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

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Regular use of glucosamine was significantly related with a 16% lower risk of lung cancer and a 12% decreased risk of lung cancer mortality https://bit.ly/3ixJAND

Abstract

Background Research on glucosamine shows anti-inflammatory and anti-cancer benefits with 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 2006 and 2010 and followed-up to 2020. The Cox proportional hazards model was 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 the main findings.

Results 439 393 participants (mean age 56 years; 53% females) with a mean follow-up of 11 years were included for analyses. 82 603 (18.80%) participants reported regular use of glucosamine at baseline. During follow-up, 1971 (0.45%) lung cancer events were documented. Glucosamine use was significantly associated with a decreased risk of lung cancer (hazard ratio (HR) 0.84, 95% CI 0.75–0.92; p<0.001) and lung cancer mortality (HR 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 with 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.

Introduction

Lung cancer remains the leading cause of death 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 drugs (NSAIDs) and risks of lung cancer and mortality was also observed in some studies [3, 4]. Nevertheless, NSAIDs were not recommended as a chemoprevention, largely due to concerns about their 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 (HR) 0.49, 95% CI 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 studies on lung cancer mortality related to glucosamine available in the literature. Therefore, in this study, we 1) 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, and 2) comprehensively explored the potential effect modifications by other risk factors for lung cancer on this relationship.

Methods

Participants and setting

Details of the UK Biobank study have 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 that aimed to enrol more than 500 000 participants in the UK aged 40–69 years between 2006 and 2010. Baseline data were collected through participants' self-reports, interviews with nurses and physical measurements. We excluded participants who had a history or baseline diagnosis of cancer (n=57 521) or did not have information on glucosamine use (n=5578) from this study (supplementary figure S1 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 Multicentre Research Ethics Committee in the UK.

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 "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 participants' self-reports were also validated by interviews with trained nurses. Detailed information on the verification of lung cancer incidence and lung cancer mortality can be found 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 21 May 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 or ⩾600 metabolic equivalent of task (MET) min per week), consumption of fruit and vegetables, 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 s (FEV_1), in litres).

Data on aspirin and non-aspirin NSAIDs were obtained from participants' self-reports in combination with the information on treatment/medication received at baseline from the interviews. Likewise, to minimise under-recognition of data on personal medical conditions at baseline, we used the information from participants' self-reports, baseline ICD-9/ICD-10 codes and the data on treatment/medication received during the interviews. To support the accuracy of self-reported data, we cross-checked the information from self-reports with ICD codes for identification of personal medical conditions at baseline. Data from self-reports were largely consistent with those from ICD codes, with a κ-statistic ranging from 0.43 (digestive disease) to 0.72 (emphysema or chronic bronchitis).

Statistical analysis

Continuous variables are shown as mean with standard deviation and categorical variables as count (percentage). We used the Kaplan–Meier method to graph survival curves for lung cancer, and compared survival between glucosamine users and non-users by the log-rank test. The Cox proportional hazards model was 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 NSAIDs, use of chondroitin, FEV_1, and nutrient supplementation. Covariates with a variance inflation factor $\geqslant 4$ were removed from the fully adjusted model to avoid the effect of multicollinearity between risk factors. Results are presented as hazard ratios with corresponding 95% confidence intervals. 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 (male *versus* female), ethnicity (White *versus* others), age (<55 *versus* ⩾55 years), family history of lung cancer (no *versus* yes), physical activity (⩾600 *versus* <600 MET min per week), obesity (no *versus* yes), smoking (never *versus* former *versus* current), drinking (never *versus* former *versus* current), use of aspirin (no *versus* yes), use of non-aspirin NSAIDs (no *versus* yes), arthritis (no *versus* yes), hypertension (no *versus* yes), diabetes (no *versus* yes), emphysema or chronic bronchitis (no *versus* yes), vitamin supplementation (no *versus* yes) and nutrient supplementation for non-vitamins (no *versus* yes). The potential effect modifications were assessed by modelling 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 FEV_1 in the fully adjusted model, taking the lowest quartile as reference.

To explore the robustness of the main findings, we undertook a sensitivity analysis by performing a competing risks 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 the analysis because those using glucosamine also tended to consume chondroitin simultaneously, 2) using the 10 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 Stata version 17 (StataCorp, College Station, TX, USA) and R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) for analyses.

