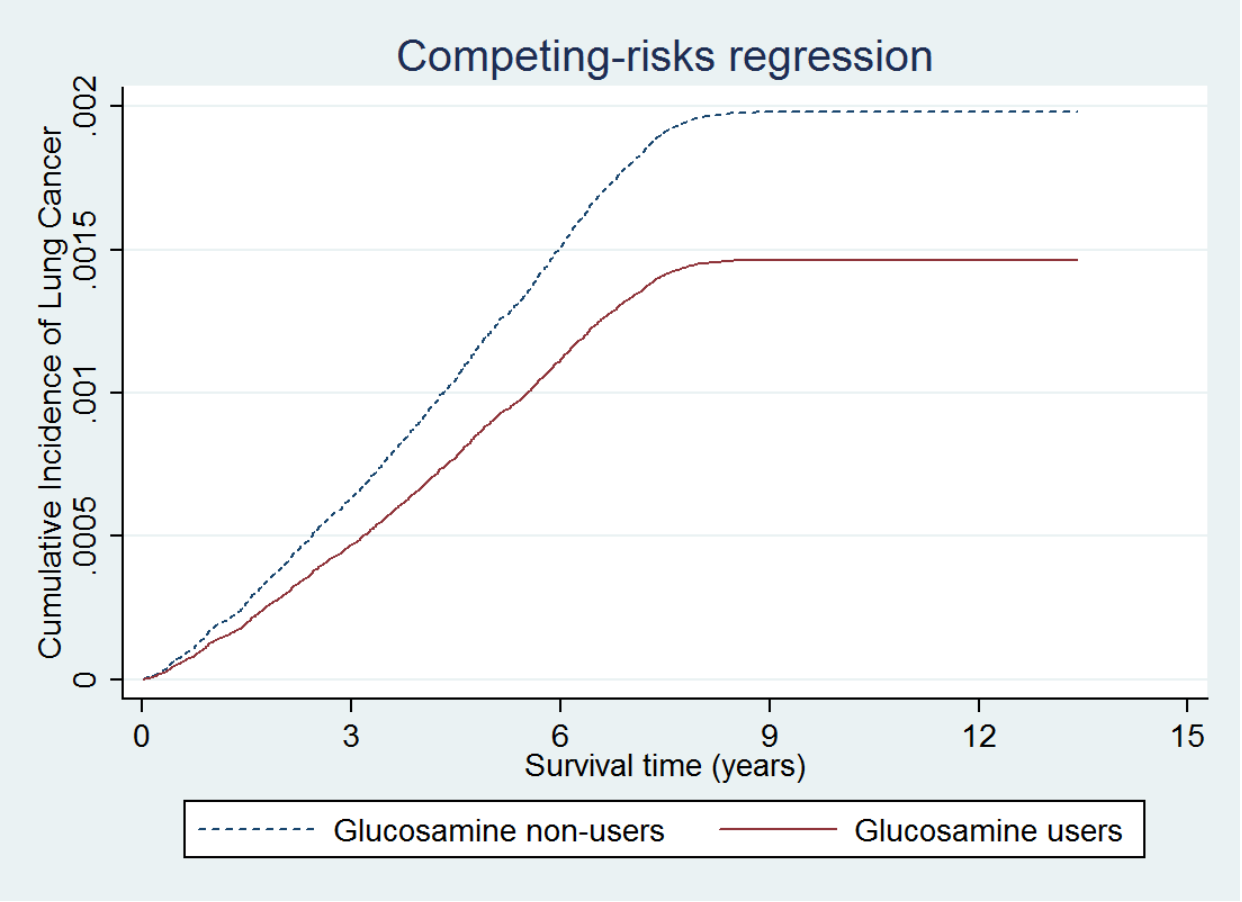

Lung cancer
Lung cancer mortality
Number of participants
Hazard ratio (95% CI)
Hazard ratio (95% CI)
P for interaction
Hazard ratio (95% CI)
Hazard ratio (95% CI)
P for inreaction
Sex
Males 206447 0.82 (0.69, 0.96) 0.75 0.87 (0.79, 0.95) 0.73
Females 232946 0.86 (0.75, 0.98) 0.90 (0.82, 0.98)
Ethnicity
White 413052 0.83 (0.72, 0.92) 0.81 0.84 (0.72, 0.96) 0.62
Others 26341 0.88 (0.57, 1.35) 0.96 (0.55, 1.67)
Age (years)
≥ 55 262052 0.81 (0.72, 0.91) 0.28 0.79 (0.65, 0.96) 0.91
< 55 177341 0.91 (0.61, 1.37) 0.90 (0.49, 1.64)
Family history of lung cancer
Yes 54119 0.59 (0.42, 0.85) 0.02 0.72 (0.61, 0.87) 0.09
No 385274 0.90 (0.77, 1.04) 0.89 (0.73, 1.03)
Physical activity (MET min/week)
≥ 600 289690 0.82 (0.71, 0.96) 0.57 0.82 (0.69, 0.97) 0.81
< 600 66620 0.89 (0.65, 1.21) 0.96 (0.68, 1.35)
Obesity
Yes 109273 0.82 (0.62, 1.01) 0.97 0.95 (0.70, 1.29) 0.23
No 330120 0.85 (0.75, 0.98) 0.81 (0.68, 0.97)
Smoking
Never 242274 0.88 (0.67, 1.20) 0.19 0.91 (0.71, 1.17) 0.97
Former 149376 0.78 (0.64, 0.95) 0.89 (0.72, 1.10)
Current 46143 0.79 (0.61, 1.03) 0.79 (0.60, 1.03)
Drinking
Never 19519 0.99 (0.43, 2.27) 0.73 0.98 (0.39, 2.45) 0.21
