ARTICLE OPEN

Check for updates

Association of habitual glucosamine use with risk of microvascular complications among individuals with type 2 diabetes: a prospective cohort study in UK biobank

Zi-Jian Cheng[1], Yu-feng Luo[1], Qing-yun Zhu[1], Yan-fei Wang[1], Wen-yan Ren[2], Fei-yan Deng[1], Lin Bo[3], Xi-Yuan Jiang[4]✉, Shu-feng Lei[1]✉ and Long-Fei Wu[1]✉

BACKGROUND: Glucosamine is a widely used supplement for treating osteoarthritis and joint pain. New evidence suggests a potential association between glucosamine and type 2 diabetes, inflammation and cardiometabolic risk. We aimed to prospectively evaluate the association of habitual glucosamine use with risk of diabetic microvascular complications based on data from the large-scale nationwide prospective UK Biobank cohort study.

METHODS: This analysis included 21,171 participants with type 2 diabetes who were free of microvascular complications from the UK Biobank. Incidence of diabetic microvascular complications was ascertained via electronic health records. The Cox proportional hazards model was used to assess the relationship between glucosamine use and the risk of diabetic microvascular complications. Subgroup analyses and sensitivity analyses were performed to explore the potential effect modifications and the robustness of the main findings.

RESULTS: At baseline, 14.5% of the participants reported habitual use of glucosamine supplements. During a median follow-up of 12.3 years, 4399 people developed diabetic microvascular complications, including 2084 cases of incident diabetic nephropathy, 2401 incident diabetic retinopathy, and 831 incident diabetic neuropathy. Glucosamine use was significantly associated with lower risks of composite microvascular complications (hazard ratio (HR) 0.89, 95% CI: 0.81 to 0.97) and diabetic nephropathy (HR 0.87, 95% CI: 0.76 to 0.98) in fully adjusted models. However, there was no significant inverse association between glucosamine use and the risk of diabetic retinopathy (HR 0.94, 95% CI: 0.83 to 1.06) or diabetic neuropathy (HR 0.88, 95% CI: 0.71 to 1.08).

CONCLUSIONS: Habitual use of glucosamine supplement was significantly associated with lower risks of composite microvascular complications and diabetic nephropathy but not retinopathy or neuropathy in individuals with type 2 diabetes.

Nutrition and Diabetes (2025)15:12 ; https://doi.org/10.1038/s41387-025-00369-8

INTRODUCTION

Type 2 diabetes (T2D) mellitus is a complex metabolic disorder with multiple metabolic and homeostatic disturbances that occur during the course of the disease and persist over time. About 537 million adults worldwide have diabetes, the majority of whom have T2D, and this number is projected to increase to 783 million by 2045 [1]. Diabetic microvascular complications, including diabetic nephropathy, diabetic retinopathy, and diabetic neuropathy, lead to increased mortality, renal failure, blindness and overall reduced quality of life in people with diabetes mellitus [2]. Therefore, it is crucial to identify cost-effective strategies to prevent and slow the progression of microvascular complications in diabetic patients.

Glucosamine is a commonly used supplement for relieving osteoarthritis and joint pain [3]. About 20% of adults in the United States and Australia consume it daily [4, 5]. Although the efficacy of glucosamine for osteoarthritis and joint pain remains debated, several recent epidemiological studies have shown that glucosamine reduces the risk of a number of diseases, such as cardiovascular disease, type 2 diabetes and lung cancer [5–7]. A 3-year clinical trial of 212 participants showed a slight glucose-lowering effect in glucosamine users [8], and studies have shown a protective effect of glycaemia control on diabetic microvascular complications [9, 10]. In addition, previous studies have suggested that glucosamine may affect the inflammatory state [11–13], which has also been linked to the risk of microvascular complications in T2D [10]. However, the relationship between habitual glucosamine uses and microvascular complications in patients with T2D remains unclear.

To fill these knowledge gaps, in the current study we aimed to prospectively evaluate the association of habitual glucosamine use with risk of microvascular complications in individuals with T2D from the UK Biobank.

[1]Center for Genetic Epidemiology and Genomics, School of Public Health, Jiangsu Key Laboratory of Preventive and Translational Medicine for Major Chronic Non-communicable Diseases, MOE Key Laboratory of Geriatric Diseases and Immunology, Suzhou Medical College of Soochow University, Suzhou, China. [2]Cambridge-Suda Genomic Resource Center, Jiangsu Key Laboratory of Neuropsychiatric Diseases, Medical College of Soochow University, Suzhou, China. [3]Department of Rheumatology, The Second Affiliated Hospital of Soochow University, Suzhou, Jiangsu, China. [4]Center of Osteoporosis, Kunshan Hospital of Traditional Chinese Medicine, Kunshan, China. ✉email: 397365264@qq.com; leisf@suda.edu.cn; lfwu@suda.edu.cn

Received: 23 June 2024 Revised: 12 February 2025 Accepted: 28 February 2025
Published online: 01 April 2025

METHODS

Study Population

The UK Biobank is a national health resource in the United Kingdom aimed at enhancing the prevention, diagnosis, and treatment of various illnesses and promoting public health [14, 15]. Between 2006 and 2010, the UK Biobank enrolled approximately 500,000 participants aged 40–69 from across the country. All participants provided informed consent, and the study was approved by the North West–Haydock Research Ethics Committee (16/NW/0274).

