Glucosamine use, smoking and risk of incident chronic obstructive pulmonary disease: A large prospective cohort study

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Abstract

Chronic inflammation exerts pleiotropic effects in the etiology and progression of chronic obstructive pulmonary disease (COPD). Glucosamine is widely used in many countries and may have anti-inflammatory properties. We aimed to prospectively evaluate the association of regular glucosamine use with incident COPD risk and explore whether such association could be modified by smoking in the UK Biobank cohort, which recruited more than half a million participants aged 40–69 years from across the UK between 2006 and 2010. Cox proportional hazards models with adjustment for potential confounding factors were used to calculate hazard ratios (HRs) as well as 95% confidence intervals (95% CIs) for the risk of incident COPD. During a median follow-up of 8.96 years (interquartile range 8.29 to 9.53 years), 9016 new-onset events of COPD were documented. We found that regular use of glucosamine was associated with a significantly lower risk of incident COPD with multivariable adjusted HR of 0.80 (95% CI, 0.75 to 0.85; P<0.001). When subgroup analyses were performed by smoking status, the adjusted HRs for the

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Informed consent to participate All participants gave written informed consent to participate in the study.

association of regular glucosamine use with incident COPD were 0.84 (0.73 to 0.96), 0.84 (0.77 to 0.92), and 0.71 (0.62 to 0.80) among never smokers, former smokers and current smokers, respectively. No significant interaction was observed between glucosamine use and smoking status (*P* for interaction=0.078). Incident COPD could be reduced by 14% to 84% through a combination of regular glucosamine use and smoking cessation.

Keywords

glucosamine use; chronic obstructive pulmonary disease; smoking status; smoking pack-years; prospective cohort study

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive life-threatening chronic respiratory disease that commonly causes breathlessness with recurrent exacerbations and serious illness[1; 2]. According to the Global Burden of Disease Study, COPD affected about 251 million people worldwide as of 2016[3]. An estimated 3.17 million deaths were caused by COPD in 2015 (accounting for 5% of all deaths globally in that year). The primary risk factor of COPD is exposure to tobacco smoke, which causes oxidative stress of lung parenchyma and peripheral airways and triggers chronic inflammatory responses[2; 4; 5; 6; 7; 8; 9]. Thus, drugs or supplements with anti-inflammatory properties may be of potential benefit for reducing risk of COPD.

Glucosamine is a very popular non-vitamin, non-mineral dietary supplement in many countries[10; 11] and commonly taken for osteoarthritis and joint pain[12; 13; 14; 15]. A number of laboratory[11; 16; 17; 18], animal[19; 20; 21], and human studies[22; 23; 24] have shown that glucosamine may have anti-inflammatory properties. Notably, different from other drugs with anti-inflammatory properties, glucosamine is considered relatively safe because it has no known serious adverse effects, such as intracerebral or gastrointestinal hemorrhage[25; 26; 27]. Thus, there is a substantial interest in assessing whether regular use of glucosamine is inversely associated with the risk of COPD. Moreover, if an association exists between glucosamine use and COPD risk, it is clinically important to determine whether smoking is a potential confounding factor or an effect modifier in the association.

We therefore evaluated the association of regular glucosamine use with the risk of incident COPD using data from the UK Biobank, a large-scale cohort of more than half a million participants. Furthermore, we explored whether the association between glucosamine use and incident COPD risk varied by different smoking subgroups.

Methods

Study setting and participants

The UK Biobank is a valuable research resource with the aim of widely exploring the prevention, diagnosis, and treatment of the most common and life-threatening illnesses[28]. As detailed elsewhere[29], this prospective cohort recruited approximately half a million community-based participants aged 40 to 69 years from across the UK between 2006 and

2010. At baseline, each participant completed a touchscreen self-reported questionnaire and a face-to-face oral interview at one of 22 assessment centers after signing an informed consent. Then, they had standardized anthropometric measurements taken and provided biological samples. Follow-up information was collected through linking to the national routine health-related data resources. We excluded participants who dropped out during the study (n=1329), those with missing information on glucosamine use (n=6156), those with history of COPD at baseline (n=9476), as well as those with missing values on smoking status before analyses (n=1860). Therefore, our analyses included 483 703 participants. Furthermore, participants with missing information on smoking pack-years (n=72 134) were also excluded (Figure 1). The research activities were approved by the North West Multi-Center Research Ethics Committee (London, UK). Additionally, ethics approvals were obtained from the National Information Governance Board for Health & Social Care in England and Wales, and the Community Health Index Advisory Group in Scotland.

Assessment of regular glucosamine use

One of the questions in the baseline electronic questionnaire was "Do you regularly take any of the following?". Each participant could select answers from a list of supplements, including glucosamine, fish oil, selenium, iron, zinc, and calcium, or select a final option of "none of the above" indicating they took none of listed supplements. According to this information, we scored regular glucosamine supplement use as "1=yes" or "0=no".

Assessment of smoking

Information on smoking was collected by touchscreen electronic questionnaire at baseline. All eligible participants were classified as the following groups: never smokers, former smokers, or current smokers based on their smoking status; or none smokers (0 pack-years), hardly ever smokers (0.1–10.0 pack-years), light smokers (10.1–20.0 pack-years), moderate smokers (20.1–30.0 pack-years), heavy smokers (>30 pack-years), or the group of no available data according to their smoking pack-years. Smoking pack-years is a composite index of smoking based on number of cigarettes per day, age stopped smoking and age start smoking. Detailed definitions of smoking status and smoking pack-years were provided in Table S1 in the Supplement.

Outcome ascertainment

Incident COPD in this cohort was determined based on having a diagnosis in hospital admission electronic records or in death register databases. Death information was obtained via linking to national death registries. Causes of death and diseases diagnoses in the UK Biobank cohort were coded using the International Classification of Diseases, 9th Revision (ICD-9) and 10th Revision (ICD-10). COPD was defined as ICD-9 codes 492, 492.0, 492.8, 496.X or ICD-10 codes J43, J43.0, J43.1, J43.2, J43.8, J43.9, J44, J44.0, J44.1, J44.8, J44.9. We calculated follow-up person-years of included participants from the date of conducting the baseline survey until the date of the first COPD diagnosis, date of death, or the date of the end of follow-up (February 28, 2017 for Scotland, and February 25, 2018 for England and Wales), whichever was earliest.

