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RESEARCH ARTICLE

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Associations of habitual glucosamine use with SARS-CoV-2 infection and hospital admission and death with COVID-19: Evidence from a large population based cohort study

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic has led to a fundamental number of morbidity and mortality worldwide. Glucosamine was indicated to help prevent and control RNA virus infection preclinically, while its potential therapeutic effects on COVID-19-related outcomes are largely unknown. To assess the association of habitual glucosamine use with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, hospital admission, and mortality with COVID-19 in a large population based cohort. Participants from UK Biobank were reinvited between June and September 2021 to have SARS-CoV-2 antibody testing. The associations between glucosamine use and the risk of SARS-CoV-2 infection were estimated by logistic regression. Hazard ratios (HRs) and 95% confidence intervals (CIs) for COVID-19-related outcomes were calculated using COX proportional hazards model. Furthermore, we carried out propensity-score matching (PSM) and stratified analyses. At baseline, 42 673 (20.7%) of the 205 704

Abbreviations: BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; DAG, directed acyclic graph; ECM, extracellular matrix; HA, hyaluronic acid; HR, hazard ratio; MCMC, Markov Chain Monte Carlo; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; PSM, propensity score matching; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; SMD, standardized mean difference.

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participants reported as habitual glucosamine users. During median follow-up of 1.67 years, there were 15 299 cases of SARS-CoV-2 infection, 4214 cases of COVID-19 hospital admission, and 1141 cases of COVID-19 mortality. The fully adjusted odds ratio of SARS-CoV-2 infection with glucosamine use was 0.96 (95% CI: 0.92–1.01). The fully adjusted HR were 0.80 (95% CI: 0.74–0.87) for hospital admission, and 0.81 (95% CI: 0.69–0.95) for mortality. The logistic regression and Cox proportional hazard analyses after PSM yielded consistent results. Our study demonstrated that habitual glucosamine use is associated with reduced risks of hospital admission and death with COVID-19, but not the incidence of SARS-CoV-2 infection.

KEYWORDS
cohort study, COVID-19, extracellular matrix, glucosamine, hospital admission, pandemics, SARS-CoV-2

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, which is caused by the critical acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has contributed to a fundamental number of severe cases and mortality worldwide.[1] As is estimated, over 18 million people have died due to COVID-19 pandemic.[1,2] As of March 16, 2023, more than 760 million diagnosed cases of COVID-19 have been reported to the World Health Organization worldwide, including over 6.8 million mortality cases (https://covid19.who.int/).[3] The most common symptoms of SARS-CoV-2 infection are fever, persistent dry cough, and shortness of breath.[4] One of the main concerns of this infection is that COVID-19 can trigger cytokine mediator in pulmonary tissues, contributing to a series of harmful pathological structures and lethal complications.[5,6] The autopsy results revealed that COVID-19 is characterized by distinct pathological changes, including diffuse thickening of the alveolar wall and pulmonary capillary endothelialitis. Inflammatory infiltration and edema in the pulmonary interstitium can manifest as ground-glass opacity on imaging. Furthermore, the inflammatory response of lung and pulmonary endothelial cells can result in microthrombosis, potentially leading to severe complications.[4] However, no established managements have been available yet.

Glucosamine is an amino sugar that naturally exists in connective tissues. Its commercial names include Viartril-S, etc.[7] Glucosamine and its related products are able to alleviate the process of inflammation by modulating inflammatory mediators such as nitric oxide and reactive oxygen species.[8–12] As a popular dietary supplement, glucosamine has been reported to be used in at least 20% of the adults in the United States.[13] Further, glucosamine is also widely used in clinical practice. Previous studies have shown that oral glucosamine is well tolerated in humans. Even if glucosamine in therapeutic drugs, it has no significant adverse effects on blood and feces parameters, and the most common adverse reaction of glucosamine is mild gastrointestinal discomfort.[14,15] Recent studies have indicated that habitual glucosamine use is associated with lower odds of developing type 2 diabetes, cardiovascular events, lung cancer, and all-cause mortality[16–18] and has been considered as an effective management of osteoarthritis.[19] However, whether there are potential benefits of habitual glucosamine use on COVID-19 remains unknown.

Given the anti-inflammatory effect and extensive use of glucosamine and the high prevalence of COVID-19 worldwide, it is critical to evaluate their linkages. Herein, by leveraging the updated and population-based cohort data extracted from the UK Biobank, we aim to assess the association between habitual glucosamine use and the risks of SARS-CoV-2 infection and hospital admission and mortality with COVID-19.

2 | MATERIALS AND METHODS

2.1 | Study population

The study population and design have been detailed in previous reports.[20] The UK Biobank recruited 502 392 participants between 2006 and 2010. Participants aged 37–73 years were invited to one of the 22 centers in the United Kingdom, where they completed baseline assessments, including face-to-face interviews, detailed touchscreen questionnaires, physical indicators, and biological samples.[20] This study was approved by the North West Multi-Center Research Ethics Committee (approval number: 11/NW/0382, 16/NW/0274, and 21/NW/0157), and written informed consent was obtained from each participant. The UK Biobank resource is open to all researchers (https://www.ukbiobank.ac.uk). The approval number for this UK Biobank project is 83339.