Individuals with T2D were identified using the Eastwood algorithm [16] and/or from measured HbA1c ≥ 48 mmol/mol (6.5%). The Eastwood algorithm combines hospital inpatient records, self-reported medical history, and medication, which is a reliable measurement with 96% accuracy. After excluding participants with prevalent diabetic microvascular complications ($n = 2{,}985$), reduced kidney function (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73m^2 [$n = 1545$]), or CVD ($n = 4{,}573$) at baseline, who had withdrawn from the UK Biobank ($n = 57$), or had incomplete data on the use of glucosamine ($n = 399$). Finally, 21,171 individuals with T2D were included in the present analysis (Fig. 1).

Exposure Assessment

Participants attended one of 22 assessment centers across the UK where they completed a touch screen questionnaire. One of the questions asked "Do you regularly take any of the following?", and participants could choose their response from a list of supplements, including glucosamine. Based on this data, we defined glucosamine use as 0 = no and 1 = yes.

Individual baseline characteristics were identified from self-report and electronic hospital records. Variables of interest included age, sex, race, smoking status, drinking status, body mass index (BMI), physical activity, dietary intakes (fruit, vegetables, fish, processed meat and red meat), personal medical condition (including arthritis, hypertension and high cholesterol), use of aspirin and non-aspirin NSAIDs, supplementation of nutrients (vitamins, minerals and other dietary supplementation, including fish oil, zinc, calcium, iron and selenium), duration of T2D, measured HbA_{1c} and drugs to treat high cholesterol, hypertension, and diabetes.

A healthy diet was defined based on the following criteria: total fruit and vegetable intake >4.5 pieces or servings/week, total fish intake >2 times/week, and processed meat intake ≤2 times per week and red meat intake <5 times per week. Meeting at least two of these criteria was considered indicative of a healthy diet [17].

According to global recommendations on physical activity for health [18], we categorized participants into two groups based on total moderate physical activity minutes each week (one vigorous physical activity minute equals two moderate physical activity minutes): <150 or ≥150 min/week. Hypertension was defined as a self-reported history of hypertension, systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or taking antihypertensive drugs [19, 20].

Ascertainment of outcomes

The primary outcome of interest was overall incident diabetic microvascular complications, a composite indicator of the first occurrence of diabetic nephropathy, diabetic retinopathy, and/or diabetic neuropathy. Secondary outcomes included the incidence of three diabetic microvascular complications subtypes (diabetic nephropathy, diabetic retinopathy, and diabetic neuropathy). Cases of nephropathy, retinopathy, and neuropathy were identified from hospital inpatient records coded according to the ICD-10 (Supplementary Table 1).

Statistical Analysis

The differences in baseline characteristics between individuals with and without glucosamine use were examined using the Student t-test for continuous variables and the χ^2 test for categorical variables. We compared event rates in participants who did and did not use glucosamine by using Cox proportional hazards models to calculate hazard ratios and 95% confidence intervals. The proportional hazards assumption was tested using Schoenfeld residuals. We adjusted for several potential confounders: age, sex, and race (white European, mixed, South Asian, black, others); body mass index; smoking status (never, former, current); drinking status (never, former, current); physical activity (<150 or ≥150 min/week); hypertension (yes or no), high cholesterol (yes or no), and arthritis (yes or no); aspirin use (yes or no), and non-aspirin non-steroidal anti-inflammatory drug use (yes or no); healthy diet (yes or no); vitamin supplement use (yes or no); and mineral and other dietary supplement use (yes or no; fish oil, zinc, calcium, iron, selenium); diabetes duration; measured HbA_{1c}; use of diabetes medication (none, only oral medication, only insulin, or insulin and oral medication). To reduce the potential for inferential bias [21], we addressed missing values through multiple imputation with chained equations, resulting in five imputed datasets. The imputation methods were predictive mean matching (PMM) for numeric data, logistic regression (LogReg) for binary data, polytomous regression (PolyReg) for unordered categorical data (factor > 2 levels) and proportional odds model (Polr) for ordered categorical data (factor > 2 levels). We checked for convergence of our imputations with trace plots (Supplementary Fig. 1**)**. The percentage of missing values are present in Supplementary Table 2.

We conducted a stratified analysis to assess potential modification effects by the following factors: sex (male or female), age (<55 or ≥55), body mass index (18.5-25.0, 25.0-29.9, or ≥30.0), smoking status (never, former, or current), drinking status (never, former, or current), physical activity (<150 or ≥150 min/week), diabetes duration (<5 or ≥5 years), HbA_{1c} (<53 or ≥53 mmol/mol). We evaluated potential effect modification by modeling the cross-product term of the stratifying variable with glucosamine use.