Ascertainment of covariates

We collected information on risk factors of COPD and correlates of glucosamine use at baseline to assess several potential confounders: sociodemographic characteristics (age, sex, ethnicity, education, and household income), lifestyle and health-related behavioral factors (body mass index [BMI], physical activity, alcohol consumption, fruit consumption, vegetable consumption, passive smoking, and occupational exposure), drug use (cholesterol lowering medication, anti-hypertensive drug, insulin, aspirin, non-aspirin non-steroidal anti-inflammatory drugs [NSAIDs], chondroitin, and cortisone), vitamin supplementation (vitamin A, vitamin B, vitamin C, vitamin D, vitamin E, folic acid, and multivitamin), mineral or other dietary supplementation (fish oil, selenium, zinc, iron, and calcium), and disease history (cardiovascular disease [CVD], hypertension, diabetes, cancer, chronic pulmonary infections, rheumatoid arthritis, osteoarthritis, joint pain, arthritis, and asthma). BMI was calculated as the weight divided by the square of the height (kg/m^2). According to the validated International Physical Activity Questionnaire embedded in the touchscreen electronic questionnaire, the intensity and duration of physical activity were ascertained[30]. Passive smoking was defined as being exposed to other people's tobacco smoking for more than one hour per week in the home or other relatively closed space. Occupational exposure was classified based on the self-reported frequency of exposure to diesel exhaust, paints, thinners, glues, pesticides, asbestos, or other chemical smog in daily work. Further details on covariates are available on the UK Biobank website (www.ukbiobank.ac.uk).

Statistical analysis

The distribution of participants' baseline characteristics was summarized by habitual glucosamine use as mean (standard deviation [SD]) for normally distributed continuous variables, median (interquartile range) for skewed distributed continuous variables, or as number (percentage [%]) for categorical variables. Correspondingly, *t* test, Wilcoxon rank sum test, or Chi-square test were used to examine the difference of participant characteristics. We conducted multiple imputation with chained equations to assigned missing values (all missing values <3%), thus minimizing the possibility for inferential bias[31].

Cox proportional hazards models with progressive adjustment for potential confounders were performed to calculate hazard ratios (HRs) along with 95% confidence intervals (95% CIs) for associations of habitual glucosamine use or smoking with incident COPD risk, respectively. Model 1 was adjusted for age (numerical variable), sex (male or female), ethnicity (white or others), education (lower qualification or higher qualification), household income (<£18 000, £18 000–£30 999, £31 000–£51 999, £52 000–£100000, or >£100 000), BMI (numerical variable), alcohol consumption (never, 1–2, 3–4, or 5 times/week), physical activity (regular physical activity, some physical activity, or no regular physical activity), fruit consumption (<1, 1–3, 3–4, or 4 servings/day), vegetable consumption (<3, 3–4, 4–6, or 6 servings/day), passive smoking (yes or no), occupational exposure (rarely/never, sometimes, or often), CVD (yes or no), hypertension (yes or no), diabetes (yes or no), cancer (yes or no), chronic pulmonary infections (yes or no), rheumatoid arthritis (yes or no), osteoarthritis (yes or no), joint pain(yes or no), arthritis (yes or no), and asthma (yes or no), aspirin use (yes or no), and Non-aspirin NSAIDs use (yes or

no). In model 2, we adjusted for not only the same confounding factors as model 1 but also for the following variables: smoking status (former, current, or never), cholesterol lowering medication use (yes or no), anti-hypertensive drug use (yes or no), insulin use (yes or no), vitamin supplementation (yes or no), mineral or other dietary supplementation (yes or no), glucosamine use (yes or no), chondroitin use (yes or no), and cortisone use (yes or no). In model 3, smoking status was replaced by smoking pack-years (numerical variable), which represented participants' total active smoking exposure. It is worth noting that glucosamine use and smoking status/pack-years were adjusted for each other. We used a Schoenfeld residuals plot to evaluate the proportional hazards assumption; no violation of this assumption was observed in our study. The linear trend test was performed by treating each smoking category as a continuous variable. Additionally, incidence rates of COPD per 1000 person-years were calculated.

Multivariable adjusted stratified analyses were conducted by smoking status (never, former, or current), or smoking pack-years (none, hardly ever, light, moderate, or heavy) to explore the association between glucosamine use and incident COPD. Additionally, we also conducted stratified analysis by sex (male or female), age (<60 or 60 years), obesity (BMI<30 or 30kg/m^2), CVD (yes or no), hypertension (yes or no), diabetes (yes or no), cancer (yes or no), osteoarthritis (yes or no), joint pain (yes or no), asthma (yes or no), vitamin use (yes or no), minerals and other dietary supplements use (yes or no), aspirin use (yes or no), and Non-aspirin NSAIDs use (yes or no) to assess the potential modification effect. The statistical interaction was evaluated by adding the cross-product term of the stratifying variable with glucosamine use to fully adjusted Cox regression models.

We performed several sensitivity analyses to examine the robustness of the results. First, we categorized all eligible participants as glucosamine/chondroitin users (who taken glucosamine alone, or chondroitin alone, or taken both of them), or glucosamine/chondroitin nonusers (who taken neither glucosamine nor chondroitin) to explore the association between glucosamine/chondroitin use and incident COPD. Second, we excluded participants who used chondroitin. Third, participants who developed COPD within the first two years of follow-up were removed in order to minimize the possibility of reverse causation. Final, given the poor health of NSAIDs users, we excluding participants who taken aspirin or non-aspirin NSAIDs at baseline.

The population-attributable fraction (PAF), an estimated fraction of all COPD cases that would not have occurred if all individuals would have been in the less smoking category and/or have taken glucosamine[32], was calculated according to Miettinen's formula[33]. We used R software version 3.6.1 (R Development Core Team, Vienna, Austria) to conduct all statistical analyses; all tests in our study were 2-sided and $P<0.05$ was considered statistically significant.

Results

Baseline characteristics of participants

Table 1 shows the baseline features of the eligible participants stratified by glucosamine use status (users versus nonusers). Of the 483 703 participants (mean [SD] age, 56.5 [8.1]

years), 263 992 (54.6%) were male. At baseline, a total of 92 593 (19.1%) participants self-reported habitual glucosamine use. Compared with nonusers, glucosamine users were older, more likely to be female, white, current non-smokers, and passive smokers. They were also likely to have a lower education qualification, lower household income, more physically activity, more alcohol consumption, and more frequent occupational exposure. They also had a higher prevalence of cancer, osteoarthritis, joint pain, and arthritis, but a lower prevalence of diabetes, hypertension, and CVD. Additionally, glucosamine users more frequently took NSAIDs, vitamins, chondroitin, and minerals and other dietary supplements than nonusers. Of note, glucosamine users have a lower C-reactive protein (CRP) concentration than nonusers.