Participants from UK Biobank were reinvited between June and September 2021 to have a SARS-CoV-2 antibody testing. Among the

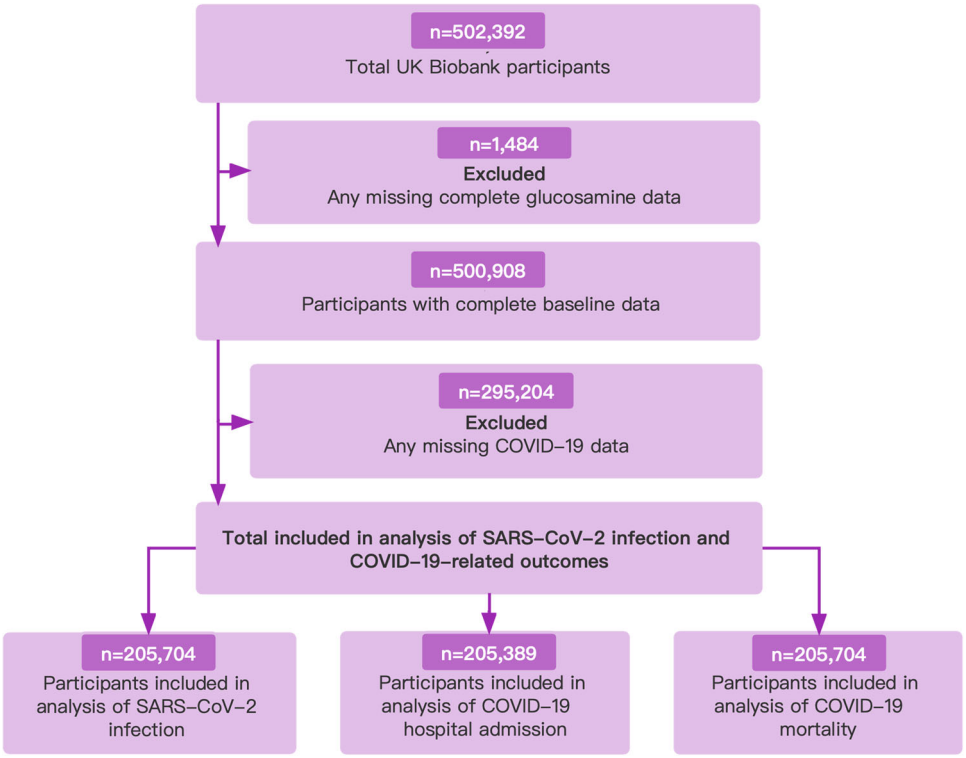

FIGURE 1 Flow chart of eligible participants selection. COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

participants, we excluded participants without complete data on glucosamine use at baseline ($n = 1484$), SARS-CoV-2 infection, or COVID-19-related outcomes (COVID-19 hospital admission and mortality) ($n = 295\,204$). Our analysis eventually included 205 704 participants (Figure 1). In addition, we compared the baseline characteristics of excluded population with included population in this study to evaluate the selection bias.

2.2 | Exposures

The touchscreen questionnaire contained a range of questions including "Do you regularly take any of the following supplements?" Participants could choose their answers from the list, including the use of glucosamine (https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=6179; id = 10007; id = 20003). Habitual glucosamine usage was defined as 0 = no and 1 = yes based on those information, and it showed great agreement and repeatability to subsequent 24-h diet assessments.[21]

2.3 | Outcomes

In our study, we set the beginning date for our study as January 30, 2020 and the selected outcomes included SARS-CoV-2 infection, COVID-19 hospital admission and COVID-19 mortality. SARS-CoV-2 infection was defined by positive tests for SARS-CoV-2 (spike antibodies and nucleocapsid antibodies testing), and even without a SARS-CoV-2 test report, participants were considered to have SARS-CoV-2 infection if they died or were hospitalized due to COVID-19. The COVID-19 hospital admission was defined as confirmed COVID-19 (ICD-10, U07.1, and U07.2) in hospital records (excluded those who died from the virus without being hospitalized [$n = 292$]). We defined COVID-19 mortality as deaths due to COVID-19 (ICD-10, U07.1, and U07.2) based on data from the death registers.

2.4 | Covariates

The baseline questionnaires were used to assess the following factors: age, sex, ethnicity, Townsend Deprivation Index, household income, educational attainment, physical activity, body mass index (BMI), smoking status, alcohol consumption, COVID-19 vaccination, raw vegetables, fresh fruit, vitamin supplementation (vitamin A, B, C, D, E, multivitamin, or folic acid), and mineral and other dietary supplementation (iron, selenium, zinc, or calcium), comorbidities (hypertension, type 2 diabetes, hypercholesterolemia, arthritis, coronary heart disease, chronic obstructive pulmonary disease (COPD), stroke, chronic nephrosis and chronic liver disease), supplement or co-medication use (antihypertensive drugs, hypolipidemic drugs, insulin, nonaspirin nonsteroidal anti-inflammatory drugs, aspirin and immunosuppressant medication). These factors were regarded as covariates that needed to be adjusted in our study, and they were also demonstrated by the directed acyclic graph based on existing literature and expert study (Figure S1).[22–26]

As an indicator of socioeconomic status, the Townsend poverty index provided by the UK Biobank was derived from the postal code of residence. Information on comorbidities, supplement and co-medication use was collected by self-report data at baseline. Hypertension was defined as frequent use of antihypertensive drugs, self-reported history of hypertension, or multiple measurements of systolic blood pressure of 140 mmHg or higher, or diastolic blood pressure of 90 mmHg or higher. Arthritis was defined according to the ICD-10 codes (M00-M03, M05-M14).