Results

In total, 439 393 participants were included in this study with 4 874 665 person-years for analyses. Among all participants, mean±SD age was 56.18±8.10 years and 53% were females (table 1). Baseline characteristics according to use of glucosamine are also shown in table 1. 82 603 (18.80%) participants reported regular use of glucosamine at baseline. Compared with non-glucosamine users, glucosamine users were older, with a higher proportion of females and a lower degree of deprivation. They tended to be more physically active, 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 fruit and 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 FEV_1 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), 1971 (0.45%) lung cancer events were documented. A significantly lower lung cancer incidence was observed in glucosamine users compared with non-users (0.37% *versus* 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, 1539 deaths (78.08%) occurred during the follow-up, in which a significantly lower lung cancer mortality incidence was reported in glucosamine users than non-users (0.28% *versus* 0.37%; p<0.001). Significantly decreased risk of lung cancer mortality was observed to be associated with use of glucosamine, with HR 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 potential subgroup effects (figure 2). A stronger relationship between glucosamine use and decreased risk of lung cancer was found in

TABLE 1 Baseline characteristics of study participants by use of glucosamine			
	All participants (n=439 393)	Use of glucosamine	
		Yes (n=82 603)	No (n=356 790)
Age, years	56.18±8.10	58.78±7.13	55.58±8.20
Female	232 946 (53.0)	50 646 (61.3)	182 300 (51.1)
BMI, kg·m^{-2}	27.44±4.79	27.37±4.65	27.46±4.82
Townsend deprivation index	−1.30±3.09	−1.79±2.80	−1.19±3.14
Annual household income, GBP			
<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)	3369 (4.8)	17 521 (5.7)
Physical activity (≥600 MET min per week)	289 690 (81.3)	57 688 (85.5)	232 002 (80.3)
Family history of lung cancer	54 119 (12.3)	10 563 (12.8)	43 556 (12.2)
White ethnicity	413 052 (94.3)	79 013 (95.9)	334 039 (94.0)
With college or university degree	143 842 (33.1)	27 456 (33.5)	116 386 (33.0)
Smoking status			
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)	5356 (6.5)	40 787 (11.5)
Drinking status			
Never	19 519 (4.5)	2856 (3.5)	16 663 (4.7)
Former	15 476 (3.5)	2323 (2.8)	13 153 (3.7)
Current	403 896 (92.0)	77 371 (93.7)	326 525 (91.6)
Fruit intake ≥4.0 servings per day	136 522 (31.5)	32 939 (40.3)	103 583 (29.5)
Vegetable intake ≥4.0 servings per day	135 295 (31.4)	28 784 (35.3)	106 511 (30.5)
Personal medical condition			
Hypertension	249 111 (56.7)	47 979 (58.1)	201 132 (56.4)
Non-hypertensive CVD	41 039 (9.3)	7301 (8.8)	33 738 (9.5)
Arthritis	27 545 (6.2)	7992 (9.6)	19 553 (5.5)
Emphysema or chronic bronchitis	8495 (1.9)	1438 (1.7)	7057 (1.9)
Diabetes	29 705 (6.8)	4438 (5.4)	25 267 (7.1)
High cholesterol	82 759 (18.8)	15 084 (18.3)	67 675 (19.0)
Digestive disease	72 433 (16.5)	13 646 (16.5)	58 787 (16.5)
Depression	67 320 (15.3)	12 881 (15.6)	54 439 (15.3)
Medication or supplementation			
Use of aspirin	61 850 (14.1)	11 663 (14.2)	50 187 (14.1)
Use of non-aspirin NSAIDs	65 020 (14.8)	15 517 (18.8)	49 503 (13.9)
Use of chondroitin	5530 (1.3)	5157 (6.2)	373 (0.1)
Use of vitamin supplementation	138 045 (31.5)	45 748 (55.6)	92 297 (26.0)
Use of minerals and other dietary supplementation	161 491 (36.8)	57 049 (69.1)	104 445 (29.3)
FEV$_1$, L	2.84±0.80	2.75±0.77	2.86±0.82

Data are presented as mean±SD or n (%); some participants did not answer all the questions, which resulted in missing data for some variables. BMI: body mass index; MET: metabolic equivalent of task; CVD: cardiovascular disease; NSAID: non-steroidal anti-inflammatory drug; FEV$_1$: forced expiratory volume in 1 s.

participants with a family history of lung cancer when compared with those without a family history (p=0.02 for interaction). A lower hazard ratio 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 >0.05.