Associations between smoking and incident COPD risk

Table 2 shows the associations between smoking and incident COPD. During a median follow-up of 8.96 years (interquartile range 8.29 to 9.53 years), a total of 9016 participants developed incident COPD. Incidence rates (IRs) and HRs (P for trend <0.001) of incident COPD were increased in association with smoking status and increases of smoking pack-years. Compared with never smokers, the multivariable adjusted HRs of former smokers and current smokers was 3.09 (95% CI, 2.91 to 3.28) and 10.61 (95% CI, 9.96 to 11.29)]; similarly, the multivariable adjusted HRs of hardly ever smokers, light smokers, moderate smokers, and heavy smokers was 1.92 (95% CI, 1.72 to 2.14), 3.24 (95% CI, 2.99 to 3.53), 5.58 (95% CI, 5.17 to 6.01), and 10.42 (95% CI, 9.79 to 11.09), respectively (Table 2).

Inverse associations between regular glucosamine use and incident COPD risk

Table 3 shows the associations between habitual glucosamine use and incident COPD. In model 1, we found a significant inverse association between regular use of glucosamine and risk of incident COPD (HR=0.73, 95% CI, 0.69 to 0.78; P<0.001). Regular glucosamine use was significantly associated with a reduced risk of incident COPD with the multivariable adjusted HRs of 0.80 (95% CI, 0.75 to 0.85; P<0.001) and 0.78 (95% CI, 0.73 to 0.84; P<0.001) in model 2 and model 3, respectively.

Joint associations of glucosamine use and smoking with incident COPD

We conducted multivariable adjusted stratified analyses by smoking to explore whether smoking status or smoking pack-years could modify the association between habitual glucosamine use and incident COPD risk (Table 4). We found that glucosamine use was associated with a lower risk on incident COPD with the adjusted HRs of 0.84 (95% CI, 0.73 to 0.96; P=0.009), 0.84 (95% CI, 0.77 to 0.92; P<0.001), and 0.71 (95% CI; 0.63 to 0.80; P<0.001) among never, former, and current smokers. The hazard ratio of incident COPD associated with glucosamine use was 0.82 (95% CI 0.72 to 0.94; P=0.003) among none smokers, 0.78 (95% CI 0.68 to 1.02; P=0.065) among hardly ever smokers, 0.70 (95% CI 0.57 to 0.85; P<0.001) among light smokers, 0.66 (95% CI 0.55 to 0.79; P<0.001) among moderate smokers, and 0.85 (95% CI 0.77 to 0.94; P=0.002) among heavy smokers. We observed a significant interaction between glucosamine use and smoking pack-years on the risk of incident COPD (P for interaction=0.019). A similar interaction pattern was not found in the analyses stratified by smoking status (P for interaction=0.078).

Other subgroup analyses

We conducted stratified analyses for the association of glucosamine use with incident COPD risk according to other potential risk factors using the fully adjusted model (Figure 2). The association between the use of glucosamine use and the risk of incident COPD was seemed not to be significantly modified by sex, age, obesity, CVD, hypertension, diabetes, cancer, osteoarthritis, joint pain, asthma, vitamin use, minerals and other dietary supplements use, aspirin use, or Non-aspirin NSAIDs (all *p* for interaction>0.05).

Sensitivity analyses

When all eligible participants were categorized as glucosamine/chondroitin users or nonusers, no substantial changes of results were observed, whether or not stratified by smoking (Table S2 and S3). Likewise, when we removed participants who regularly took chondroitin (Table S4), or who reported COPD events within the first two years of follow-up (Table S5), there was no significant change on the association between glucosamine use and incident COPD. When the analyses were restricted NSAIDs nonusers, the result still shown significant inverse associations between the glucosamine use and the new-onset COPD events risk (Table S6).

Population Attributable Fractions

We calculated the population-attributable fraction (PAF). If current smokers who were glucosamine nonusers regularly took glucosamine supplements before the baseline evaluation, new-onset COPD cases could be reduced by 25.53% (95% CI, 17.49 to 32.70). If all individuals who currently smoke actively and did not regularly take glucosamine quit smoking during follow-up and regularly took glucosamine before baseline, 61.74% (95% CI, 59.98 to 63.30) of incident COPD could be prevented. If they had never smoked and regularly took glucosamine before baseline, the new-onset COPD events could be reduced by 83.72% (95% CI, 82.79 to 84.52).

When the heavy smokers and glucosamine nonusers were defined as the reference group, COPD events could be reduced by 13.83% (95% CI, 6.35 to 20.62), 61.45% (95% CI, 455.37 to 66.63), 75.29% (95% CI, 71.14 to 78.75), 83.19% (95% CI, 79.52 to 86.08), and 83.83% (95% CI, 82.91 to 84.72) for groups who i) regularly took glucosamine, ii) were moderate smokers as well as regularly took glucosamine, iii) were light smokers as well as regularly took glucosamine, iv) were hardly ever smokers as well as regularly took glucosamine, and v) were none smokers as well as regularly took glucosamine before baseline, respectively (Table 5).

Discussion

In this large-scale prospective cohort study involving 483 703 individuals, we found a significant inverse association of regular glucosamine use with incident COPD risk. This association was independent of potential confounders, including socioeconomics characteristics, lifestyle and health-related behavioral factors, other dietary supplementation consumption, health conditions, and drugs use. Furthermore, we observed a prominent interaction between glucosamine use and smoking pack-years on the risk of incident COPD.

In our study, 19.1% of participants reported regular glucosamine use. Similarly, regular glucosamine use has been reported by 22.0% of Australians aged 45+ years[11], and 16.7% of Americans aged 50+ years[10]. To our knowledge, this is first study exploring the relationship between regular glucosamine use and incident COPD risk in human populations; thus, it is challenging to contextualize our finding with respect to the current knowledge-base. Of note, several previous epidemiological studies have demonstrated glucosamine supplementation use was associated with a lower risk of incident diseases[34; 35; 36; 37; 38] and mortality[38; 39; 40]. For instance, the VITamins And Lifestyle (VITAL) cohort study suggested negative associations of glucosamine use with incident lung cancer and colorectal cancer[34; 35]. A recent study including 43 163 individuals from the Health Professionals Follow-up Study (HPFS), Nurses' Health Study (NHS), and NHS II indicated that glucosamine use may have a protective effect on new-onset colorectal carcinogenesis events in older adults[36]. The results from a surveillance, epidemiology and end results (SEER) cancer registry suggested that glucosamine use was associated with a lower total mortality and with reductions of some broad causes of death in adults aged 50–76 years[39]. Based on the UK Biobank cohort, Ma and colleagues found that habitual use of glucosamine was associated with lower risk of multiple conditions including, 17% for incident type 2 diabetes (T2D)[37], 18% for incident coronary heart disease (CHD), 18% for incident stroke, and 22% for cardiovascular disease (CVD) death[38]; Li and colleagues also reported that regular use of glucosamine was associated lower risk of multiple conditions including, 15% for all-cause mortality, 27% for respiratory mortality, 26% for digestive mortality, 18% for CVD mortality, and 6% for cancer mortality.[40]

