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Habitual glucosamine use and mortality risk among individuals with type 2 diabetes: A prospective study

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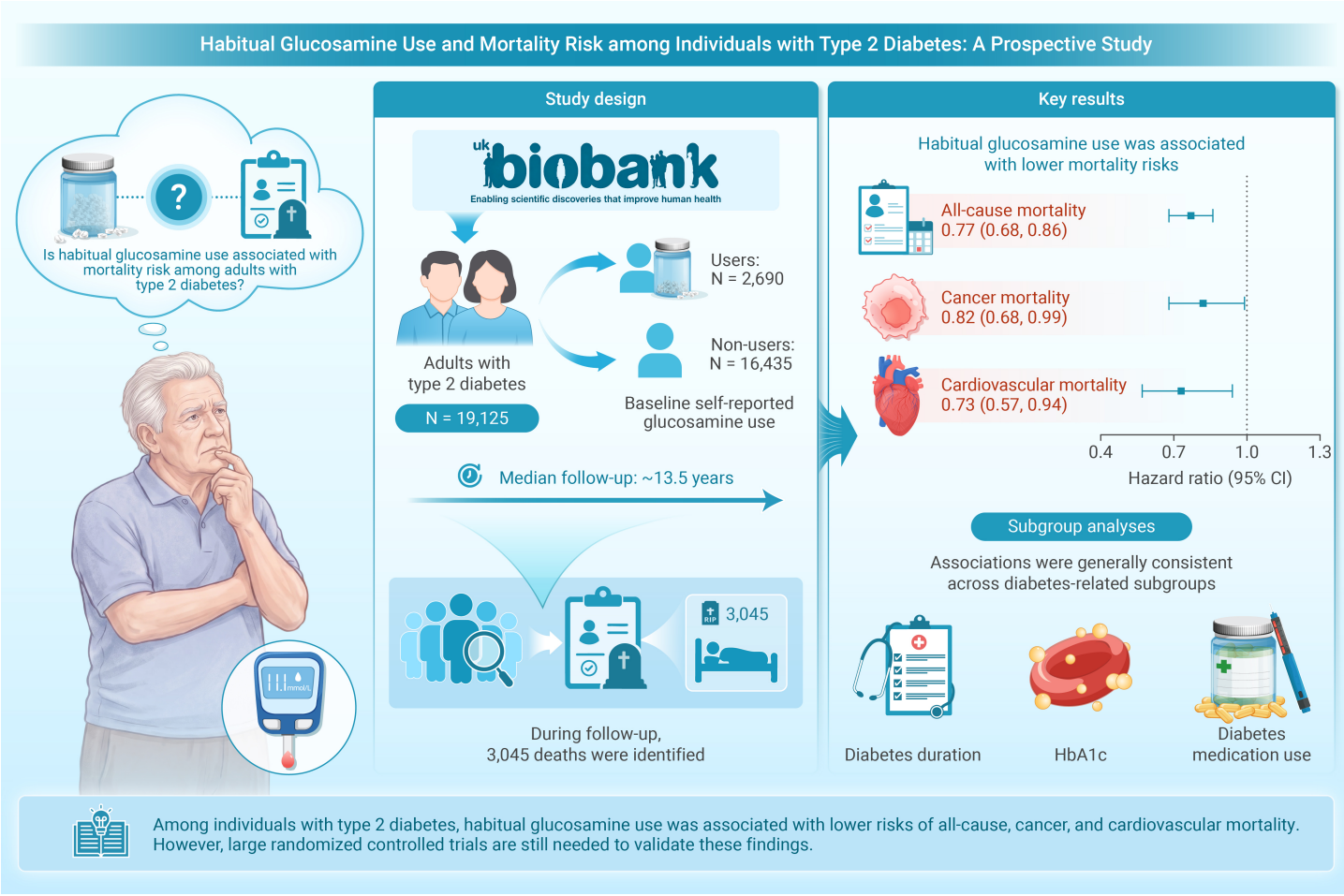
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Habitual glucosamine use was associated with lower mortality risks among individuals with type 2 diabetes.
- The associations were generally similar across diabetes-related factors, demographic, and lifestyle subgroups.
- Blood biomarkers of inflammation, kidney and liver function, and lipids may partly explain these associations.