A similar relationship between glucosamine use and risk of lung cancer was observed based on the quartiles of FEV$_1$, with HRs ranging from 0.84 to 0.88 (supplementary table S1 and figure 3). There was no significant dose–response relationship for quartiles of FEV$_1$ regarding the association between glucosamine use and lung cancer risk (p=0.39).

13 592 deaths as competing events were documented during follow-up in participants without lung cancer. Supplementary figure S2 depicts the cumulative incidence curves according to the use of glucosamine,
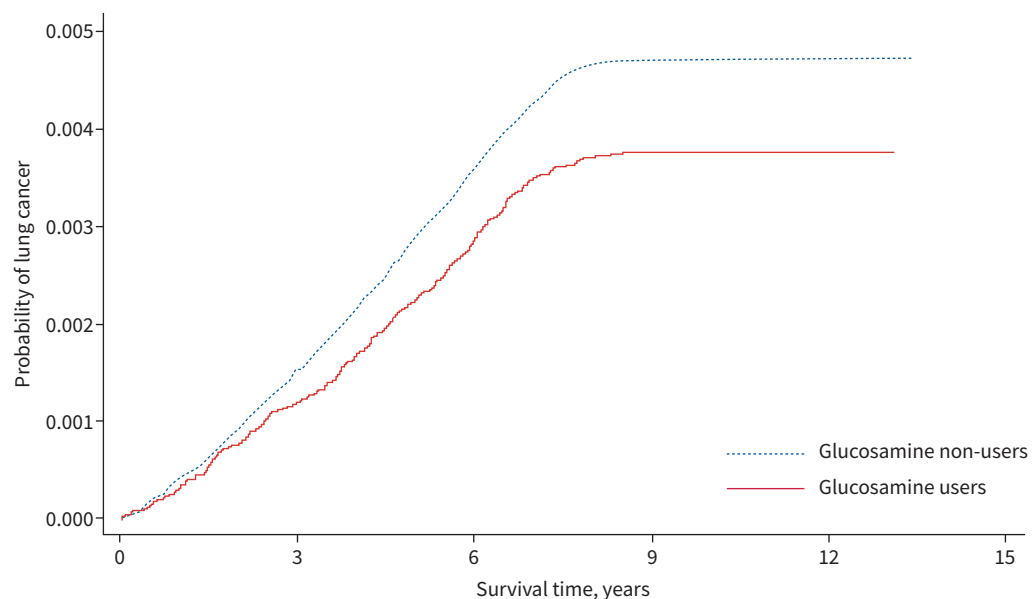
FIGURE 1 Kaplan–Meier curves for the probability of lung cancer between glucosamine users and non-users.

which show a similar pattern to the Kaplan–Meier curves. The competing risks analysis yielded consistent findings with those from the Cox proportional hazards model (supplementary table S2). 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 1) regular use of glucosamine was significantly related with a 16% lower risk of lung cancer and a 12% decreased risk of lung cancer mortality, and 2) 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 FEV_1 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

TABLE 2 Relationship between glucosamine use and risk of lung cancer and lung cancer mortality			
	Glucosamine non-user	**Glucosamine user**	**p-value**
Lung cancer			
Cases, n (%)	1664 (0.47)	307 (0.37)	<0.001
HR (95% CI) from age-, sex- and smoking-adjusted model	Reference	0.73 (0.65–0.83)	<0.001
HR (95% CI) from fully adjusted model#	Reference	0.84 (0.75–0.92)	<0.001
Lung cancer mortality			
Cases, n (%)	1304 (0.37)	235 (0.28)	<0.001
HR (95% CI) from age-, sex- and smoking-adjusted model	Reference	0.72 (0.63–0.84)	<0.001
HR (95% CI) from fully adjusted model#	Reference	0.88 (0.81–0.96)	0.002