Although the precise biological mechanisms underlying the inverse association between regular use of glucosamine and risk of COPD remain to be determined, a wealth of emerging evidence provides various plausible explanations for the inverse association. Given the detrimental roles of inflammation in the development of COPD, we assumed that glucosamine supplementation might reduce the incident COPD risk at least partly through the anti-inflammatory effect. First, glucosamine may achieve its beneficial effect by reducing the translocation of nuclear factor kappa B [NF-kB] and inhibiting the activation of NF-kB, a well-characterized transcription factor involved in inflammatory response, and thus suppress the subsequent cascade of related events[41; 42]. An animal study in which mice received an injection of lipopolysaccharide to induce endotoxic shock and systemic inflammation has demonstrated that glucosamine decreased the production of inflammatory cytokines related to NF-kB activation[43]. A number of vitro and vivo studies suggested glucosamine use decreases levels of various proinflammatory cytokines[16; 17; 18; 19; 20; 44; 45; 46; 47; 48], such as IL-1β, PGE$_2$, COX-2, and TNF-α, which lies downstream stream of NF-kB[49; 50]. Second, some evidence, even if limited, indicated a potential mechanism by which glucosamine exerts an anti-inflammatory effect by regulating the metabolic, composition, or immunological activities of gut microbiota[51; 52]. Additionally, glucosamine, a significant component of intestinal mucin, could potentially affect intestinal immune responses and gut permeability[53; 54].

Several previous human studies[22; 23; 24; 55] also have shown that circulating levels of CRP, a marker of low-grade systemic inflammation, were significantly lower in glucosamine users compared with nonusers; a small randomized controlled cross-over clinical trial also

suggested that glucosamine use may significantly reduce CRP concentrations compared with the placebo group[23]. Interestingly, we found that the CRP level at baseline was significantly lower in glucosamine users than in nonusers.

Although some previous studies suggested the positive effect of aspirin use among patients with COPD[56; 57], results of our study (Table S7) and other studies showed that the use of either aspirin or ibuprofen was not associated with COPD or lung function[58; 59]. The potential benefit of glucosamine supplementation for incident COPD was significant and was independent of a series of potential confounding factors. Additionally, glucosamine is considered relatively safe because no known serious adverse effects related to it have been reported[21]. Furthermore, even though we observed a significantly positive association between cigarette smoking and new-onset COPD events, regular glucosamine use could reverse this relationship to a certain extent. Glucosamine seems promising as a recommended protective agent for prevention of COPD. It should be noted that, given the limitations in this study, including potential residual confounding, and a sparse dose and duration information, PARs may provide an overestimation and misrepresentation of the potential preventive effect glucosamine has on COPD.

This study has several notable strengths, including the large sample size, the prospective cohort study design, and detailed information on socioeconomic characteristics, lifestyle and health-related behavioral factors, supplementation use, drugs use, health status, and other covariates.

Nevertheless, there are several limitations of our study. First, information on regular dietary supplements intake was obtained via self-reported baseline questionnaire; and detailed information on the formulation of supplements was not collected. Some participants who take compound preparation containing glucosamine and chondroitin might only reported the glucosamine use. Second, dosage, duration and frequency of glucosamine use was not collected; further studies are needed to explore those associations. Third, glucosamine users were likely to have a healthier lifestyle. However, it is difficult to distinguish the effects of a healthy lifestyle from habitual glucosamine use in this observational study. Although we carefully adjusted for a great many potential confounding factors, the observed inverse associations might have been driven by some unmeasured health-related lifestyles. Additionally, the possibility of residual confounders due to other unknown factors or imprecise measurements cannot be eliminated in our study.

Conclusions

In summary, this large-scale prospective cohort study showed that a considerable proportion (19.1%) of the UK population reported regular glucosamine use. Our study suggests that regular glucosamine use is inversely associated with incident COPD. The inverse association was modified by smoking pack-years. Functional studies and clinical trials are needed to enhance our understanding of potential benefits of glucosamine supplementation for incident COPD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Data availability statement

Data are available in a public, open access repository. The UK Biobank data are available from the UK Biobank on request (www.ukbiobank.ac.uk/).