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Habitual glucosamine use and mortality risk among individuals with type 2 diabetes: A prospective study

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Glucosamine is a commonly used supplement, but concerns persist regarding its use in individuals with diabetes. This study aimed to examine the association of habitual glucosamine use with risks of all-cause and cause-specific mortality among individuals with type 2 diabetes, and to explore the potential mediating role of blood biomarkers in these associations. We included 19125 participants with type 2 diabetes from the UK Biobank who provided self-reported information on glucosamine use at baseline. Cox proportional hazards models were used to estimate the associations, with results presented as hazard ratios (HRs) and its 95% confidence intervals (CIs). Mediation analyses were conducted to estimate the extent to which selected blood biomarkers may be involved in these associations. Over a median follow-up of 13.5 years, 3045 deaths were recorded, including 1095 cancer deaths and 741 cardiovascular deaths. In multivariable-adjusted analyses, glucosamine use was associated with lower risks of all-cause, cancer, and cardiovascular mortality, with HRs (95% CIs) of 0.77 (0.68, 0.86), 0.82 (0.68, 0.99), and 0.73 (0.57, 0.94), respectively. These associations were generally consistent across several subgroups, including diabetes-related factors, demographic characteristics, lifestyle, medication use and health conditions. Furthermore, blood biomarkers (such as cystatin C, alkaline phosphatase, and C-reactive protein) explained 13.61% (95% CI, 8.26, 34.14) of the association between glucosamine use and all-cause mortality. Our findings suggest that glucosamine use was inversely associated with mortality in individuals with type 2 diabetes, with several blood biomarkers partly explaining this association; however, clinical trials are needed to confirm these findings.

INTRODUCTION

Type 2 diabetes has evolved into an intensifying public health threat worldwide, affecting about 589 million adults in 2024,[1] around 30% of whom are estimated to have osteoarthritis.[2] Glucosamine is a commonly used dietary supplement for alleviating osteoarthritis and joint pain.[3] However, observational evidence suggests that glucosamine use is less common among people with diabetes than among those without diabetes,[4-6] despite the higher prevalence of osteoarthritis in this population.

Previous studies have suggested that short-term exposure to high doses of glucosamine may disrupt glycemic regulation and impair insulin sensitivity in both animals and humans.[7-10] Although clinical trials have not identified significant adverse effects of glucosamine at oral doses,[11-14] their relatively small sample sizes and short follow-up durations limit confidence in these findings.[15] Given these contradictory results, the long-term safety of glucosamine use among individuals with type 2 diabetes warrants further investigation. In recent years, several large prospective cohort studies in the general population have reported associations between habitual glucosamine use and lower risks of mortality.[5,16-17] However, whether these associations exist among individuals with type 2 diabetes remains unclear. Moreover, previous studies have indicated that glucosamine may possess anti-inflammatory properties,[18-20] and be associated with a range of blood biomarkers.[21-22] It is unknown whether and to what extent blood biomarkers could explain the association of glucosamine use with all-cause and cause-specific mortality.

Using data from the UK Biobank, our study prospectively examined the associations between habitual glucosamine use and mortality among individuals with type 2 diabetes. Additionally, we explored the potential role of blood biomarkers in these associations.

METHODS

Study population

The UK Biobank is a large-scale cohort study based on a population sample from the United Kingdom, with more than half a million participants aged 37 to 73 years recruited between 2006 and 2010. Details of the study design have been reported in previous studies.[23] Comprehensive data were collected at enrollment via touchscreen questionnaires and physical examinations. Prevalent type 2 diabetes at baseline was defined by glycated hemoglobin A1c (HbA_{1c}) levels exceeding 48 mmol/mol (6.5%) and a validated classification algorithm. This algorithm was developed through the integration of self-reported medical history, medication data, and hospital admission records, and it has been reported to be a reliable method with 96% accuracy.[24] We further excluded participants with cardiovascular disease or cancer (n= 9529) at baseline and who had missing data on the use of glucosamine (n= 306). Finally, 19125 individuals with type 2 diabetes were included in our analysis (Figure S1). Ethical approval for UK Biobank was obtained from the North West Multi-Centre Research Ethics Committee, and all participants provided written informed consent. This research was conducted using the UK Biobank Resource under Application No. 109546.