2.5 | Statistical analyses

Baseline characteristics of included participants were illustrated by percentage (categorical variables), mean and standard deviation (*SD*) (continuous variables) based on data distribution. Table S1 provides the detailed number of missing covariates. Covariates with missing number higher than 20% will not be considered in our study. The multiple imputation method, which is based on the Markov Chain Monte Carlo method to combine the estimated datasets generated from each dataset insertion, was applied to the missing data of covariates to reduce the data deviation.

We used the Kaplan–Meier method to estimate the event-free probability of outcomes and the stratified log-rank tests to assess differences. Based on the cross-sectional seroprevalence study, the relationship between glucosamine use and the odds ratio (OR) of SARS-CoV-2 infection was analyzed by logistic regression analysis.[27] Hazard ratios (HRs) and 95% confidence intervals (CIs) for COVID-19-related outcomes were calculated using the Cox proportional hazards model. The proportional hazards assumption was examined by Schoenfeld residuals test and no obvious violation was found. Four groups of models were constructed. The nonadjusted model was set as Model I. Model II was adjusted for age and sex. Model III was adjusted for age, sex, ethnicity, the Townsend Deprivation Index, educational attainment, physical activity, BMI, smoking status, alcohol consumption. In addition, we further adjusted for all selected covariates in Model IV.

To assess potential effect modifications, we performed stratified analyses by the following factors: age (<60 or ≥60), sex (female or male), household income (<52 000 or ≥52 000), smoking (never, previous, or current), alcohol consumption (≥3 times/week, <3 times/week or never), educational attainment (college or university degree, noncollege, or university degree), physical activity (<150 or ≥150 min per week), hypertension (yes/no), type 2 diabetes (yes/no), COVID-19 vaccination (not or partially vaccinated or fully vaccinated), immunosuppressant medication (use or nonuse), COPD (yes or no), stroke (yes or no), and chronic nephrosis (yes or no). Simultaneously, the multiplicative interaction between glucosamine use and each covariate on the study outcomes was examined by likelihood ratio tests, which was expressed as $P_{interaction}$.

As for sensitivity analysis, we performed logistic regression analyses on COVID-19 related outcomes to test the results of Cox regression models. In addition, logistic regression analysis and Cox proportional hazards models were also performed for the first repeat assessment (n = 20 343), the second repeat assessment (n = 52 240) and recent 3-year repeat assessment (n = 36 532) from the UK Biobank database.

Furthermore, to reduce potential confounding effects, we carried out propensity score matching (PSM) based on glucosamine use. We matched glucosamine users to nonusers at 1:1 ratio by the MATCHIT package in R, using the greedy nearest neighbor method. We evaluated the overall quality of matched samples by comparing standardized mean differences (SMDs) for the covariates. Among them, the unbalanced covariates between groups (SMD ≥ 0.1) were further adjusted in Cox proportional hazards models to recalculate HR and 95% CI. Additionally, the data for COVID-related outcomes in the current analysis met the proportional hazards assumption in the Cox regression model.

A p value less than 0.05/3 was considered statistically significant. All the results were analyzed using the R software (version 4.2.0, https://www.r-project.org/) in RStudio.

2.6 | Role of the funding source

The funders were not involved in the study design, interpretation of the results, writing of the manuscript, or decision of submission.

3 | RESULTS

3.1 | Participant characteristics

The baseline characteristics of included individuals were classified, based on glucosamine use (Table 1). The median follow-up duration was 1.67 (range: 0.09–1.67) years. Overall, the average age of included participants was 55.58 (*SD*) years, and 43.3% (num/total) of the participants were male. Among them, 42 673 (20.7%) were glucosamine users, and 163 031 (79.3%) were glucosamine nonusers. Compared with glucosamine nonusers, participants who habitually use glucosamine were more inclined to be female, previous smoker, had lower Deprivation index, with fully vaccinated, and had a high prevalence of arthritis. Simultaneously, glucosamine users were more likely to take supplements or in partial co-medication.

3.2 | Glucosamine use and outcomes

During a median follow-up of 1.67 (interquartile range) years, there were 15 299 cases of SARS-CoV-2 infection, 4214 cases of COVID-19 hospital admission, and 1141 cases of COVID-19 mortality.

Initially, although habitual glucosamine use was found to be associated with SARS-CoV-2 infection in fully adjusted logistic regression Model IV (OR: 0.96, 95% CI: 0.92–1.01; p = 0.08) showed no association between habitual glucosamine use and the outcome of SARS-CoV-2 infection. Using Cox proportional hazards, we discovered significant inverse associations between glucosamine use and the risk of COVID-19 hospital admission or mortality (all p < 0.001) in

TABLE 1 Baseline characteristics of UK Biobank participants by habitual glucosamine use.