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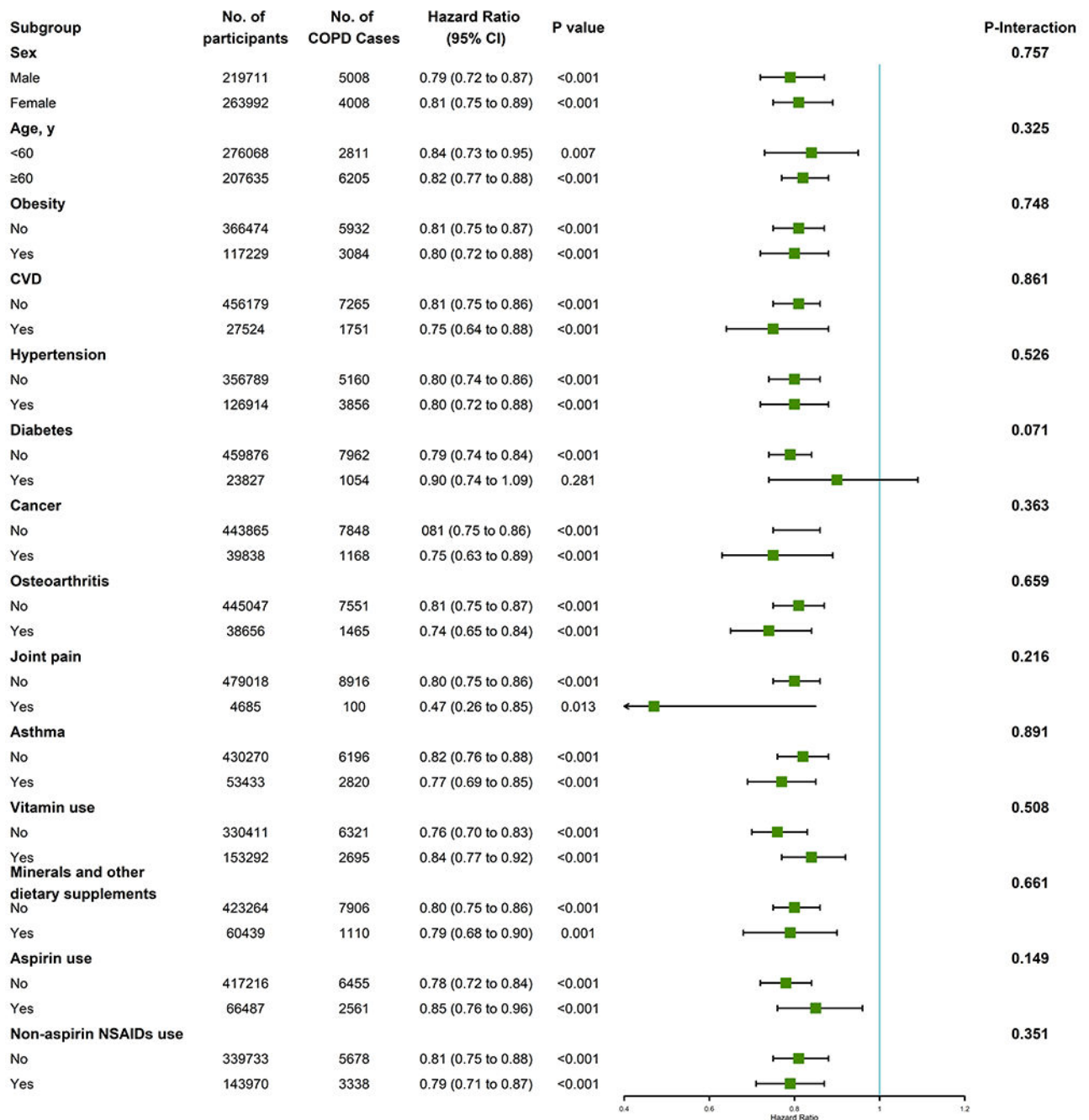
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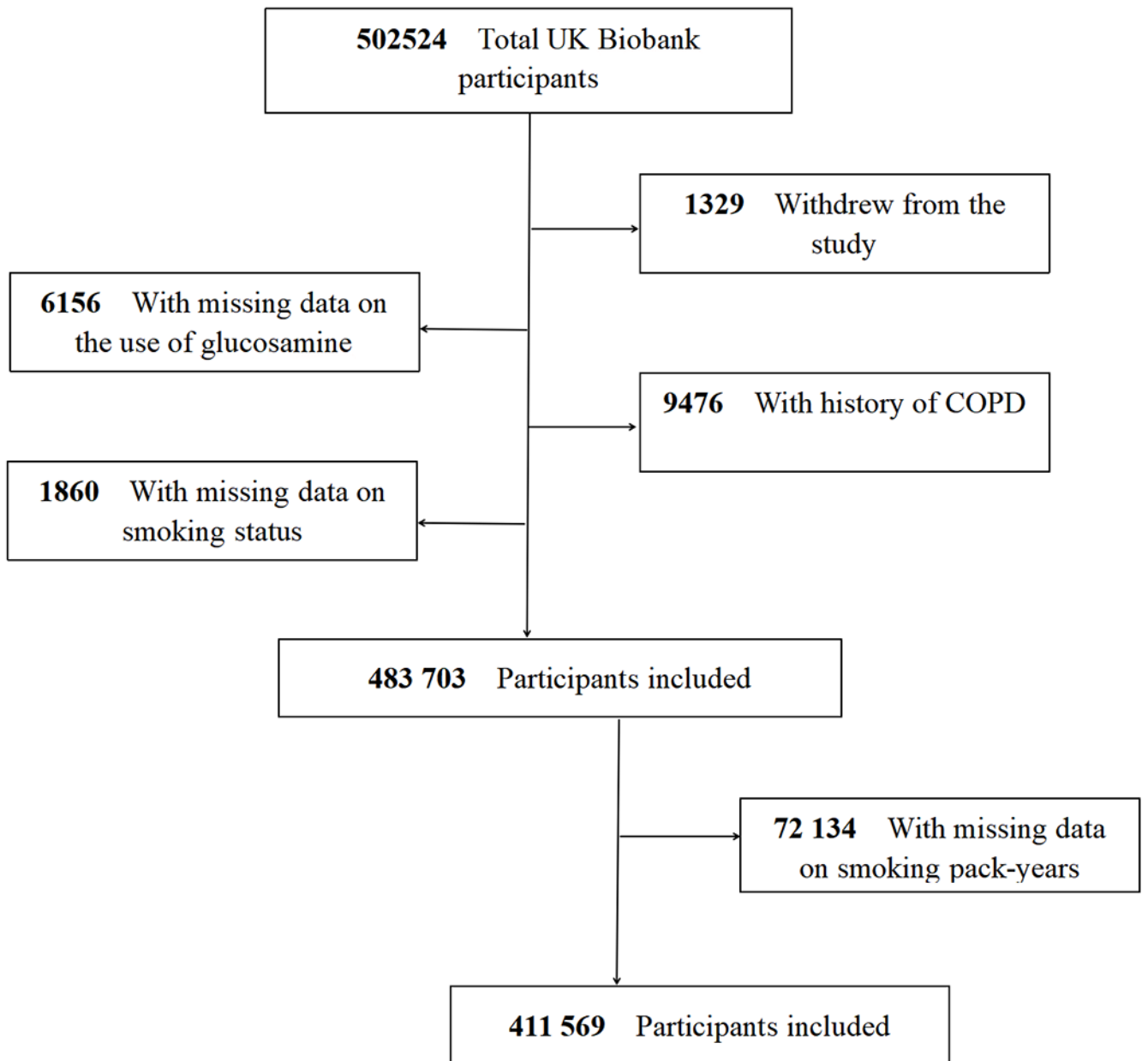
Figure 1.
Flowchart of participant enrolment