HR: hazard ratio. #: model adjusted for age, ethnicity, sex, family history of lung cancer, education, annual income, Townsend deprivation index, smoking and drinking, body mass index, physical activity, fruit and vegetable intake, health condition, non-steroidal anti-inflammatory drug use, chondroitin use, forced expiratory volume in 1 s, and nutrient supplementation.
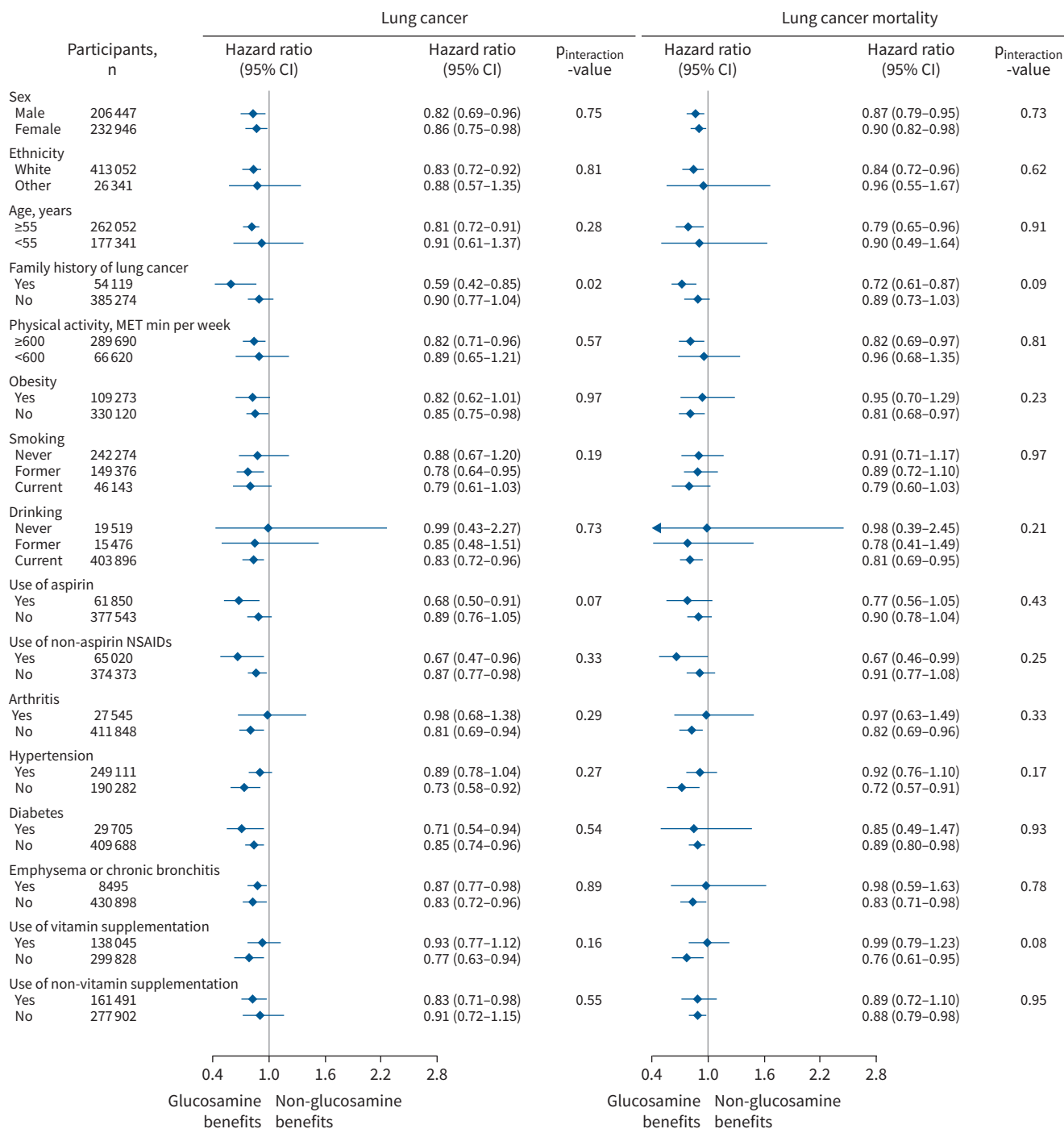
	Participants, n	Lung cancer — Hazard ratio (95% CI)	Lung cancer — $p_{interaction}$-value	Lung cancer mortality — Hazard ratio (95% CI)	Lung cancer mortality — $p_{interaction}$-value
Sex					
Male	206 447	0.82 (0.69–0.96)	0.75	0.87 (0.79–0.95)	0.73
Female	232 946	0.86 (0.75–0.98)		0.90 (0.82–0.98)	
Ethnicity					
White	413 052	0.83 (0.72–0.92)	0.81	0.84 (0.72–0.96)	0.62
Other	26 341	0.88 (0.57–1.35)		0.96 (0.55–1.67)	
Age, years					
≥55	262 052	0.81 (0.72–0.91)	0.28	0.79 (0.65–0.96)	0.91
<55	177 341	0.91 (0.61–1.37)		0.90 (0.49–1.64)	
Family history of lung cancer					
Yes	54 119	0.59 (0.42–0.85)	0.02	0.72 (0.61–0.87)	0.09
No	385 274	0.90 (0.77–1.04)		0.89 (0.73–1.03)	
Physical activity, MET min per week					
≥600	289 690	0.82 (0.71–0.96)	0.57	0.82 (0.69–0.97)	0.81
<600	66 620	0.89 (0.65–1.21)		0.96 (0.68–1.35)	
Obesity					
Yes	109 273	0.82 (0.62–1.01)	0.97	0.95 (0.70–1.29)	0.23
No	330 120	0.85 (0.75–0.98)		0.81 (0.68–0.97)	