Characteristics	Glucosamine nonuser	Glucosamine user	Overall
Number of participants, *n* (%)	163 031 (79.3)	42 673 (20.7)	205 704
Age [mean (*SD*)], years	54.94 (7.73)	58.02 (6.83)	55.58 (7.65)
Sex			
Male, *n* (%)	73 251 (44.9)	15 819 (37.1)	89 070 (43.3)
Female, *n* (%)	89 780 (55.1)	26 854 (62.9)	116 634 (56.7)
Ethnicity			
White, *n* (%)	157 806 (96.8)	41 623 (97.5)	199 429 (96.9)
Other, *n* (%)	5225 (3.2)	1050 (2.5)	6275 (3.1)
Education			
College or University degree, *n* (%)	22 406 (13.7)	5513 (12.9)	27 919 (13.6)
Not or partially vaccinated, *n* (%)	140 625 (86.3)	37 160 (87.1)	177 785 (86.4)
TD index [mean (*SD*)]	−1.67 (2.86)	−2.02 (2.64)	−1.74 (2.82)
BMI [mean (*SD*)], kg/m^2	26.87 (4.58)	26.88 (4.45)	26.87 (4.55)
Household income (£)			
<18 000, *n* (%)	25 095 (15.4)	6756 (15.8)	31 851 (15.5)
18 000–30 999, *n* (%)	36 847 (22.6)	11 206 (26.3)	48 053 (23.4)
31 000–51 999, *n* (%)	46 455 (28.5)	12 372 (29.0)	58 827 (28.6)
52 000–100 000, *n* (%)	42 449 (26.0)	9844 (23.1)	52 293 (25.4)
>100 000, *n* (%)	12 185 (7.5)	2495 (5.8)	14 680 (7.1)
Alcohol consumption			
Daily or almost daily, *n* (%)	35 357 (21.7)	10 178 (23.9)	45 535 (22.1)
Three or four times a week, *n* (%)	42 078 (25.8)	11 710 (27.4)	53 788 (26.1)
Once or twice a week, *n* (%)	42 394 (26.0)	10 546 (24.7)	52 940 (25.7)
One to three times a month, *n* (%)	18 045 (11.1)	4396 (10.3)	22 441 (10.9)
Special occasions only, *n* (%)	15 527 (9.5)	3767 (8.8)	19 294 (9.4)
Never, *n* (%)	9630 (5.9)	2076 (4.9)	11 706 (5.7)
Smoking status			
Never smoker, *n* (%)	94 541 (58.0)	24 180 (56.7)	118 721 (57.7)
Previous smoker, *n* (%)	55 221 (33.9)	16 228 (38.0)	71 449 (34.7)
Current smoker, *n* (%)	13 269 (8.1)	2265 (5.3)	15 534 (7.6)
Physical activity			
≥150 min/week, *n* (%)	131 853 (80.9)	36 240 (84.9)	168 093 (81.7)
<150 min/week, *n* (%)	31 178 (19.1)	6433 (15.1)	37 611 (18.3)
Fresh fruit (tablespoons/day)			
<2, *n* (%)	58 158 (35.7)	11 295 (26.5)	69 453 (33.8)
2–3.9, *n* (%)	79 943 (49.0)	22 970 (53.8)	102 913 (50.0)
≥3.9, *n* (%)	24 930 (15.3)	8408 (19.7)	33 338 (16.2)
Raw vegetable (tablespoons/day)			
<2, *n* (%)	74 040 (45.4)	16 970 (39.8)	91 010 (44.2)

(Continues)

TABLE 1 (Continued)

Characteristics	Glucosamine nonuser	Glucosamine user	Overall
2–3.9, *n* (%)	62 791 (38.5)	17 414 (40.8)	80 205 (39.0)
≥3.9, *n* (%)	26 200 (16.1)	8289 (19.4)	34 489 (16.8)
COVID-19 vaccination			
Fully vaccinated, *n* (%)	63 329 (38.8)	18 014 (42.2)	81 343 (39.5)
Not or partially vaccinated, *n* (%)	99 702 (61.2)	24 659 (57.8)	124 361 (60.5)
Supplement or co-medication use:			
Vitamin supplementation			
Use, *n* (%)	42 553 (26.1)	23 512 (55.1)	66 065 (32.1)
Nonuse, *n* (%)	120 478 (73.9)	19 161 (44.9)	139 639 (67.9)
Mineral and other dietary supplementation			
Use, *n* (%)	16 360 (10.0)	10 123 (23.7)	26 483 (12.9)
Nonuse, *n* (%)	146 671 (90.0)	32 550 (76.3)	179 221 (87.1)
Antihypertensive drug			
Use, *n* (%)	27 513 (16.9)	7175 (16.8)	34 688 (16.9)
Nonuse, *n* (%)	135 518 (83.1)	35 498 (83.2)	171 016 (83.1)
Hypolipidemic drug			
Use, *n* (%)	22 427 (13.8)	5958 (14.0)	28 385 (13.8)
Nonuse, *n* (%)	140 604 (86.2)	36 715 (86.0)	177 319 (86.2)
Insulin			
Use, *n* (%)	1246 (0.8)	216 (0.5)	1462 (0.7)
Nonuse, *n* (%)	161 785 (99.2)	42 457 (99.5)	204 242 (99.3)
Aspirin			
Use, *n* (%)	18 375 (11.3)	5225 (12.2)	23 600 (11.5)
Nonuse, *n* (%)	144 656 (88.7)	37 448 (87.8)	182 104 (88.5)
Nonaspirin NSAID			
Use, *n* (%)	44 769 (27.5)	14 056 (32.9)	58 825 (28.6)
Nonuse, *n* (%)	118 262 (72.5)	28 617 (67.1)	146 879 (71.4)
Immunosuppressant medication			
Use, *n* (%)	2767 (1.7)	603 (1.4)	3370 (1.6)
Nonuse, *n* (%)	160 264 (98.3)	42 070 (98.6)	202 334 (98.4)
Comorbidities:			
Hypertension			
Yes, *n* (%)	37 993 (23.3)	10 913 (25.6)	48 906 (23.8)
No, *n* (%)	125 038 (76.7)	31 760 (74.4)	156 798 (76.2)
Type 2 diabetes			
Yes, *n* (%)	8647 (5.3)	1910 (4.5)	10 557 (5.1)
No, *n* (%)	154 384 (94.7)	40 763 (95.5)	195 147 (94.9)
Hypercholesterolemia			
Yes, *n* (%)	17 193 (10.5)	4951 (11.6)	22 144 (10.8)
No, *n* (%)	145 838 (89.5)	37 722 (88.4)	183 560 (89.2)