We performed several sensitivity analyses. First, given that participants taking glucosamine were also more likely to use other supplements, we conducted a sensitivity analysis excluding participants who used any other supplements. Second, to reduce the impact of reverse causation, we conducted an analysis excluding participants who developed diabetic microvascular complications within one year of follow-up. Third, to assess the potential mediation by inflammation and lipids, we additionally adjusted for C-reactive protein (CRP) levels (continues, milligrams per liter) and lipid profiles, including HDL, LDL, and triglycerides (TG) (all continuous,

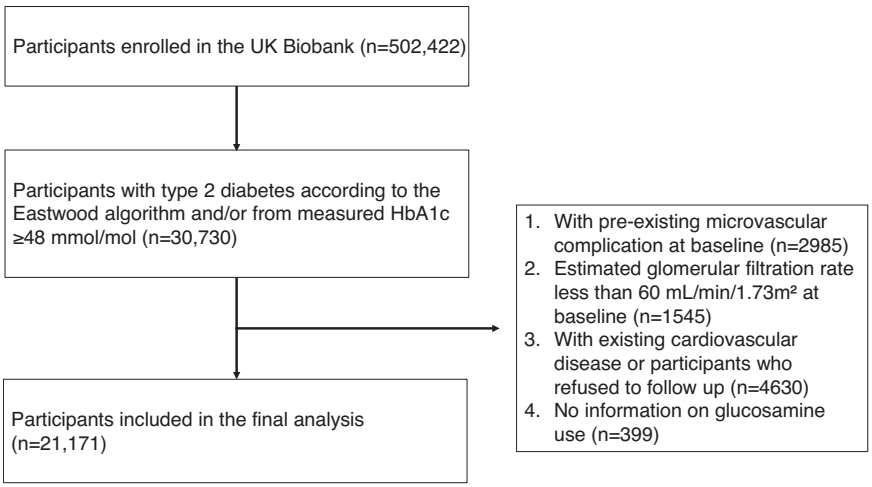

Fig. 1 Flow chart of participant enrolment.

Table 1. Baseline characteristics of UK biobank participants with type 2 diabetes by glucosamine use.

Characteristics	Overall (n = 21171)	Glucosamine non-user (n = 18092)	Glucosamine user (n = 3079)	*P* value
Mean (SD) age (years)	58.6 (7.5)	58.2 (7.6)	60.7 (6.3)	<0.001
Female	9144 (43.2)	7577 (41.9)	1567 (50.9)	<0.001
Race:				<0.001
White European	18552 (87.6)	15787 (87.2)	2765 (89.8)	
Mixed	1132 (5.4)	1021 (5.6)	111 (3.6)	
South Asian	804 (3.8)	967 (3.9)	107 (3.5)	
Black	293 (1.4)	250 (1.4)	43 (1.4)	
Others	390 (1.8)	337 (1.9)	53 (1.7)	
Mean (SD) body mass index	31.2 (5.9)	31.2 (5.9)	31.4 (5.6)	0.279
Physical activity (min/week):				<0.001
<150	5524 (26.1)	4868 (26.9)	656 (21.3)	
≥150	15647 (73.9)	13224 (73.1)	2423 (78.7)	
Smoking status:				<0.001
Current	2375 (11.2)	2154 (11.9)	221 (7.2)	
Former	8518 (40.2)	7106 (39.3)	1412 (45.8)	
Never	10278 (48.6)	8832 (48.8)	1446 (47.0)	
Drinking status				<0.001
Current	18008 (85.1)	15289 (84.5)	2719 (88.3)	
Former	1327 (6.3)	1177 (6.5)	150 (4.9)	
Never	1836 (8.6)	1626 (9.0)	210 (6.8)	
Healthy diet	17431 (82.3)	14770 (81.6)	2661 (86.4)	<0.001
Disease history				
Hypertension	16617 (78.8)	14183 (78.4)	2434 (79.1)	0.425
High cholesterol	13832 (65.3)	11789 (65.2)	2043 (66.4)	0.206
Arthritis	2503 (11.8)	1830 (10.1)	673 (21.9)	<0.001
Drug use:				
Aspirin	8010 (37.8)	6805 (37.6)	1205 (39.1)	0.112
Non-aspirin NSAID	2940 (13.9)	2343 (13.0)	597 (19.4)	<0.001
Supplement use:				
Vitamins	6081 (28.7)	4411 (24.4)	1670 (54.2)	<0.001
Minerals and other dietary supplements	7220 (34.1)	5155 (28.5)	2065 (67.1)	<0.001
Diabetes medication use:				<0.001
None	9129 (43.1)	7684 (42.5)	1445 (46.9)	
Only oral medication	9026 (42.6)	7786 (43.0)	1240 (40.3)	
Only insulin	1564 (7.4)	1349 (7.5)	215 (7.0)	
Insulin and oral medication	1452 (6.9)	1273 (7.0)	179 (5.8)	
Mean (SD) HbA1c (mmol/mol)	52.6 (14.7)	52.9 (15.0)	51.2 (12.6)	<0.001
Mean (SD) diabetes duration (years)	6.4 (9.3)	6.5 (9.4)	6.0 (8.7)	0.004

Values are numbers (%) unless stated otherwise.
NSAID, non- steroidal anti- inflammatory drug; HbA1c, glycated hemoglobin A1c.

millimoles per liter). We used R V.4.2.0 (R Development Core Team, Vienna, Austria) for all statistical analyses, and $p < 0.05$ (two-sided) were considered significant.