Subgroup	No. of participants	No. of COPD Cases	Hazard Ratio (95% CI)	P value		P-Interaction
Sex						0.757
Male	219711	5008	0.79 (0.72 to 0.87)	<0.001		
Female	263992	4008	0.81 (0.75 to 0.89)	<0.001		
Age, y						0.325
<60	276068	2811	0.84 (0.73 to 0.95)	0.007		
≥60	207635	6205	0.82 (0.77 to 0.88)	<0.001		
Obesity						0.748
No	366474	5932	0.81 (0.75 to 0.87)	<0.001		
Yes	117229	3084	0.80 (0.72 to 0.88)	<0.001		
CVD						0.861
No	456179	7265	0.81 (0.75 to 0.86)	<0.001		
Yes	27524	1751	0.75 (0.64 to 0.88)	<0.001		
Hypertension						0.526
No	356789	5160	0.80 (0.74 to 0.86)	<0.001		
Yes	126914	3856	0.80 (0.72 to 0.88)	<0.001		
Diabetes						0.071
No	459876	7962	0.79 (0.74 to 0.84)	<0.001		
Yes	23827	1054	0.90 (0.74 to 1.09)	0.281		
Cancer						0.363
No	443865	7848	081 (0.75 to 0.86)	<0.001		
Yes	39838	1168	0.75 (0.63 to 0.89)	<0.001		
Osteoarthritis						0.659
No	445047	7551	0.81 (0.75 to 0.87)	<0.001		
Yes	38656	1465	0.74 (0.65 to 0.84)	<0.001		
Joint pain						0.216
No	479018	8916	0.80 (0.75 to 0.86)	<0.001		
Yes	4685	100	0.47 (0.26 to 0.85)	0.013		
Asthma						0.891
No	430270	6196	0.82 (0.76 to 0.88)	<0.001		
Yes	53433	2820	0.77 (0.69 to 0.85)	<0.001		
Vitamin use						0.508
No	330411	6321	0.76 (0.70 to 0.83)	<0.001		
Yes	153292	2695	0.84 (0.77 to 0.92)	<0.001		
Minerals and other dietary supplements						0.661
No	423264	7906	0.80 (0.75 to 0.86)	<0.001		
Yes	60439	1110	0.79 (0.68 to 0.90)	0.001		
Aspirin use						0.149
No	417216	6455	0.78 (0.72 to 0.84)	<0.001		
Yes	66487	2561	0.85 (0.76 to 0.96)	<0.001		
Non-aspirin NSAIDs use						0.351
No	339733	5678	0.81 (0.75 to 0.88)	<0.001		
Yes	143970	3338	0.79 (0.71 to 0.87)	<0.001		

Figure 2. Association between glucosamine use and incident COPD risk stratified by other potential risk factors

Abbreviations:COPD, chronic obstructive pulmonary disease; CI, confidence interval.

Results were adjusted for age, sex, ethnicity, education, household income, body mass index, physical activity, smoking status, alcohol consumption, fruit consumption, vegetable consumption, passive smoking, occupational exposure, CVD, hypertension, diabetes, cancer, chronic pulmonary infections, rheumatoid arthritis, osteoarthritis, joint pain, asthma, arthritis, cholesterol lowering medication use, anti-hypertensive drug use, insulin use, aspirin

use, Non-aspirin NSAIDs use, vitamin use, minerals and other dietary supplements use, chondroitin use, and cortisone use.

Table 1.

Baseline Characteristics of Study Participants by Glucosamine Use

Characteristics	Overall (N=483 703)	Glucosamine nonuser (N=391 110)	Glucosamine user (N=92 593)	P Value
Age, mean (SD), y	56.5 (8.1)	55.9 (8.2)	59.0 (7.1)	<0.001
Sex				<0.001
Female	263 992 (54.6)	205 951 (52.7)	58 041 (62.7)	
Male	219 711 (45.4)	185 159 (47.3)	34 552 (37.3)	
Ethnicity				<0.001
White	457 744 (94.6)	368 704 (94.3)	89 040 (96.2)	
Others	25 959 (5.4)	22 406 (5.7)	3553 (3.8)	
Education				<0.001
Lower qualification	248 915 (51.5)	200 742 (51.3)	48 173 (52.0)	
Higher qualification	234 788 (48.5)	190 368 (48.7)	44 420 (48.0)	
Household income (£)				<0.001
<18 000	111 453 (23.0)	91 246 (23.3)	20 207 (21.8)	
18 000–30 999	124 574 (25.8)	98 090 (25.1)	26 484 (28.6)	
31 000–51 999	125 990 (26.0)	101 522 (26.0)	24 468 (26.4)	
52 000–100 000	96 332 (19.9)	79 116 (20.2)	17 216 (18.6)	
>100 000	25 354 (5.2)	21 136 (5.4)	4218 (4.6)	
Body mass index (kg/m²)				<0.001
Mean (SD)	27.4 (4.8)	27.4 (4.8)	27.3 (4.6)	<0.001
<18.5	2406 (0.5)	2080 (0.5)	326 (0.4)	
18.5–24.9	158 040 (32.7)	127 522 (32.6)	30 518 (33.0)	
25–29.9	206 028 (42.6)	165 756 (42.4)	40 272 (43.5)	
30	117 229 (24.2)	95 752 (24.5)	21 477 (23.2)	
Physical activity (min/week)				<0.001
Regular physical activity	281 573 (58.2)	222 403 (56.9)	59 170 (63.9)	
Some physical activity	147 517 (30.5)	121 952 (31.2)	25 565 (27.6)	
No regular physical activity	54 613 (11.3)	46 755 (12.0)	7858 (8.5)	
Smoking status				<0.001
Never	267 855 (55.4)	216 421 (55.3)	51 434 (55.5)	

Characteristics	Overall (N=483 703)	Glucosamine nonuser (N=391 110)	Glucosamine user (N=92 593)	P Value
Former	166 271 (34.4)	131 021 (33.5)	35 250 (38.1)	
Current	49 577 (10.2)	43 668 (11.2)	5909 (6.4)	
Pack-years of smoking				
Not available	72 134 (14.9)	56 966 (14.6)	15 168 (16.4)	<0.001
None (0)	268 989 (55.6)	217 369 (55.6)	51 620 (55.7)	
Hardly ever (0.1–10.0)	37 329 (7.7)	29 610 (7.6)	7719 (8.3)	
Light (10.1–20.0)	39 141 (8.1)	31 668 (8.1)	7473 (8.1)	
Moderate (20.1–30.0)	28 268 (5.8)	23 367 (6.0)	4901 (5.3)	
Heavy (>30.0)	37 842 (7.8)	32 130 (8.2)	5712 (6.2)	
Alcohol consumption(times/week)				
Never	147 743 (30.5)	122 315 (31.3)	25 428 (27.5)	<0.001
1–2	125 267 (25.9)	10 1949 (26.1)	23 318 (25.2)	
3–4	112 265 (23.2)	89 169 (22.8)	23 096 (24.9)	
5	98 428 (20.3)	77 677 (19.9)	20 751 (22.4)	
Vegetable consumption (servings/day)				
<3.0	84 629 (17.5)	72 761 (18.6)	11 868 (12.8)	<0.001
3–4	82 273 (17.0)	67 606 (17.3)	14 667 (15.8)	
4–6	163 740 (33.9)	130 554 (33.4)	33 186 (35.8)	
6	153 061 (31.6)	120 189 (30.7)	32 872 (35.5)	
Fruit consumption (servings/day)				
<1	38 700 (8.0)	34 646 (8.9)	4054 (4.4)	<0.001
1–3	200 799 (41.5)	168 333 (43.0)	32 466 (35.1)	
3–4	89 974 (18.6)	71 507 (18.3)	18 467 (19.9)	
4	154 230 (31.9)	116 624 (29.8)	37 606 (40.6)	
Passive smoking				
No	381 755 (78.9)	306 575 (78.4)	75 180 (81.2)	<0.001
Yes	101 948 (21.1)	84 535 (21.6)	17 413 (18.8)	
Occupational exposure				
Rarely/never	383 788 (79.3)	312 651 (79.9)	71 137 (76.8)	<0.001
Sometimes	62 019 (12.8)	48 443 (12.4)	13 576 (14.7)	
Often	37 896 (7.8)	30 016 (7.7)	7880 (8.5)	