TABLE 1 (Continued)

Characteristics	Glucosamine nonuser	Glucosamine user	Overall
Arthritis			
Yes, *n* (%)	11 231 (6.9)	4511 (10.6)	15 742 (7.7)
No, *n* (%)	151 800 (93.1)	38 162 (89.4)	189 962 (92.3)
Chronic liver disease			
Yes, *n* (%)	1142 (0.7)	251 (0.6)	1393 (0.7)
No, *n* (%)	161 889 (99.3)	42 422 (99.4)	204 311 (99.3)
Chronic obstructive pulmonary disease			
Yes, *n* (%)	4278 (2.6)	1044 (2.4)	5322 (2.6)
No, *n* (%)	158 753 (97.4)	41 629 (97.6)	200 382 (97.4)
Coronary heart disease			
Yes, *n* (%)	13 493 (8.3)	3351 (7.9)	16 844 (8.2)
No, *n* (%)	149 538 (91,7)	39 322 (92.1)	188 860 (91.8)
Chronic nephrosis			
Yes, *n* (%)	4269 (2.6)	1108 (2.6)	5377 (2.6)
No, *n* (%)	158 762 (97.4)	41 565 (97.4)	200 327 (97.4)
Stroke			
Yes, *n* (%)	2886 (1.8)	742 (1.7)	3628 (1.8)
No, *n* (%)	160 145 (98.2)	41 931 (98.3)	202 076 (98.2)

Note: Categorical variables were described as number (%).

Abbreviations: BMI, body mass index; NSAID, nonsteroidal anti-inflammatory drug; *SD*, standard deviation.

four groups of models. Moreover, in the Cox proportional hazards fully adjusted models, the risk for hospital admission with glucosamine users were reduced by 20% (HR: 0.80, 95% CI: 0.74–0.87; $p < 0.001$), and 19% (HR: 0.81, 95% CI: 0.69–0.95; $p = 0.01$) for mortality (Table 2). The Kaplan–Meier curves for the incidence of COVID-19-related hospital admission and mortality in the glucosamine and nonglucosamine use groups in the overall-sample were illustrated in Figure 2.

3.3 | Subgroup analyses and sensitivity analyses

The associations between glucosamine use and COVID-19 hospital admission were generally consistent in all subgroups, but were more prominent among participants aged under 60 years old (0.77, 95% CI: 0.66–0.89), participants without COPD (0.76, 95% CI: 0.69–0.84), or chronic nephrosis (0.78, 95% CI: 0.71–0.86) (Figure 3). Further, we discovered significant multiplicative interactions between glucosamine use and age ($P_{interaction} = 0.003$), COPD ($P_{interaction} = 0.001$), and chronic nephrosis ($P_{interaction} = 0.03$) on the risk of COVID-19 hospital admission outcome.

Besides, significant multiplicative interaction was found between glucosamine use and immunosuppressant medication ($P_{interaction} = 0.03$) on the risk of COVID-19 mortality outcome (Figure 3). In contrast, no significant interaction effect was found between habitual glucosamine users and other selected risk factors on lethal COVID-19 outcome (all $P_{interaction} > 0.050$). Table S2 showed baseline comparisons between excluded population ($n = 296\,688$) and included population ($n = 205\,704$), and there was no significant selection bias between them.

Logistic regression was used to analyze sensitivity analyses for COVID-19-related outcomes. In four groups of models, there were significant inverse relationships between glucosamine users and COVID-19-related outcomes (both $p < 0.050$). In fully adjusted logistic regression model (Model IV), the ORs of COVID-19 hospital admission was 0.77 (95% CI: 0.70–0.85; $p < 0.001$) and the ORs of mortality was 0.80 (95% CI: 0.67–0.94; $p = 0.007$) (Table 2). The repeated statistical analyses were performed to analyze the associations with glucosamine users and the risk of three outcomes (Table S3). Glucosamine use was significantly associated with COVID-19 hospital admission in three repeated assessments ($p < 0.05$).

3.4 | Propensity score-matching analysis

In PSM analysis, 42 673 glucosamine users were matched with 42 673 nonglucosamine users. All SMD values were less than 0.10. Therefore, the baseline demographic and clinical characteristics of participants were more similar (Table S4). The HRs associated with

TABLE 2 Associations of use of glucosamine with the risk of SARS-CoV-2 infection and COVID-19-related outcomes.