Smoking					
Never	242 274	0.88 (0.67–1.20)	0.19	0.91 (0.71–1.17)	0.97
Former	149 376	0.78 (0.64–0.95)		0.89 (0.72–1.10)	
Current	46 143	0.79 (0.61–1.03)		0.79 (0.60–1.03)	
Drinking					
Never	19 519	0.99 (0.43–2.27)	0.73	0.98 (0.39–2.45)	0.21
Former	15 476	0.85 (0.48–1.51)		0.78 (0.41–1.49)	
Current	403 896	0.83 (0.72–0.96)		0.81 (0.69–0.95)	
Use of aspirin					
Yes	61 850	0.68 (0.50–0.91)	0.07	0.77 (0.56–1.05)	0.43
No	377 543	0.89 (0.76–1.05)		0.90 (0.78–1.04)	
Use of non-aspirin NSAIDs					
Yes	65 020	0.67 (0.47–0.96)	0.33	0.67 (0.46–0.99)	0.25
No	374 373	0.87 (0.77–0.98)		0.91 (0.77–1.08)	
Arthritis					
Yes	27 545	0.98 (0.68–1.38)	0.29	0.97 (0.63–1.49)	0.33
No	411 848	0.81 (0.69–0.94)		0.82 (0.69–0.96)	
Hypertension					
Yes	249 111	0.89 (0.78–1.04)	0.27	0.92 (0.76–1.10)	0.17
No	190 282	0.73 (0.58–0.92)		0.72 (0.57–0.91)	
Diabetes					
Yes	29 705	0.71 (0.54–0.94)	0.54	0.85 (0.49–1.47)	0.93
No	409 688	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	430 898	0.83 (0.72–0.96)		0.83 (0.71–0.98)	
Use of vitamin supplementation					
Yes	138 045	0.93 (0.77–1.12)	0.16	0.99 (0.79–1.23)	0.08
No	299 828	0.77 (0.63–0.94)		0.76 (0.61–0.95)	
Use of non-vitamin supplementation					
Yes	161 491	0.83 (0.71–0.98)	0.55	0.89 (0.72–1.10)	0.95
No	277 902	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