RESULTS

Table 1 shows baseline characteristics of the study participants according to the use of glucosamine. Overall, 14.5% of the study population reported glucosamine use at baseline. Compared with non-users, glucosamine users were older, more likely to be women, more physically active, not current smokers, had a healthy diet, and had a higher prevalence of arthritis. Glucosamine users also tended to take more non-aspirin non-steroidal anti-inflammatory drugs, vitamins, minerals, and other dietary supplements than non-users. They were also more prone to have a shorter duration of diabetes, lower HbA1c levels, less likely to use diabetes medication at baseline.

Table 2 shows the associations between glucosamine use and incident diabetic microvascular complications. During a median of 12.3 years of follow-up, 4,399 people developed diabetic microvascular complications, including 2,084 cases of incident diabetic nephropathy, 2,401 incident diabetic retinopathy, and

Table 2. Association of glucosamine supplement use with risk of microvascular complications among individuals with type 2 diabetes.

	Glucosamine non-user	Glucosamine user
Composite microvascular complications		
Events, n (%)	3766 (20.8)	633 (20.5)
Incidence rate per 1000 person-years (95% CI)	18.5 (17.9, 19.1)	18.0 (16.6, 19.4)
Model 1 (HR, 95% CI)	1 (Reference)	0.88 (0.80, 0.95)
Model 2 (HR, 95% CI)	1 (Reference)	0.86 (0.78, 0.94)
Model 3 (HR, 95% CI)	1 (Reference)	0.89 (0.81, 0.97)
Diabetic nephropathy		
Events, n (%)	1778 (9.8)	306 (9.9)
Incidence rate per 1,000 person-years (95% CI)	8.3 (7.9, 8.7)	8.3 (7.4, 9.2)
Model 1 (HR, 95% CI)	1 (Reference)	0.86 (0.76, 0.97)
Model 2 (HR, 95% CI)	1 (Reference)	0.85 (0.74, 0.96)
Model 3 (HR, 95% CI)	1 (Reference)	0.87 (0.76, 0.98)
Diabetic retinopathy		
Events, n (%)	2057 (11.4)	344 (11.2)
Incidence rate per 1,000 person-years (95% CI)	9.8 (9.4, 10.2)	9.5 (8.5, 10.5)
Model 1 (HR, 95% CI)	1 (Reference)	0.91 (0.81, 1.02)
Model 2 (HR, 95% CI)	1 (Reference)	0.91 (0.81, 1.03)
Model 3 (HR, 95% CI)	1 (Reference)	0.94 (0.83, 1.06)
Diabetic neuropathy		
Events, n (%)	720 (4.0)	111 (3.6)
Incidence rate per 1,000 person-years (95% CI)	3.3 (3.1, 3.5)	2.9 (2.4, 3.4)
Model 1 (HR, 95% CI)	1 (Reference)	0.87 (0.71, 1.06)
Model 2 (HR, 95% CI)	1 (Reference)	0.83 (0.67, 1.02)
Model 3 (HR, 95% CI)	1 (Reference)	0.88 (0.71, 1.08)

HR hazard ratio, *CI* confidence interval.
Model 1: age (continuous, years), sex (male, female), and race (white European, mixed, South Asian, black, others).
Model 2: Model1 + body mass index (continuous), smoking status (never, former or current), drinking status (never, former or current), physical activity (<150 or ≥150 min/week), hypertension (yes or no), high cholesterol (yes or no), arthritis (yes or no), aspirin use (yes or no), non-aspirin non-steroidal anti-inflammatory drug use (yes or no), vitamin supplement use (yes or no), mineral and other dietary supplement use (yes or no), and healthy diet (yes or no).
Model 3: (main model): Model2 + diabetes duration (continuous, years), HbA1c (continuous, mmol/mol), and use of diabetes medication (none, only oral medication, only insulin, or insulin and oral medication).

831 incident diabetic neuropathy. In the multivariable adjusted analyses, the hazard ratios associated with glucosamine use were 0.89 (95% CI: 0.81, 0.97) for composite diabetic microvascular complications; and 0.87 (95% CI: 0.76, 0.98) for diabetic nephropathy, but there was no significant inverse association between glucosamine use and risk of diabetic retinopathy 0.94 (95% CI: 0.83, 1.06) or diabetic neuropathy 0.88 (95% CI: 0.71, 1.08).