	Logistic model		Cox model	
	OR (95% CI)	*p* value	HR (95% CI)	*p* value
Model I[a]				
SARS-CoV-2 infection	0.85 (0.82–0.89)	**<0.001**	–	–
COVID-19 hospital admission	0.74 (0.68–0.80)	**<0.001**	0.74 (0.68–0.81)	**<0.001**
COVID-19 mortality	0.76 (0.65–0.89)	**<0.001**	0.76 (0.65–0.89)	**<0.001**
Model II[b]				
SARS-CoV-2 infection	0.90 (0.86–0.94)	**<0.001**	–	–
COVID-19 hospital admission	0.65 (0.60–0.70)	**<0.001**	0.65 (0.60–0.71)	**<0.001**
COVID-19 mortality	0.60 (0.51–0.71)	**<0.001**	0.61 (0.52–0.71)	**<0.001**
Model III[c]				
SARS-CoV-2 infection	0.92 (0.88–0.96)	**<0.001**	–	–
COVID-19 hospital admission	0.73 (0.67–0.79)	**<0.001**	0.74 (0.68–0.80)	**<0.001**
COVID-19 mortality	0.71 (0.60–0.83)	**<0.001**	0.71 (0.61–0.83)	**<0.001**
Model IV[d]				
SARS-CoV-2 infection	0.96 (0.92–1.01)	0.08	–	–
COVID-19 hospital admission	0.77 (0.70–0.85)	**<0.001**	0.80 (0.74–0.87)	**<0.001**
COVID-19 mortality	0.80 (0.67–0.94)	**0.007**	0.81 (0.69–0.95)	**0.01**

Note: All *p* values were calculated by logistic regression or COX proportional hazards model. *$p > 0.05$, not regarded as significant. The statistically significant *p* values are highlighted in bold.

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; HR, hazard ratio; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]**Model I**: The OR or HR was nonadjusted.

[b]**Model II**: The adjusted OR or HR was obtained after adjusting the effect from age, sex.

[c]**Model III**: The adjusted OR or HR was obtained after adjusting the effect from age, sex, Ethnicity (white European, others), Townsend Deprivation Index, body mass index, smoking status (never, former, current), alcohol intake.

[d]**Model IV**: The adjusted OR or HR was obtained after adjusting the effect from age, sex, Ethnicity (white European, others), Townsend Deprivation Index, average total annual household income (<£18 000, £18 000–£30 999, £31 000–£51 999, £52 000–£100 000, >£100 000), body mass index, smoking status (never, former, current), alcohol intake, vaccine (fully vaccinated, not or partially vaccinated), education (with college or university degree, no college degree), physical activity(<150, ≥150 min/week), fresh fruit consumption (<2.0, 2.0–3.9, or ≥3.9 tablespoons/day), raw vegetable consumption (<2.0, 2.0–3.9, or ≥3.9 tablespoons/day), vitamin supplement use (use or nonuse), mineral and other dietary supplement use (use or nonuse), antihypertensive drugs (use or nonuse), hypercholesterolemia (use or nonuse), insulin treatment (use or nonuse), aspirin use (use or nonuse), nonaspirin NSAID use (use or nonuse), immunosuppressant medication (use or nonuse), type 2 diabetes (yes or no), hypertension (yes or no), hypercholesterolemia (yes or no), arthritis (yes or no), coronary heart disease (yes or no), chronic obstructive pulmonary disease (yes or no), stroke (yes or no), chronic nephrosis (yes or no), chronic liver disease (yes or no).

glucosamine users was 0.72 (95% CI: 0.65–0.80; $p < 0.001$) for COVID-19 hospital admission, and 0.71 (95% CI: 0.59–0.86; $p < 0.001$) for COVID-19 mortality. For SARS-CoV-2 infection, the OR associated with glucosamine users was 0.95 (95% CI: 0.90–0.99; $p = 0.048$). These results were consistent with the results of Cox proportional hazards analyses described above (Table S5).

4 | DISCUSSION

Although there was no significant association of glucosamine use and COVID-19 infection, we did observe that habitual use of glucosamine was associated with a 20% decreased risk of hospital admission and a 19% reduced risk of death in patients with COVID-19 from this large population-based cohort study. The associations for COVID-19 hospital admission and mortality are independent of age, gender, household income, smoking, alcohol consumption, educational attainment, physical activity, hypertension, type 2 diabetes, COVID-19 vaccination, immunosuppressant medication, COPD, chronic nephrosis, and stroke, while the risks of hospital admission could be modified by age, COPD, and chronic nephrosis.

Nowadays, several studies on other dietary supplements, including vitamin C,[28] vitamin D,[29] and folic acid,[30] did not identify any significantly reduced risks for the COVID-19-related outcomes under their use. But to our knowledge, none of the previous literature has evaluated the effects of habitual glucosamine use on COVID-19.