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, body mass index, physical activity, fruit and vegetable intake, health condition, non-steroidal anti-inflammatory drug (NSAID) use, chondroitin use, forced expiratory volume in 1 s, and nutrient supplementation. MET: metabolic equivalent of task.

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 is well known to have 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
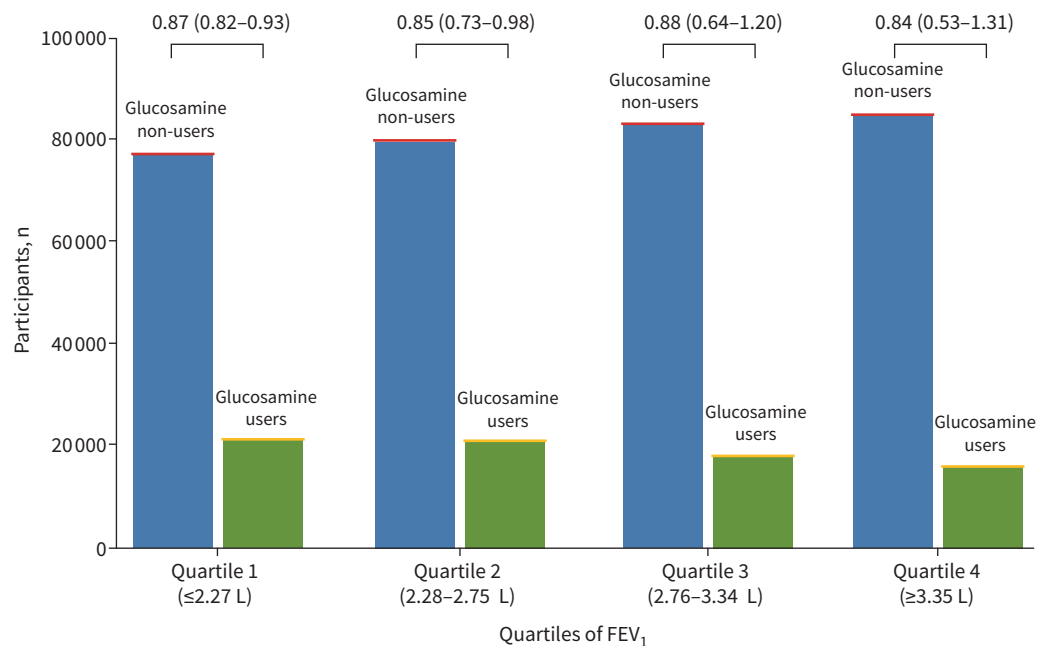
FIGURE 3 Dose–response relationship in quartiles of forced expiratory volume in 1 s (FEV_1) regarding the association between glucosamine use and lung cancer risk. The red colour (on top of blue) represents the number of lung cancer cases in glucosamine non-users, while the yellow colour (on top of green) 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, body mass index, physical activity, fruit and vegetable intake, health condition, non-steroidal anti-inflammatory drug use, chondroitin use, forced expiratory volume in 1 s, and nutrient supplementation. Hazard ratios are indicated with 95% confidence intervals.

pulmonary inflammation in lung carcinogenesis [14]. Other plausible biological effects for the potential protective effect of glucosamine on lung cancer include 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 the nucleus to the cytoplasm, potentially reducing the risk of developing lung cancer [6]. Moreover, glucosamine was involved into anti-oxidant activities by scavenging superoxide and hydroxyl radicals, and protecting macromolecules. While oxidative stress had been consistently identified to associate with increased lung cancer risk [16, 17], the anti-oxidant 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, 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 have been 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 in those without (HR 0.59 *versus* 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 ~85% higher risk when compared with no family history, with a pooled OR of 1.87 from case–control studies and a pooled relative risk of 1.82 from cohort studies [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 anti-oxidant 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 an exploratory nature and primarily hypothesis generating, and therefore results should be interpreted with caution. More prospective studies and intervention trials are required to investigate the favourable 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 effects in an observational study because potential information bias or residual confounding effects 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 the UK Biobank study reported that adding FEV_1 could modestly enhance discriminatory accuracy of the prediction model for 2-year lung cancer risk, suggesting the important predictive value of FEV_1 in lung cancer risk assessment [9]. Nevertheless, glucosamine users were found to have a lower FEV_1 than non-users at baseline. Furthermore, no dose–response relationship of FEV_1 was observed in the measures of association between glucosamine use and lung cancer risk. Likewise, we could not fully exclude the moderating effect of FEV_1 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 FEV_1 further supported the favourable effect of glucosamine, regardless of participants' measures of lung function.

Comparison with other studies

While glucosamine use has been found to be significantly associated with decreased risk of colorectal cancer [25, 26], cardiovascular disease [27, 28], diabetes [29] and all-cause death [27, 30], evidence on the relationship between glucosamine use and risk of lung cancer remains sparse and limited. The VITAL study, as the only clinical investigation, collected dietary supplement data *via* mailed questionnaires from 76 904 US participants, and reported a significant association between glucosamine and decreased lung cancer risk [7]. In our study, data on glucosamine were collected from participants' self-reports and interviews with nurses in assessment centres based on a nationwide and multicentred 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 risks analysis taking all-cause death as a competing event for lung cancer. These analyses strengthened the inverse association between glucosamine use and lung cancer risk. Nevertheless, given the non-randomised 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 the 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 from the 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 pattern of glucosamine consumption, 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 generalisability of the 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 a large nationwide prospective cohort study.

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