Former 15476 0.85 (0.48, 1.51) 0.78 (0.41, 1.49)
Current 403896 0.83 (0.72, 0.96) 0.81 (0.69, 0.95)
Use of aspirin
Yes 61850 0.68 (0.50, 0.91) 0.07 0.77 (0.56, 1.05) 0.43
No 377543 0.89 (0.76, 1.05) 0.90 (0.78, 1.04)
Use of non-aspirin NSAIDs
Yes 65020 0.67 (0.47, 0.96) 0.33 0.67 (0.46, 0.99) 0.25
No 374373 0.87 (0.77, 0.98) 0.91 (0.77, 1.08)
Arthritis
Yes 27545 0.98 (0.68, 1.38) 0.29 0.97 (0.63, 1.49) 0.33
No 411848 0.81 (0.69, 0.94) 0.82 (0.69, 0.96)
Hypertension
Yes 249111 0.89 (0.78, 1.04) 0.27 0.92 (0.76, 1.10) 0.17
No 190282 0.73 (0.58, 0.92) 0.72 (0.57, 0.91)
Diabetes
Yes 29705 0.71 (0.54, 0.94) 0.54 0.85 (0.49, 1.47) 0.93
No 409688 0.85 (0.74, 0.96) 0.89 (0.80, 0.98)
Emphysema or chronic bronchitis
Yes 8495 0.87 (0.77, 0.98) 0.89 0.98 (0.59, 1.63) 0.78
No 430898 0.83 (0.72, 0.96) 0.83 (0.71, 0.98)
Use of vitamin supplementation
Yes 138045 0.93 (0.77, 1.12) 0.16 0.99 (0.79, 1.23) 0.08
No 299828 0.77 (0.63, 0.94) 0.76 (0.61, 0.95)
Use of non-vitamin supplementation
Yes 161491 0.83 (0.71, 0.98) 0.55 0.89 (0.72, 1.10) 0.95
No 277902 0.91 (0.72, 1.15) 0.88 (0.79, 0.98)
0.4
1.0
1.6
2.2
2.8
Glucosamine benefits
Non-glucosamine benefits
0.4
1.0
1.6
2.2
2.8
Glucosamine benefits
Non-glucosamine benefits