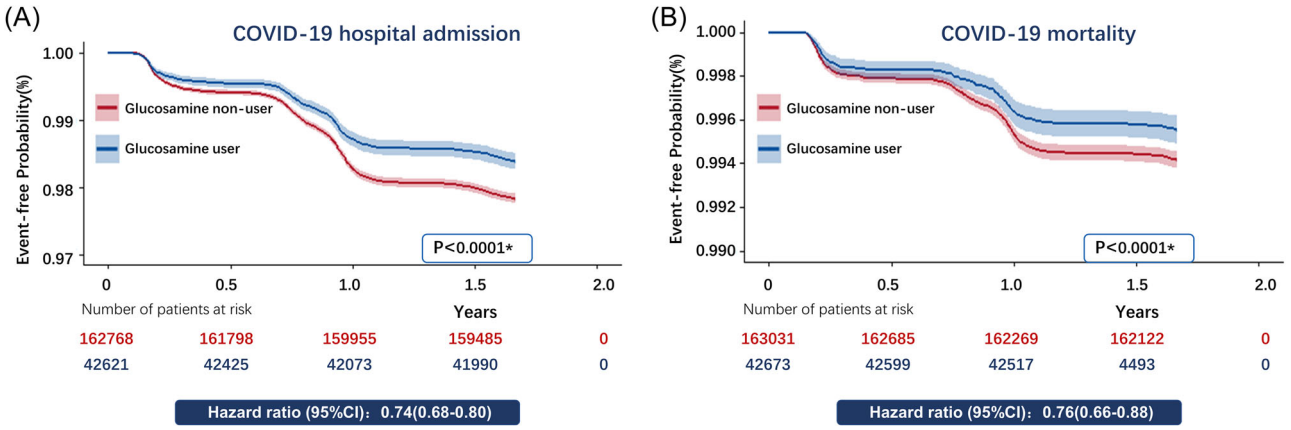

FIGURE 2 Kaplan–Meier curve comparing COVID-19 hospital admission and mortality in participants with or without glucosamine use. The event-free probabilities and hazard ratios for hospital admission (A) and death (B) with COVID-19 are depicted for glucosamine users as compared to nonusers, with 95% confidence intervals shown in parentheses. All *p* values were calculated using the stratified log-rank test. COVID-19, coronavirus disease 2019.

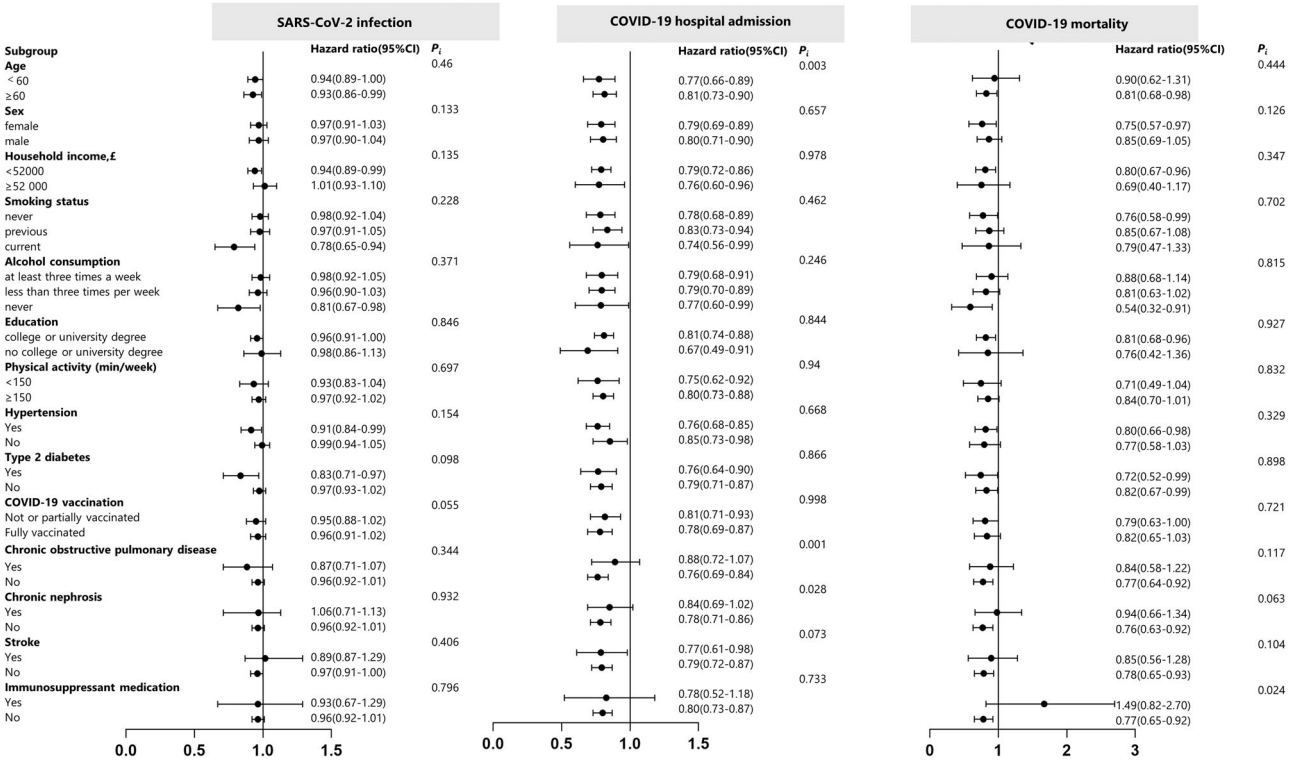

FIGURE 3 Stratified analysis of glucosamine habitual users and the risk of SARS-CoV-2 infection and COVID-19-related outcomes. The effect estimates were adjusted on age, sex, household income, smoking, alcohol consumption, educational attainment, physical activity, hypertension, type 2 diabetes, COVID-19 vaccination, immunosuppressant medication, COPD, stroke, and chronic nephrosis using the fully adjusted model. CI, confidence interval; COVID-19, coronavirus disease 2019; HR, hazard ratio; OR, odds ratio; P:P, value for interaction.

Although habitual glucosamine use has been identified to reduce the risk of type 2 diabetes, cardiovascular diseases, lung cancer, and all-cause mortality by several observational studies,[16–18,31–33] its association with COVID-19 needs to be further explored.