Characteristics	Overall (N=483 703)	Glucosamine nonuser (N=391 110)	Glucosamine user (N=92 593)	P Value
C-reactive protein, median (interquartile range), mg/L	1.31 (0.65–2.72)	1.32 (0.65–2.74)	1.29 (0.65–2.63)	<0.001
Supplement or drug use				
Cholesterol lowering medication	82 813 (17.1)	67 287 (17.2)	15 526 (16.8)	0.002
Anti-hypertensive drug	99 607 (20.6)	81 162 (20.8)	18 445 (19.9)	<0.001
Insulin	5260 (1.1)	4636 (1.2)	624 (0.7)	<0.001
Aspirin	66 487 (13.7)	53 587 (13.7)	12 900 (13.9)	0.068
Non-aspirin NSAIDs	143 970 (29.8)	112 175 (28.7)	31 795 (34.3)	<0.001
Chondroitin	5973 (1.2)	147 (0.0)	5826 (6.3)	<0.001
Cortisone	4323 (0.9)	3662 (0.9)	661 (0.7)	<0.001
Vitamin	153 292 (31.7)	101 927 (26.1)	51 365 (55.5)	<0.001
Minerals and other dietary supplements	60 439 (12.5)	38 629 (9.9)	21 810 (23.6)	<0.001
Disease history				
CVD	27 524 (5.7)	23 457 (6.0)	4067 (4.4)	<0.001
Hypertension	126 914 (26.2)	103 039 (26.3)	23 875 (25.8)	<0.001
Diabetes	23 827 (4.9)	20626 (5.3)	3201 (3.5)	<0.001
Cancer	39 838 (8.2)	31391 (8.0)	8447 (9.1)	<0.001
Chronic Pulmonary Infections	4373 (0.9)	3419 (0.9)	954 (1.0)	<0.001
Rheumatoid arthritis	5269 (1.1)	4131 (1.1)	1138 (1.2)	<0.001
Osteoarthritis	38 656 (8.0)	23 060 (5.9)	15 596 (16.8)	<0.001
Joint pain	4685 (1.0)	3237 (0.8)	1448 (1.6)	<0.001
Arthritis	3754 (0.8)	2371 (0.6)	1383 (1.5)	<0.001
Asthma	53 433 (11.0)	42 912 (11.0)	10 521 (11.4)	<0.001

Values are numbers (%) unless stated otherwise.

Abbreviations: CVD, cardiovascular disease; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation.

Table 2.

Risk of COPD According to Smoking Categories

Smoking	Total No. of participants	No. of COPD cases (%)	Person-years	IR[a]	Model 1[b]			Model 2[c]		
					HR (95% CI)	P value	P for trend	HR (95% CI)	P value	P for trend
Smoking status										
Never	267 855	1586 (0.59)	2 377 156	0.67	1.00 (reference)	-	<0.001	1.00 (reference)	-	<0.001
Former	166 271	4000 (2.41)	1 454 015	2.75	3.10 (2.92 to 3.29)	<0.001		3.09 (2.91 to 3.28)	<0.001	
Current	49 577	3430 (6.92)	423 520	8.10	10.67 (10.03 to 11.36)	<0.001		10.61 (9.96 to 11.29)	<0.001	
Smoking pack-years										
Never (0)	268 989	1662 (0.62)	2 386 656	0.70	1.00 (reference)	-	<0.001	1.00 (reference)	-	<0.001
Hardly ever (0.1–10.0)	37 329	415 (1.11)	330 209	1.26	1.92 (1.72 to 2.14)	<0.001		1.92 (1.72 to 2.14)	<0.001	
Light (10.1–20.0)	39 141	855 (2.18)	343 461	2.49	3.25 (2.99 to 3.53)	<0.001		3.24 (2.99 to 3.53)	<0.001	
Moderate (20.1–30.0)	28 268	1213 (4.29)	245 238	4.95	5.60 (5.20 to 6.04)	<0.001		5.58 (5.17 to 6.01)	<0.001	
Heavy (>30.0)	37 842	3811 (10.07)	3 143 608	12.12	10.51 (9.88 to 11.18)	<0.001		10.42 (9.79 to 11.09)	<0.001	

Abbreviations: CI, confidence interval; COPD, Chronic Obstructive Pulmonary Disease; HR, hazard ratio; IR, incidence rate.

[a] Incidence rates are provided per 1000 person-years;

[b] Model 1: Cox proportional hazards regression adjusted for age and sex, ethnicity, education, household income, body mass index, physical activity, alcohol consumption, fruit consumption, vegetable consumption, passive smoking, occupational exposure, CVD, hypertension, diabetes, cancer, chronic pulmonary infections, rheumatoid arthritis, osteoarthritis, joint pain, asthma, arthritis, aspirin use, and Non-aspirin NSAIDs use.

[c] Model 2: Cox proportional hazards regression adjusted for Model 1 and cholesterol lowering medication use, anti-hypertensive drug use, insulin use, vitamin use, minerals and other dietary supplements use, chondroitin use, glucosamine use, and cortisone use.

Table 3.

Risk of Incident COPD According to Glucosamine Use

glucosamine/ chondroitin use	Total No. of participants	No. of COPD cases (%)	Person-years	IR[a]	Model 1[b]		Model 2[c]		Model 3[d]		Model 4[e]	
					HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Non-user	391 110	7638 (1.95)	3437363	2.22	1.00 (reference)	-	1.00 (reference)	-	1.00 (reference)	-	1.00 (reference)	-
User	92 593	1378 (1.49)	81 7327	1.69	0.73 (0.69 to 0.78)	<0.001	0.80 (0.75 to 0.85)	<0.001	0.78 (0.73 to 0.84)	<0.001	0.83 (0.78 to 0.89)	<0.001

Abbreviations: CI, confidence interval; COPD, Chronic Obstructive Pulmonary Disease; HR, hazard ratio; IR, incidence rate.