Exposure assessment

In line with previous studies, habitual glucosamine use was assessed once at baseline via touchscreen questionnaire.[5,16] Participants responded to the question "Do you regularly take any of the following supplements?", in which glucosamine was included among the listed options.

Covariates assessment

Baseline sociodemographic characteristics, lifestyle behaviors, comorbidities, and medication use were collected via standardized touchscreen questionnaires. These variables included sex, age, ethnicity, lifestyle factors (physical activity, smoking status, drinking status and healthy diet), chronic conditions (hypertension and arthritis), as well as medication and supplement use (aspirin, antihypertensive, lipid-lowering, and non-aspirin non-steroidal anti-inflammatory drugs [NSAIDs], multivitamins, and mineral supplements). Ethnicity was dichotomized as White or others. Body mass index (BMI) was calculated by dividing body weight in kilograms by the square of height in meters. The Townsend deprivation index reflects socioeconomic status, which was derived from non-home ownership, household overcrowding, unemployment, and non-car ownership.[25] Smoking and drinking status were categorized as current, former, or never. Physical activity was classified as active (≥ 150 min/week) or inactive (< 150 min/week) according to the total moderate physical activity minutes per week. Adherence to a healthy dietary pattern was defined as meeting at least 5 out of 10 predefined criteria. These criteria included adequate intake of vegetables, fruits, whole grains, dairy products, fish, and vegetable oils, as well as decreased or no consumption of refined grains, processed meats, unprocessed red meats, and sugar-sweetened beverages.[26] Hypertension was defined by any of the following criteria:

(1) self-reported history of hypertension; (2) systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg; and (3) self-report of antihypertensive drug use. Prevalent arthritis prior to study recruitment was defined using codes M15–M19 from the ICD-10 (International Classification of Diseases, Tenth Revision). HbA_{1c} level at baseline was measured on the VARIANT II TURBO platform (Bio-Rad Laboratories). Diabetes duration was determined as the interval between the date of enrollment and the date of the initial diabetes diagnosis.

Measurement of blood biomarkers

Blood samples were collected at baseline and subsequently stored at −80°C until testing. A set of candidate biomarkers was selected for mediation analysis, covering markers of renal function (creatinine, cystatin C, urea, and urate), liver function (alanine aminotransferase, alkaline phosphatase, gamma glutamyl transferase, aspartate aminotransferase, total protein, total bilirubin, and albumin), lipid profiles (triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, lipoprotein A, apolipoprotein A, and apolipoprotein B), and inflammatory indicators (C-reactive protein, lymphocyte count, neutrophil count, and white blood cell count). Biochemical markers were obtained under strict quality control in accordance with the manufacturer's recommendations. Detailed information on these biomarkers has been described on the website (https://biobank.ctsu.ox.ac.uk/showcase).

Ascertainment of outcomes

Primary underlying cause and the date of death were ascertained from the National Health Service Information Centre (for England and Wales) and the National Health Service Central Register (for Scotland). All-cause and cause-specific mortality were classified according to ICD-10 codes, with cause-specific mortality categorized as cancer, cardiovascular disease, digestive disease, respiratory disease, or other causes (Table S1). The person-years were calculated from the date of enrollment to the occurrence of death, loss to follow-up or censoring date, whichever came first.

Statistical analysis

Student's *t*-test and chi-squared test were applied to compare baseline characteristics by glucosamine use status for continuous and categorical variables, respectively. We further compared the characteristics of participants retained in the study and those excluded because of missing data on glucosamine use. Cox proportional hazards models were used to assess the associations of glucosamine use with both all-cause and cause-specific mortality among individuals with type 2 diabetes. The proportional hazards assumption was examined using Schoenfeld residuals and no violation of the assumption was found. The results are presented as hazard ratios (HRs) and 95% confidence intervals (CIs). For handling missing covariates, multiple imputation by chained equations was adopted, with a total of 5 imputations carried out using the MICE software package. The proportion of missing covariate data varied between 0.17% (Townsend deprivation index) and 9.17% (physical activity). Table S2 provides detailed information on missing covariates. In model 1, we adjusted for age and sex. In model 2, we additionally adjusted for ethnicity, Townsend deprivation index, BMI, smoking status, drinking status, physical activity, healthy diet, use of multivitamin, use of mineral supplements, history of hypertension, history of arthritis, use of antihypertensive medication, use of lipid-lowering medication, use of aspirin, use of NSAID, use of diabetes medication, diabetes duration, and HbA_{1c}.