As the first attempt on this field, our study might have critical impacts on future research and clinical practice. In spite of the controversial evidence on the treatment of osteoarthritis by glucosamine,[34] its supplementation could have additional benefits in improving other outcomes of the users. The reduced risks of hospital admission and fatal COVID-19 emphasize the potential benefits of glucosamine. Several studies have indicated that full COVID-19 vaccination could help reduce the incidence of infection and serious outcomes. However, the impact of vaccination on the association between habitual glucosamine use and COVID-19 was

not statistically significant in our study, which remained to be further studied.[22]

Several proposed mechanisms might account for those observed protective effect of glucosamine use and COVID-19-related outcomes. The activation of immune cells, generation of cytokines and chemokines, as well as the positive proinflammatory feedback loops are involved in the inflammatory responses to SARS-CoV-2.[35–37] In consequence, controlling the inflammatory response is important in improving the hospital admission of COVID-19. Administration of glucosamine in mice decreases the production of inflammatory cytokines and alleviates systemic inflammation.[38] Glucosamine also alleviates oxidative stress and lung inflammation though the inhibition of reactive oxygen species-sensitive inflammatory signaling.[11] Glucosamine can not only inhibit the initiation and activation of inflammasome, but also upregulate the activation of mitochondrial antiviral-signaling proteins, which plays a significant role in the prevention of RNA virus infection and inflammation.[39] By contrast, the initial infection of SARS-CoV-2 can trigger, but might not directly involve massive inflammatory responses, and therefore glucosamine use does not alter the susceptibility to COVID-19 positivity. In addition, previous research confirmed that N-acetyl-D-glucosamine, the acetylated derivative of glucosamine, held the potential to suppress several SARS-CoV-2 proteins, and induced an immune response against the virus in the host.[40] Moreover, glucosamine has been shown to promote the formation of other structures within various extracellular matrices (ECMs).[41] For instance, hyaluronic acid (HA), a critical ECM component in several vital organ systems, acts as a scaffold and plays a significant role in lung function. Dysregulation of HA production and degradation can lead to respiratory abnormalities in COVID-19 patients, such as the HA obstruction of alveoli seen in postmortem pathology. Compared to normal lung tissue, HA is present in exudate, plugs, or thickened perialveolar interstitium.[42] This suggests that the systemic inflammatory response exhibited by COVID-19 is linked to the abnormal expression of ECM.[43] The ECM is affected by SARS-CoV-2 infection, and an overactive ECM can exacerbate COVID-19.

This study's main strength is the novel insights it provides. Our study utilized data from the UK Biobank, which is distinguished by its large sample size, long-term follow-up, and prospective design, and provided reliable evidence of the association between glucosamine and COVID-19. In addition, the use of large-scale longitudinal data from the UK Biobank also limits the information bias. By using large-scale longitudinal data from the UK Biobank, we were able to minimize information bias. We employed a variety of statistical analyses to demonstrate the reliability of our research findings, including adjustments for multiple covariates and verification through both traditional logistic regression and propensity-score matching designs. We also enhanced the reliability of our outcome measures by conducting repeated assessments. To the best of our knowledge, our study first discovered that habitual glucosamine use had significant protective effects on COVID-19 hospital admission and COVID-19 mortality. As for potential clinical value, our findings provided new evidence for the clinical application of nutritional supplements, including glucosamine in COVID-19.

Several limitations also exist in our study. First, information on glucosamine supplements is based on self-reported questionnaires, which could not be verified by other sources based on the design of UK Biobank. Further, lacking the dose and duration of glucosamine use as supplement in the UK Biobank limits further assessment of the causal relationship between glucosamine use and COVID-19. Second, the association between glucosamine use and the risk of COVID-19 re-infection could not be assessed due to limitations in UK Biobank information. Third, given the observational nature of the current study, the results might still suffer from residual confounding, and it is difficult to fully eliminate the effects of healthier lifestyles and awareness of seeking medical treatment possessed by glucosamine users. However, we adjusted a wide range of covariates in our study and applied PSM to reduce potential bias. Finally, although the single-recorded glucosamine use data could lead to bias results, people who use glucosamine supplement tend to be consumed habitually for a long period of time in UK Biobank, and multiple repeat assessment analyses have been used to ensure good reproducibility and habituation in our study.

5 | CONCLUSIONS

Habitual glucosamine use is associated with reduced risks of hospital admission and death with COVID-19. Further well-designed randomized-controlled trials are warranted to confirm its benefits.

AUTHOR CONTRIBUTIONS

Meijun Meng, Yanjun Wu, Weihong Sha, and Ruijie Zeng: contributed equally to this work. **Hao Chen, Yuliang Feng, Chongyang Duan, and Felix W. Leung**: are senior and corresponding authors who also contributed equally to this study. **Ruijie Zeng, Weihong Sha, and Hao Chen**: contributed to data extraction, data analyses, and manuscript drafting. **Meijun Meng, Yanjun Wu, and Dongling Luo**: contributed to data interpretation and manuscript drafting. **Dongling Luo, Rui Jiang, Huihuan Wu, Zewei Zhuo, Qi Yang, and Jingwei Li**: contributed to manuscript drafting. **Hao Chen, Yuliang Feng, Chongyang Duan, and Felix W. Leung**: contributed to study design, data interpretation, and final approval of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The UK Biobank resource is open to all researchers (https://www.ukbiobank.ac.uk). The authors thank the UK Biobank for the access of data, and this research has been conducted under Application Number 83339.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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