0.87 (0.82-0.93)*
0.85 (0.73-0.98)*
0.88 (0.64-1.20)*
0.84 (0.53-1.31)*
100000
80000
60000
40000
20000
0
Number of participants
Glucosamine non-users
Glucosamine users
Q1
(≤ 2.27 liters)
Q2
(2.28 - 2.75 liters)
Q3
(2.76 - 3.34 liters)
Q4
(≥ 3.35 liters)
Quartiles of FEV1

Supplemental figure 1. Flow diagram showing participants selection process in this study



Supplemental Figure 2. Cumulative incidence curves for the marginal probability of lung cancer in the presence of competing events between glucosamine users and non-users



Supplemental Table 1. Results for the relationship between glucosamine use and lung cancer risk according to quartiles of FEV1*

Quartiles of FEV1[#]	**Glucosamine users**		**Glucosamine non-users**		**Hazard ratio (95% CI)**
	Number of participants	Number of lung cancer cases	Number of participants	Number of lung cancer cases	
Q1	21,488	122	77,794	655	0.87 (0.82 - 0.93)
Q2	20,811	74	80,051	352	0.85 (0.73 - 0.98)
Q3	17,810	40	83,025	235	0.88 (0.64 - 1.20)
Q4	15,935	29	84,918	138	0.84 (0.53 - 1.31)

[*] model adjusted for age, ethnicity, sex, family history of lung cancer, education, annual income, Townsend Deprivation Index, smoking and drinking, BMI, physical activity, fruit and vegetable intake, health condition, NSAID use, chondroitin use and nutrient supplementation

[#] if 0≤FEV1< 2.28 liters, then participants were grouped into Q1; if 2.28≤FEV1< 2.76, then participants were grouped into Q2; if 2.76≤FEV1< 3.35, then participants were grouped into Q3; if FEV1≥3.35, then participants were grouped into Q4

Supplemental table 2. Results from sensitivity analyses for the relationship between glucosamine use and risk of lung cancer and lung cancer mortality

Sensitivity analysis	HR (95% CI)	P-value
Lung cancer		
Performing competing risk analysis[1]	0.83 (0.74 - 0.92)	< 0.001
Excluding participants taking chondroitin[2]	0.85 (0.77 - 0.94)	< 0.001
Using multiple imputation for missing data[3]	0.81 (0.71 - 0.92)	0.003
Adjusting for propensity score[3,4]	0.79 (0.69 - 0.91)	< 0.001
Lung cancer mortality		
Excluding participants taking chondroitin[2]	0.87 (0.78 - 0.95)	0.006
Using multiple imputation for missing data[3]	0.85 (0.75 - 0.94)	0.008
Adjusting for propensity score[3,4]	0.90 (0.79 - 0.98)	0.010

HR = hazard ratio; CI = confidence interval

[1] there were 13,592 deaths as competing events for lung cancer; model adjusted for age, ethnicity, sex, family history of lung cancer, education, annual income, Townsend Deprivation Index, smoking and drinking, BMI, physical activity, fruit and vegetable intake, health condition, NSAID use, chondroitin use, FEV1, and nutrient supplementation

[2] there were 5,530 chondroitin users excluded for analyses; model adjusted for age, ethnicity, sex, family history of lung cancer, education, annual income, Townsend Deprivation Index, smoking and drinking, BMI, physical activity, fruit and vegetable intake, health condition, NSAID use, FEV1, and nutrient supplementation

[3] propensity score was calculated based on logistic regression with independent variables including age, ethnicity, sex, family history of lung cancer, education, annual income, Townsend Deprivation Index, smoking and drinking, physical activity, fruit and vegetable intake, arthritis, use of NSAIDs and chondroitin, FEV1, and nutrient supplementation

[4] model adjusted for age, ethnicity, sex, family history of lung cancer, education, annual income, Townsend Deprivation Index, smoking and drinking, BMI, physical activity, fruit and vegetable intake, health condition, NSAID use, chondroitin use, FEV1, and nutrient supplementation