We conducted an exploratory analysis of the difference in life expectancy between glucosamine users and non-users using flexible parametric survival models,[27] which were fitted with the stpm2 command in STATA using restricted cubic splines.[28,29] Mediation analyses were conducted using the CMAverse package in R under a counterfactual mediation framework.[30] Biomarkers significantly associated with both glucosamine use and outcomes were retained for subsequent mediation analyses.[31] Regression-based mediation models were used to estimate natural direct and indirect associations, with adjustment for the same covariates as in the main analysis. The mediated proportion was estimated on the log-HR scale, with 95% CIs and *P* values obtained using 1000 bootstrap resamples. Multiple-mediator analyses were further performed by simultaneously including the identified biomarkers for each outcome. Moreover, we conducted a series of stratified analyses to examine whether the associations were modified by the following factors: sex (male or female), age (< 55 or ≥ 55 years), BMI (< 25, 25-30, or ≥ 30 kg/m^2), physical activity (inactive, active), smoking status (never, former, or current), drinking status (never, former, or current), healthy diet (yes or no), hypertension (yes or no), arthritis (yes or no), HbA_{1c} (< 53 or ≥ 53 mmol/mol [7%]), diabetes duration (< 3, 3-10, or ≥ 10 years), diabetes medication use (yes or no), lipid-lowering drug use (yes or no), aspirin use (yes or no), and non-aspirin NSAID use (yes or no). Effect modification was assessed by including interaction terms between glucosamine use and each stratification variable in the fully adjusted Cox models. For each subgroup analysis, the corresponding stratification variable was excluded from the adjustment model.

To test the robustness of our findings, we also conducted several sensitivity analyses. First, to minimize potential reverse causation, we conducted the main analyses after excluding individuals who died within two years of follow-up. Second, we excluded individuals with incomplete covariate data. Third, we estimated propensity scores for each individual using multivariable logistic regression model, and performed 1:4 nearest-neighbor propensity score matching to enhance comparability between glucosamine users and non-users at baseline. Fourth, E-values were calculated to assess the potential impact of unmeasured confounding on the observed associations. Fifth, to account for competing risks, Fine–Gray subdistribution hazard regression models were fitted for cause-specific mortality outcomes.

A two-sided *P* value below 0.05 was considered indicative of statistical significance. Regarding the multiple testing issue, Bonferroni corrections for *P* values were implemented where applicable.

RESULTS

Baseline characteristics

In total, 19125 participants with type 2 diabetes were included, with a mean age of 58.72 ± 7.36 years; 11646 (60.9%) were male and 2690 (14.1%) reported regular glucosamine use at enrollment. The baseline characteristics of the study participants, categorized according to glucosamine use, are presented in Table 1. In comparison with non-users, those who used glucosamine were more likely to be female, older individuals, white, less socioeconomically deprived, more physically active, not current smokers, current drinkers, adherent to a healthy diet, and had higher prevalence of arthritis, lower HbA_{1c}, shorter duration of diabetes. Participants who used glucosamine were more likely to report higher intake of vitamins and minerals, non-aspirin NSAID, and lower intake of diabetes medications. In addition, participants excluded due to missing glucosamine use data were younger, more socioeconomically deprived, and more likely to be non-white, less physically active, current smokers, never drinkers, and had higher HbA_{1c} (Table S3).

Habitual glucosamine use and mortality

Over a median follow-up duration of 13.55 years (interquartile range 12.77-14.39), 3045 all-cause deaths were identified, including 1095 cancer deaths, 741 cardiovascular deaths, 236 respiratory disease deaths, 172 digestive disease deaths and 801 other disease-related deaths. Table 2 presents the associations of habitual glucosamine use with mortality. In model 1, after adjustment for age and sex, glucosamine use was significantly associated with lower risks of all-cause mortality and mortality from cancer, cardiovascular disease, respiratory disease, and other causes. In model 2, after further adjusting for potential confounders, the association attenuated slightly but remained significant, with HRs (95% CI) of 0.77 (0.68, 0.86) for all-cause mortality; 0.82 (0.68, 0.99) for cancer mortality; 0.73 (0.57, 0.94) for cardiovascular mortality; 0.58 (0.35, 0.94) for respiratory disease mortality and 0.78 (0.62, 0.97) for other disease mortality. At age 45, habitual glucosamine use among individuals with type 2 diabetes was associated with a difference of 3.20 years (95% CI 2.24, 4.16) in estimated life expectancy compared with non-use, with corresponding differences of 2.96 (1.71, 4.21) years in men and 2.71 (1.23, 4.17) years in women (Figure S2).