In stratified analyses, the association between glucosamine supplement use and incident diabetic microvascular complications was not significantly modified by any of the subgroup factors (Supplementary Figs. 2–5). In our sensitivity analyses, the associations between glucosamine use and diabetic microvascular complications remained stable: first, when we excluded participants who used any other supplements (Supplementary Table 3); second, when we excluded participants who developed diabetic microvascular complications within one year of follow-up (Supplementary Table 4); and third, after further adjustment for CRP and lipid profiles (Supplementary Table 5).

DISCUSSION

In this large prospective study, habitual glucosamine use was associated with a 11% lower risk of composite microvascular complications and a 13% lower risk of diabetic nephropathy. These associations were independent of other potential confounders, such as sociodemographic factors, lifestyle behaviors, health status, drug use and other supplements use. Results from sensitivity analyses further supported the robustness of the main findings.

To the best of our knowledge, this is the first prospective cohort study to explore the association between glucosamine use and the risk of diabetic microvascular complications. It is notable that previous studies have indicated that short-term, high-dose glucosamine administration can negatively impact glucose tolerance and insulin sensitivity, causing endothelial dysfunction in both animals and humans [22–28]. However, several clinical trials have found that long-term administration of glucosamine at oral dose levels does not adversely affect glucose metabolism and endothelial function in both healthy individuals and diabetics [29–32]. In contrast, a long-term controlled trial involving 212 arthritis patients reported a mild glucose-lowering effect after a 3-year glucosamine intervention [8]. In another prospective cohort study, glucosamine administration was found to reduce the risk of developing type 2 diabetes [7], and a meta-analysis of clinical trials reported similar results [33]. Consistent with these findings, our current study observed a slight association between habitual glucosamine use and lower baseline blood glucose levels. The inconsistency between animal and human results may partly stem from the substantially higher glucosamine doses used in animal research (100-200 times higher) compared to typical oral doses in humans [33].

There are several potential mechanisms that may explain the observed protective effect of glucosamine use on diabetic microvascular complications. First, glucosamine use may influence inflammation by inhibiting the translocation of the transcription factor NF-κB into the nucleus [12, 34], with the activation of its p65 subunit considered a key factor in the development of diabetic complications [10, 35, 36]. In experimental studies, NF-κB inhibitors have shown nephroprotective effects in both diabetic and nondiabetic nephropathy models [37, 38]. Additionally, findings from the National Health and Nutrition Examination Survey (NHANES) indicate that regular glucosamine use is associated with significantly reduced levels of C-reactive protein, a marker indicating systemic inflammation [39]. Clinical studies also reveal that individuals with type 2 diabetes exhibit elevated levels of circulating inflammatory markers, which seem to predict the onset and progression of diabetic complications [10]. In addition, Moreover, glucosamine's antioxidant and free radical scavenging effects are well-documented [40–43]. At a concentration of 0.8 mg/ml, glucosamine demonstrated scavenging activity of 84% against superoxide radicals and 55% against hydroxyl radicals [43]. Superoxide, generated due to mitochondrial dysfunction in diabetes, is thought to play a significant role in the development of diabetic complications [44]; Thus, the antioxidant capabilities of glucosamine may partly elucidate its potential protective mechanism against diabetic microvascular complications. Furthermore, an earlier animal study indicated that glucosamine imitates the effects of a low-carbohydrate diet by decreasing glycolysis and enhancing amino acid catabolism in mice [45]. Low-carbohydrate diets have been linked to improved

metabolic profiles in patients with type 2 diabetes [46, 47]. While other mechanisms may also play a role, further prospective studies and intervention trials are essential to clarify the potential benefits of glucosamine in preventing microvascular complications in type 2 diabetes.

Our study indicates that glucosamine use may help prevent nephropathy, although its effects on retinopathy and neuropathy appear less pronounced. This can be explained by inherent differences in the etiology of each microvascular complication that may influence the range of mechanisms potentially targeted by glucosamine. For instance, hyperglycemia plays a primary role in the onset of diabetic retinopathy [48–50], while nephropathy risk is influenced by hyperglycemia in combination with other metabolic factors such as obesity, insulin resistance, inflammation, dyslipidemia, and hypertension [51]. Glucosamine has been shown to improve several of these metabolic risk factors [12, 34, 39], which may explain the more substantial risk reduction observed for kidney disease. The absence of a statistically significant association between glucosamine use and neuropathy may be result from the small number of participants who developed neuropathy.