[a]Incidence rates are provided per 1000 person-years;

[b]Model 1: Cox proportional hazards regression adjusted for age and sex, ethnicity, education, household income, body mass index, physical activity, alcohol consumption, fruit consumption, vegetable consumption, passive smoking, occupational exposure, CVD, hypertension, diabetes, cancer, chronic pulmonary infections, rheumatoid arthritis, osteoarthritis, joint pain, asthma, arthritis, aspirin use, and Non-aspirin NSAIDs use;

[c]Model 2: Cox proportional hazards regression adjusted for Model 1 and smoking status, cholesterol lowering medication use, anti-hypertensive drug use, insulin use, vitamin use, minerals and other dietary supplements use, chondroitin use, and cortisone use;

[d]Model 3: Cox proportional hazards regression adjusted for Model 1 and smoking pack-years (numerical variable), cholesterol lowering medication use, anti-hypertensive drug use, insulin use, vitamin use, minerals and other dietary supplements use, chondroitin use, and cortisone use.

[e]Model 4: Cox proportional hazards regression adjusted for Model 2 and smoking pack-years.

Table 4.

Risk of COPD According to Glucosamine Use Within Each Smoking Category

Subgroup	Total No. of participants	No. of COPD cases (%)	Person-years	IR[a]	HR (95% CI)[b]	P value	P for interaction
Smoking status and glucosamine							0.078
Never smoking							
Non-user	216 421	1275 (0.59)	1 920 589	0.66	1.00 (reference)	-	
User	51 434	311 (0.60)	456 567	0.68	0.84 (0.73 to 0.96)	0.009	
Former smoking							
Non-user	131 021	3258 (2.49)	1 144 262	2.85	1.00 (reference)	-	
User	35 250	742 (2.10)	309 753	2.40	0.84 (0.77 to 0.92)	<0.001	
Current smoking							
Non-user	43 668	3105 (7.11)	372 512	8.34	1.00 (reference)	-	
User	5909	325 (5.50)	51 008	6.37	0.71 (0.63 to 0.80)	<0.001	
Smoking pack-years and glucosamine							0.019
None smoking (0)							
Non-user	217 369	1343 (0.62)	1 928 471	0.70	1.00 (reference)	-	
User	51 620	319 (0.62)	458 184	0.70	0.82 (0.72 to 0.94)	0.003	
Hardly ever smoking (0.1–10.0)							
Non-user	29 610	335 (1.13)	261 763	1.28	1.00 (reference)	-	
User	7719	80 (1.04)	68 446	1.17	0.78 (0.68 to 1.02)	0.065	
Light smoking (10.1–20.0)							
Non-user	31 668	727 (2.30)	277 697	2.62	1.00 (reference)	-	
User	7473	128 (1.71)	65 765	1.95	0.70 (0.57 to 0.85)	<0.001	
Moderate smoking (20.1–30.0)							
Non-user	23 367	1059 (4.53)	202 325	5.23	1.00 (reference)	-	
User	4901	154 (3.14)	42 912	3.59	0.66 (0.55 to 0.79)	<0.001	
Heavy smoking (>30.0)							
Non-user	32 130	3315 (10.32)	266 394	12.44	1.00 (reference)	-	
User	5712	496 (8.68)	47 966	10.34	0.85 (0.77 to 0.94)	0.002	

Abbreviations: CI, confidence interval; COPD, Chronic Obstructive Pulmonary Disease; HR, hazard ratio; IR, incidence rate.

[a]Incidence rates are provided per 1000 person-years;

[b] Cox proportional hazards regression adjusted for age, sex, ethnicity, education, household income, body mass index, physical activity, alcohol consumption, fruit consumption, vegetable consumption, passive smoking, occupational exposure, CVD, hypertension, diabetes, cancer, chronic pulmonary infections, rheumatoid arthritis, osteoarthritis, joint pain, asthma, arthritis, cholesterol lowering medication use, anti-hypertensive drug use, insulin use, aspirin use, Non-aspirin NSAIDs use, vitamin use, minerals and other dietary supplements use, chondroitin use, and cortisone use.

Table 5.

Population Etiologic Fraction According to Smoking Category and Glucosamine Use

Subgroup	HR (95% CI)[a]	PAF (%)	95% CI (%)	P value
Smoking status and glucosamine				
Current smoking				
Non-user	1.00 (reference)			-
User	0.72 (0.70 to 0.81)	25.53	17.49 to 32.70	<0.001
Former smoking				
Non-user	0.29 (0.27 to 0.30)	34.79	34.02 to 35.49	<0.001
User	0.23 (0.22 to 0.26)	61.74	59.98 to 63.30	<0.001
Never smoking				
Non-user	0.09 (0.09 to 0.10)	64.37	63.91 to 64.77	<0.001
User	0.08 (0.07 to 0.09)	83.72	82.79 to 84.52	<0.001
Smoking pack-years and glucosamine				
Heavy smoking (>30.0)				
Non-user	1.00 (reference)			-
User	0.84 (0.76 to 0.93)	13.83	6.35 to 20.62	0.001
Moderate smoking (20.1–30.0)				
Non-user	0.55 (0.52 to 0.59)	33.73	30.63 to 36.55	<0.001
User	0.36 (0.30 to0.42)	61.45	55.37 to 66.63	<0.001
Light smoking (10.1–20.0)				
Non-user	0.32 (0.30 to 0.35)	55.61	53.29 to 57.65	<0.001
User	0.22 (0.18 to0.26)	75.29	71.14 to 78.75	<0.001
Hardly ever smoking (0.1–10.0)				
Non-user	0.19 (0.17 to 0.21)	74.02	71.98 to 75.88	<0.001
User	0.15 (0.12 to 0.19)	83.19	79.52 to 86.08	<0.001
None smoking (0)				
Non-user	0.10 (0.09 to 0.10)	64.41	63.95 to 64.87	<0.001
User	0.08 (0.07 to 0.09)	83.83	82.91 to 84.72	<0.001

Abbreviations: CI, confidence interval; HR, hazard ratio; PAF, population etiologic fraction.

[a]Cox proportional hazards regression adjusted for age, sex, ethnicity, education, household income, body mass index, physical activity, alcohol consumption, fruit consumption, vegetable consumption, passive smoking, occupational exposure, CVD, hypertension, diabetes, cancer, chronic pulmonary infections, rheumatoid arthritis, osteoarthritis, joint pain, asthma, arthritis, cholesterol lowering medication use, anti-hypertensive drug use, insulin use, aspirin use, Non-aspirin NSAIDs use, vitamin use, minerals and other dietary supplements use, chondroitin use, and cortisone use.