Mediation analysis

The associations of all the blood biomarkers with glucosamine use and mortality are summarized in Tables S4-S5. In the fully adjusted model, the identified biomarkers collectively explained a modest proportion of the

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

Characteristics	Overall	Glucosamine non-user	Glucosamine user	*P* value
No of participants	19125	16435 (85.9)	2690 (14.1)	
Age, years	58.72 (7.36)	58.39 (7.47)	60.75 (6.25)	< 0.001
Male	11646 (60.9)	10215 (62.2)	1431 (53.2)	< 0.001
Townsend deprivation index	-0.46 (3.40)	-0.37 (3.42)	-1.06 (3.20)	< 0.001
White race	16274 (85.1)	13903 (84.6)	2371 (88.1)	< 0.001
BMI, kg/m^2	31.45 (5.89)	31.42 (5.89)	31.64 (5.91)	0.07
Smoking status				< 0.001
Never	9312 (49.0)	8067 (49.4)	1245 (46.7)	
Former	7573 (39.8)	6352 (38.9)	1221 (45.8)	
Current	2122 (11.2)	1922 (11.8)	200 (7.5)	
Drinking status				< 0.001
Never	1731 (9.1)	1530 (9.3)	201 (7.5)	
Former	1223 (6.4)	1091 (6.7)	132 (4.9)	
Current	16135 (84.5)	13782 (84.0)	2353 (87.6)	
Physical activity, min/week				0.002
<150	4290 (24.7)	3737 (25.1)	553 (22.3)	
≥150	13081 (75.3)	11149 (74.9)	1932 (77.7)	
Healthy diet	3742 (21.1)	3103 (20.4)	639 (25.1)	< 0.001
HbA_{1c}, mmol/mol	54.04 (14.76)	54.29 (15.06)	52.54 (12.62)	< 0.001
Duration of type 2 diabetes, years	6.97 (9.10)	7.02 (9.17)	6.60 (8.66)	0.03
Drug use				
Antihypertensive medication	12183 (63.7)	10513 (64.0)	1670 (62.1)	0.06
Lipid-lowering medication	13095 (68.5)	11251 (68.5)	1844 (68.6)	0.94
Aspirin	7681 (40.2)	6591 (40.1)	1090 (40.5)	0.70
Non-aspirin NSAID	2492 (13.0)	1998 (12.2)	494 (18.4)	< 0.001
Diabetes medication	11848 (62.0)	10312 (62.7)	1536 (57.1)	< 0.001
Supplement use				
Vitamin	5409 (28.5)	3958 (24.3)	1451 (54.2)	< 0.001
Minerals and other dietary supplements	6441 (33.7)	4639 (28.2)	1802 (67.0)	< 0.001
Disease history				
Arthritis	3143 (16.4)	2400 (14.6)	743 (27.6)	< 0.001
Hypertension	14238 (74.4)	12243 (74.5)	1995 (74.2)	0.73

Data are presented as mean (SD) for continuous variables or n (%) for categorical variables. BMI, body mass index, SD, standard deviation; NSAID, non-steroidal anti-inflammatory drug.

observed association between glucosamine use and mortality outcomes. For all-cause mortality, cystatin C, alkaline phosphatase, albumin, C-reactive protein, white blood cell count, and neutrophil count jointly explained 13.61% (95% CI: 8.26, 34.14) of the association. For cause-specific mortality outcomes, the proportion of the association explained by outcome-specific sets of biomarkers ranged from 6.09% to 16.89% (Table 3). Across different mortality outcomes, C-reactive protein was consistently identified in the models, whereas other biomarkers varied by outcome.