The main strengths of this study are its use of prospective cohort data with a substantial sample size, the extensive information available on covariates, and the robust, consistent results across multiple sensitivity analyses. However, there are some limitations in our study. First, the UK Biobank did not collect comprehensive information regarding glucosamine use, such as dose and duration of use [14]. And differences in nutrient intake doses can produce very different or even conflicting results. Therefore, further studies are needed to investigate this association. Second, the UK Biobank did not collect data on the side effects associated with glucosamine use. Nonetheless, glucosamine is considered one of the safest supplements for osteoarthritis, with only minimal side effects reported, including rare allergic reactions, diarrhea, constipation, nausea, and heartburn [3]. While some earlier studies suggested that glucosamine might impair glucose tolerance in those at high risk for diabetes [52, 53], clinical trials have demonstrated that glucosamine does not affect glucose metabolism or lipid profiles at any oral dose in either healthy individuals or diabetes patients [29, 30]. Third, in an observational study, distinguishing the impact of a healthy lifestyle from the habitual use of supplements can be challenging. In this context, regular glucosamine use may serve as an indicator of a healthier lifestyle among participants. Consequently, we cannot rule out the possibility that the observed inverse associations may be influenced by healthy lifestyle factors among those using glucosamine, despite our thorough adjustments for potential confounders, including obesity, physical activity, smoking, and diet, in the analyses. In addition, microvascular complications were diagnosed based on cumulative hospital records and linkage to national death registries using ICD codes. Consequently, any misclassification of patients with these complications could dilute the study results, potentially underestimating the true strength of the association. Furthermore, due to the observational study design, residual or unknown confounders could not be excluded, although we endeavored to adjust for potential confounders. Finally, the UK Biobank study is known to have a selection bias toward healthy volunteers with healthy lifestyles and lower rates of diabetes [14]; therefore, the findings may not be generalizable to other populations. Future research could strengthen these findings through randomized controlled trials to better assess the associations in more diverse and representative cohorts.

In this large prospective study of patients with type 2 diabetes, we found that habitual use of glucosamine, a commonly used supplement for the treatment of osteoarthritis and joint pain, was associated with lower risks of composite microvascular complications and diabetic nephropathy in patients with type 2 diabetes. These findings suggest that glucosamine could be considered as part of a comprehensive management strategy for patients with type 2 diabetes. Integrating glucosamine into patient care may help reduce the risk of microvascular complications, thereby improving overall health outcomes. However, further research is needed to explore the biological mechanisms underlying these associations and to establish causality through randomized controlled trials. Additionally, examining the long-term effects of glucosamine in diverse populations will provide a robust evidence base for clinical guidelines and public health policies aimed at managing diabetes and its complications effectively.

DATA AVAILABILITY

The UK Biobank genotype and phenotype data is available on application to the UK Biobank project (ID: 76875) at http://www.ukbiobank.ac.uk.

REFERENCES

1. Ahmad E, Lim S, Lamptey R, Webb DR, Davies MJ. Type 2 diabetes. Lancet. 2022;400:1803–20.
2. Cole JB, Florez JC. Genetics of diabetes mellitus and diabetes complications. Nat Rev Nephrol. 2020;16:377–90.
3. Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, et al. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis. 2003;62:1145–55.
4. Barnes, PM, B Bloom, Nahin RL. Complementary and alternative medicine use among adults and children: United States, 2007. Natl Health Stat Report, 2008: p. 1–23.
5. Ma H, Li X, Sun D, Zhou T, Ley SH, Gustat J, et al. Association of habitual glucosamine use with risk of cardiovascular disease: prospective study in UK Biobank. Bmj. 2019;365:l1628.
6. Li G, Zhang X, Liu Y, Zhang J, Li L, Huang X, et al. Relationship between glucosamine use and the risk of lung cancer: data from a nationwide prospective cohort study. Eur Respir J, 2022;59.
7. Ma H, Li X, Zhou T, Sun D, Liang Z, Li Y, et al. Glucosamine Use, Inflammation, and Genetic Susceptibility, and Incidence of Type 2 Diabetes: A Prospective Study in UK Biobank. Diabetes Care. 2020;43:719–25.
8. Reginster JY, Deroisy R, Rovati LC, Lee RL, Lejeune E, Bruyere O, et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. Lancet. 2001;357:251–6.
9. Cameron NE, Gibson TM, Nangle MR, Cotter MA. Inhibitors of advanced glycation end product formation and neurovascular dysfunction in experimental diabetes. Ann N. Y Acad Sci. 2005;1043:784–92.
10. Forbes JM, Cooper ME. Mechanisms of diabetic complications. Physiol Rev. 2013;93:137–88.
11. Azuma K, Osaki T, Wakuda T, Tsuka T, Imagawa T, Okamoto Y, et al. Suppressive effects of N-acetyl-D-glucosamine on rheumatoid arthritis mouse models. Inflammation. 2012;35:1462–5.
12. Largo R, Alvarez-Soria MA, Díez-Ortego I, Calvo E, Sánchez-Pernaute O, Egido J, et al. Glucosamine inhibits IL-1beta-induced NFkappaB activation in human osteoarthritic chondrocytes. Osteoarthritis Cartilage. 2003;11:290–8.
13. Yomogida S, Hua J, Sakamoto K, Nagaoka I. Glucosamine suppresses interleukin-8 production and ICAM-1 expression by TNF-alpha-stimulated human colonic epithelial HT-29 cells. Int J Mol Med. 2008;22:205–11.
14. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, et al. Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. Am J Epidemiol. 2017;186:1026–34.
15. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12:e1001779.
16. Eastwood SV, Mathur R, Atkinson M, Brophy S, Sudlow C, Flaig R, et al. Algorithms for the Capture and Adjudication of Prevalent and Incident Diabetes in UK Biobank. PLoS One. 2016;11:e0162388.
17. Chen X, Wan Z, Geng T, Zhu K, Li R, Lu Q, et al. Vitamin D Status, Vitamin D Receptor Polymorphisms, and Risk of Microvascular Complications Among Individuals With Type 2 Diabetes: A Prospective Study. Diabetes Care. 2023;46:270–7.
18. World Health, O. Global recommendations on physical activity for health. 2010, World Health Organization: Geneva.
19. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). Jama. 2014;311:507–20.

20. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. Jama. 2003;289:2560–72.
21. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. Journal Statistical Software. 2011;45:1–67.
22. Fiorentino TV, Procopio T, Mancuso E, Arcidiacono GP, Andreozzi F, Arturi F, et al. SRT1720 counteracts glucosamine-induced endoplasmic reticulum stress and endothelial dysfunction. Cardiovasc Res. 2015;107:295–306.
23. Robinson KA, Sens DA, Buse MG. Pre-exposure to glucosamine induces insulin resistance of glucose transport and glycogen synthesis in isolated rat skeletal muscles. Study of mechanisms in muscle and in rat-1 fibroblasts overexpressing the human insulin receptor. Diabetes. 1993;42:1333–46.
24. Rossetti L, Hawkins M, Chen W, Gindi J, Barzilai N. In vivo glucosamine infusion induces insulin resistance in normoglycemic but not in hyperglycemic conscious rats. J Clin Invest. 1995;96:132–40.
25. Monauni T, Zenti MG, Cretti A, Daniels MC, Targher G, Caruso B, et al. Effects of glucosamine infusion on insulin secretion and insulin action in humans. Diabetes. 2000;49:926–35.
26. Marshall S, Bacote V, Traxinger RR. Discovery of a metabolic pathway mediating glucose-induced desensitization of the glucose transport system. Role of hexosamine biosynthesis in the induction of insulin resistance. J Biol Chem. 1991;266:4706–12.
27. Wallis MG, Smith ME, Kolka CM, Zhang L, Richards SM, Rattigan S, et al. Acute glucosamine-induced insulin resistance in muscle in vivo is associated with impaired capillary recruitment. Diabetologia. 2005;48:2131–9.
28. Patti ME, Virkamäki A, Landaker EJ, Kahn CR, Yki-Järvinen H. Activation of the hexosamine pathway by glucosamine in vivo induces insulin resistance of early postreceptor insulin signaling events in skeletal muscle. Diabetes. 1999;48:1562–71.
29. Simon RR, Marks V, Leeds AR, Anderson JW. A comprehensive review of oral glucosamine use and effects on glucose metabolism in normal and diabetic individuals. Diabetes Metab Res Rev. 2011;27:14–27.
30. Albert SG, Oiknine RF, Parseghian S, Mooradian AD, Haas MJ, McPherson T. The effect of glucosamine on Serum HDL cholesterol and apolipoprotein AI levels in people with diabetes. Diabetes Care. 2007;30:2800–3.
31. Tannis AJ, Barban J, Conquer JA. Effect of glucosamine supplementation on fasting and non-fasting plasma glucose and serum insulin concentrations in healthy individuals. Osteoarthritis Cartilage. 2004;12:506–11.
32. Muniyappa R, Karne RJ, Hall G, Crandon SK, Bronstein JA, Ver MR, et al. Oral glucosamine for 6 weeks at standard doses does not cause or worsen insulin resistance or endothelial dysfunction in lean or obese subjects. Diabetes. 2006;55:3142–50.
33. Anderson JW, Nicolosi RJ, Borzelleca JF. Glucosamine effects in humans: a review of effects on glucose metabolism, side effects, safety considerations and efficacy. Food Chem Toxicol. 2005;43:187–201.
34. Imagawa K, de Andrés MC, Hashimoto K, Pitt D, Itoi E, Goldring MB, et al. The epigenetic effect of glucosamine and a nuclear factor-kappa B (NF-kB) inhibitor on primary human chondrocytes-implications for osteoarthritis. Biochem Biophys Res Commun. 2011;405:362–7.
35. Barnes PJ, Karin M. Nuclear factor-kappaB: a pivotal transcription factor in chronic inflammatory diseases. N Engl J Med. 1997;336:1066–71.
36. Bierhaus A, Schiekofer S, Schwaninger M, Andrassy M, Humpert PM, Chen J, et al. Diabetes-associated sustained activation of the transcription factor nuclear factor-kappaB. Diabetes. 2001;50:2792–808.
37. Lee FT, Cao Z, Long DM, Panagiotopoulos S, Jerums G, Cooper ME, et al. Interactions between angiotensin II and NF-kappaB-dependent pathways in modulating macrophage infiltration in experimental diabetic nephropathy. J Am Soc Nephrol. 2004;15:2139–51.
38. Rangan GK, Wang Y, Tay YC, Harris DC. Inhibition of nuclear factor-kappaB activation reduces cortical tubulointerstitial injury in proteinuric rats. Kidney Int. 1999;56:118–34.