Subgroup and sensitivity analyses

The associations of glucosamine use with mortality risks were generally consistent after stratification by HbA_{1c} level, diabetes duration, diabetes medication use, age, sex, BMI, smoking status, drinking status, physical activity, healthy diet, hypertension, arthritis, aspirin use, lipid-lowering drug use, and non-aspirin NSAID use. No evidence of interaction was observed for habitual glucosamine use across the stratified factors in relation to mortality outcomes (interaction $P \geq 0.14$ for all interaction terms; Figure 1). The results were generally consistent in analyses excluding deaths occurring within the first 2 years of follow-up (Table S6), excluding participants with missing covariate data (Table S7), and using propensity score matching (Table S8). The E-values for the point estimates ranged from 1.74 to 2.86 across mortality outcomes (Table S9), suggesting moderate robustness of the observed associations to unmeasured confounding. Moreover, the associations also remained generally robust after accounting for competing risks of death

Table 2. Associations of habitual glucosamine use with the risk of all-cause and cause-specific mortality among individuals with type 2 diabetes.

Outcomes	Glucosamine non-user [a]	Glucosamine user [a]	Model 1 HR (95% CI)	P_{value}	Model 2 HR (95% CI)	P_{value}
All-cause mortality	2688 (16.4)	357 (13.3)	0.72 (0.64, 0.80)	< 0.001	0.77 (0.68, 0.86)	< 0.001
Cancer mortality	955 (5.8)	140 (5.2)	0.79 (0.66, 0.94)	0.01	0.82 (0.68, 0.99)	0.04
Cardiovascular mortality	664 (4.0)	77 (2.9)	0.64 (0.51, 0.82)	< 0.001	0.73 (0.57, 0.94)	0.01
Respiratory disease mortality	217 (1.3)	19 (0.7)	0.48 (0.30, 0.77)	0.003	0.58 (0.35, 0.94)	0.03
Digestive disease mortality	150 (0.9)	22 (0.8)	0.82 (0.52, 1.28)	0.40	0.73 (0.46, 1.18)	0.20
Other disease mortality	702 (4.3)	99 (3.7)	0.75 (0.61, 0.92)	0.01	0.78 (0.62, 0.97)	0.03

Model 1: adjusted for age and sex. Model 2: additionally adjusted for ethnicity, Townsend deprivation index, BMI, smoking status, drinking status, physical activity, healthy diet, use of multivitamin, use of mineral supplements, history of hypertension, history of arthritis, use of antihypertensive medication, use of lipid-lowering medication, use of aspirin, use of non-steroidal anti-inflammatory drug, use of diabetes medication, diabetes duration, and HbA_{1c}. BMI, body mass index; CI, confidence interval; HR, hazard ratio. [a] Values are numbers (%) of the outcomes in the group.

Table 3. Mediation analysis of the associations between habitual glucosamine use and outcomes through blood biomarkers among individuals with type 2 diabetes.

Mediators	Total Effect, (95% CI)	Direct Effect, (95% CI)	Indirect Effect, (95% CI)	Proportion Mediated, % (95% CI)	*P* value
All-cause mortality					
Cystatin C	0.766 (0.670, 0.864)	0.778 (0.684, 0.879)	0.984 (0.975, 0.989)	5.48 (2.80, 10.93)	< 0.001
Alkaline phosphatase	0.758 (0.669, 0.844)	0.761 (0.672, 0.848)	0.996 (0.988, 0.999)	1.23 (0.29, 3.46)	< 0.001
Albumin	0.759 (0.675, 0.879)	0.769 (0.688, 0.887)	0.986 (0.977, 0.997)	4.42 (0.82, 10.71)	< 0.001
C-reactive protein	0.758 (0.669, 0.863)	0.766 (0.676, 0.870)	0.990 (0.984, 0.995)	3.18 (1.67, 7.36)	< 0.001
White blood cell count	0.755 (0.652, 0.858)	0.760 (0.657, 0.866)	0.993 (0.989, 0.997)	2.19 (1.02, 4.75)	< 0.001
Neutrophil count	0.754 (0.667, 0.853)	0.763 (0.674, 0.863)	0.988 (0.981, 0.995)	3.69 (1.86, 8.09)	< 0.001
Total mediation	0.768 (0.669, 0.973)	0.800 (0.699, 0.935)	0.961 (0.951, 0.973)	13.61 (8.26, 34.14)	< 0.001
Cancer mortality					
Cystatin C	0.791 (0.663, 0.936)	0.797 (0.667, 0.941)	0.993 (0.988, 0.998)	2.75 (0.37, 11.40)	0.02
LDL-cholesterol	0.784 (0.636, 0.920)	0.790 (0.638, 0.924)	0.993 (0.985, 0.998)	2.44 (0.78, 14.62)	< 0.001
Apolipoprotein B	0.793 (0.670, 0.968)	0.798 (0.675, 0.973)	0.994 (0.989, 0.999)	2.43 (0.31, 9.01)	0.04
C-reactive protein	0.795 (0.673, 0.941)	0.803 (0.679, 0.951)	0.991 (0.984, 0.996)	3.46 (1.07, 11.83)	< 0.001
Total mediation	0.788 (0.667, 0.933)	0.805 (0.678, 0.952)	0.978 (0.970, 0.988)	8.16 (3.25, 29.25)	0.02
Cardiovascular mortality					
C-reactive protein	0.781 (0.605, 0.972)	0.786 (0.609, 0.977)	0.993 (0.987, 1.000)	2.41 (0.43, 19.15)	< 0.001
White blood cell count	0.739 (0.562, 0.891)	0.745 (0.567, 0.903)	0.991 (0.983, 0.997)	2.65 (0.75, 10.57)	< 0.001
Neutrophil count	0.738 (0.582, 0.916)	0.751 (0.591, 0.930)	0.982 (0.971, 0.992)	5.11 (1.81, 18.81)	< 0.001
Total mediation	0.763 (0.594, 0.963)	0.777 (0.604, 0.980)	0.981 (0.970, 0.993)	6.09 (1.17, 30.73)	0.04
Other disease mortality					
Cystatin C	0.740 (0.599, 0.938)	0.754 (0.610, 0.955)	0.981 (0.971, 0.988)	5.55 (2.58, 29.10)	< 0.001
Alkaline phosphatase	0.724 (0.581, 0.854)	0.727 (0.585, 0.857)	0.995 (0.986, 0.999)	1.36 (0.25, 4.95)	< 0.001
Albumin	0.748 (0.613, 0.921)	0.762 (0.626, 0.927)	0.982 (0.971, 0.994)	5.46 (1.48, 16.08)	0.04
C-reactive protein	0.722 (0.575, 0.909)	0.731 (0.582, 0.921)	0.988 (0.981, 0.994)	3.18 (1.23, 14.23)	< 0.001
White blood cell count	0.701 (0.562, 0.829)	0.707 (0.565, 0.834)	0.992 (0.981, 0.997)	1.93 (0.56, 4.58)	< 0.001
Neutrophil count	0.699 (0.561, 0.844)	0.710 (0.569, 0.852)	0.985 (0.976, 0.993)	3.44 (1.32, 8.88)	< 0.001
Total mediation	0.772 (0.595, 0.905)	0.810 (0.627, 0.952)	0.952 (0.933, 0.968)	16.89 (6.99, 47.84)	< 0.001

Results were adjusted for age, sex, ethnicity, Townsend deprivation index, BMI, smoking status, drinking status, physical activity, healthy diet, use of multivitamin, use of mineral supplements, history of hypertension, history of arthritis, use of antihypertensive medication, use of lipid-lowering medication, use of aspirin, use of non-steroidal anti-inflammatory drug, use of diabetes medication, diabetes duration, and HbA_{1c}. BMI, body mass index; CI, confidence interval; LDL, low-density lipoprotein.