39. Kantor ED, Lampe JW, Vaughan TL, Peters U, Rehm CD, White E. Association between use of specialty dietary supplements and C-reactive protein concentrations. Am J Epidemiol. 2012;176:1002–13.
40. Mendis E, Kim MM, Rajapakse N, Kim SK. Sulfated glucosamine inhibits oxidation of biomolecules in cells via a mechanism involving intracellular free radical scavenging. Eur J Pharmacol. 2008;579:74–85.
41. Jamialahmadi K, Arasteh O, Matbou Riahi M, Mehri S, Riahi-Zanjani B, Karimi G. Protective effects of glucosamine hydrochloride against free radical-induced erythrocytes damage. Environ Toxicol Pharmacol. 2014;38:212–9.
42. Wu YL, Lin AH, Chen CH, Huang WC, Wang HY, Liu MH, et al. Glucosamine attenuates cigarette smoke-induced lung inflammation by inhibiting ROS-sensitive inflammatory signaling. Free Radic Biol Med. 2014;69:208–18.
43. Xing R, Liu S, Guo Z, Yu H, Li C, Ji X, et al. The antioxidant activity of glucosamine hydrochloride in vitro. Bioorg Med Chem. 2006;14:1706–9.
44. Nishikawa T, Edelstein D, Du XL, Yamagishi S, Matsumura T, Kaneda Y, et al. Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. Nature. 2000;404:787–90.
45. Weimer S, Priebs J, Kuhlow D, Groth M, Priebe S, Mansfeld J, et al. D-Glucosamine supplementation extends life span of nematodes and of ageing mice. Nat Commun. 2014;5:3563.
46. Snorgaard O, Poulsen GM, Andersen HK, Astrup A. Systematic review and meta-analysis of dietary carbohydrate restriction in patients with type 2 diabetes. BMJ Open Diabetes Res Care. 2017;5:e000354.
47. Boden G, Sargrad K, Homko C, Mozzoli M, Stein TP. Effect of a low-carbohydrate diet on appetite, blood glucose levels, and insulin resistance in obese patients with type 2 diabetes. Ann Intern Med. 2005;142:403–11.
48. Jampol LM, Glassman AR, Sun J. Evaluation and Care of Patients with Diabetic Retinopathy. N Engl J Med. 2020;382:1629–37.
49. Hammes HP. Diabetic retinopathy: hyperglycaemia, oxidative stress and beyond. Diabetologia. 2018;61:29–38.
50. Wong TY, Cheung CM, Larsen M, Sharma S, Simó R. Diabetic retinopathy. Nat Rev Dis Primers. 2016;2:16012.
51. Thomas MC, Brownlee M, Susztak K, Sharma K, Jandeleit-Dahm KA, Zoungas S, et al. Diabetic kidney disease. Nat Rev Dis Primers. 2015;1:15018.
52. Biggee BA, Blinn CM, Nuite M, Silbert JE, McAlindon TE. Effects of oral glucosamine sulphate on serum glucose and insulin during an oral glucose tolerance test of subjects with osteoarthritis. Ann Rheum Dis. 2007;66:260–2.
53. Pham T, Cornea A, Blick KE, Jenkins A, Scofield RH. Oral glucosamine in doses used to treat osteoarthritis worsens insulin resistance. Am J Med Sci. 2007;333:333–9.

ACKNOWLEDGEMENTS

The authors would like to thank all participants in the UK Biobank for their gratitude and all the staff of the UK Biobank.

AUTHOR CONTRIBUTIONS

LFW, ZJC, XYJ, SFL, YFL, YFW, LB and FYD conceived and designed the research; ZJC, WYR, and QYZ wrote the manuscript; ZJC and YFL performed the data analysis. All authors contributed to the interpretations of the findings.

FUNDING

This work was supported by the Natural Science Foundation of China (82471841), Science and Technology Project of Suzhou (SKY2023122) and Interdisciplinary Basic Frontier Innovation Program of Suzhou Medical College of Soochow University (YXY2304042, YXY2304056).

COMPETING INTERESTS

The authors declare that they have no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the North West–Haydock Research Ethics Committee (16/NW/0274). All participants provided informed consent. All methods were performed in accordance with the relevant guidelines and regulations.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41387-025-00369-8.

Correspondence and requests for materials should be addressed to Xi-Yuan Jiang, Shu-feng Lei or Long-Fei Wu.