	All-cause mortality		Cancer mortality		Cardiovascular mortality	
	HR (95% CI)	*P* interaction	HR (95% CI)	*P* interaction	HR (95% CI)	*P* interaction
HbA_{1c}, mmol/mol		0.32		0.45		0.22
<53	0.74 (0.63, 0.87)		0.82 (0.64, 1.05)		0.73 (0.52, 1.03)	
≥53	0.81 (0.67, 0.96)		0.85 (0.63, 1.14)		0.72 (0.49, 1.06)	
Diabetes duration		0.45		0.53		0.44
<3	0.75 (0.61, 0.92)		0.91 (0.68, 1.23)		0.57 (0.36, 0.91)	
3–10	0.81 (0.67, 0.98)		0.79 (0.59, 1.07)		0.90 (0.60, 1.33)	
≥10	0.73 (0.58, 0.92)		0.72 (0.48, 1.09)		0.74 (0.47, 1.17)	
Diabetes medication use		0.97		0.73		0.51
No	0.77 (0.64, 0.93)		0.82 (0.61, 1.09)		0.68 (0.44, 1.05)	
Yes	0.77 (0.66, 0.89)		0.83 (0.65, 1.06)		0.77 (0.57, 1.03)	
Age		0.19		0.17		0.17
<55	0.85 (0.57, 1.27)		0.78 (0.38, 1.59)		0.45 (0.16, 1.25)	
≥55	0.76 (0.67, 0.86)		0.82 (0.67, 1.00)		0.76 (0.58, 0.98)	
Sex		0.95		0.46		0.52
Male	0.79 (0.68, 0.91)		0.80 (0.62, 1.02)		0.70 (0.51, 0.96)	
Female	0.74 (0.61, 0.90)		0.85 (0.64, 1.15)		0.82 (0.54, 1.24)	
BMI		0.25		0.38		0.29
Normal	0.76 (0.52, 1.13)		1.02 (0.56, 1.88)		0.74 (0.28, 1.96)	
Overweight	0.75 (0.61, 0.93)		0.68 (0.48, 0.96)		0.76 (0.48, 1.20)	
Obesity	0.78 (0.67, 0.91)		0.87 (0.68, 1.11)		0.71 (0.52, 0.98)	
Smoking		0.68		0.95		0.87
Never	0.74 (0.61, 0.90)		0.80 (0.58, 1.10)		0.75 (0.50, 1.11)	
Former	0.81 (0.69, 0.95)		0.84 (0.65, 1.10)		0.73 (0.51, 1.06)	
Current	0.72 (0.51, 1.03)		0.86 (0.52, 1.45)		0.75 (0.38, 1.47)	
Drinking		0.57		0.46		0.78
Never	0.63 (0.41, 0.98)		0.50 (0.21, 1.18)		0.60 (0.25, 1.46)	
Former	0.74 (0.47, 1.18)		0.85 (0.38, 1.90)		0.66 (0.23, 1.88)	
Current	0.78 (0.69, 0.89)		0.84 (0.69, 1.03)		0.75 (0.58, 0.99)	
Physical activity		0.27		0.56		0.16
Inactive	0.91 (0.72, 1.15)		0.97 (0.65, 1.44)		1.04 (0.67, 1.62)	
Active	0.72 (0.62, 0.83)		0.77 (0.62, 0.97)		0.63 (0.46, 0.86)	
Healthy diet		0.96		0.16		0.85
No	0.78 (0.68, 0.89)		0.93 (0.75, 1.15)		0.73 (0.54, 0.97)	
Yes	0.72 (0.56, 0.92)		0.53 (0.34, 0.83)		0.77 (0.44, 1.38)	
Hypertension		0.35		0.29		0.60
No	0.61 (0.45, 0.83)		0.62 (0.39, 0.98)		0.52 (0.23, 1.18)	
Yes	0.79 (0.70, 0.90)		0.87 (0.71, 1.07)		0.75 (0.58, 0.97)	
Arthritis		0.83		0.14		0.77
No	0.77 (0.67, 0.89)		0.91 (0.74, 1.13)		0.76 (0.57, 1.02)	
Yes	0.76 (0.62, 0.94)		0.62 (0.42, 0.91)		0.66 (0.40, 1.07)	
Lipid-lowering drug		0.36		0.14		0.88
No	0.70 (0.56, 0.88)		0.62 (0.43, 0.90)		0.70 (0.43, 1.16)	
Yes	0.79 (0.69, 0.91)		0.91 (0.73, 1.14)		0.74 (0.56, 0.99)	
Aspirin use		0.76		0.73		0.76
No	0.74 (0.63, 0.87)		0.84 (0.66, 1.08)		0.71 (0.50, 1.01)	
Yes	0.79 (0.67, 0.94)		0.80 (0.59, 1.07)		0.77 (0.54, 1.09)	
Non-aspirin NSAID use		0.81		0.66		0.88
No	0.75 (0.66, 0.86)		0.82 (0.66, 1.00)		0.75 (0.57, 0.99)	
Yes	0.82 (0.62, 1.09)		0.84 (0.52, 1.34)		0.68 (0.38, 1.21)	

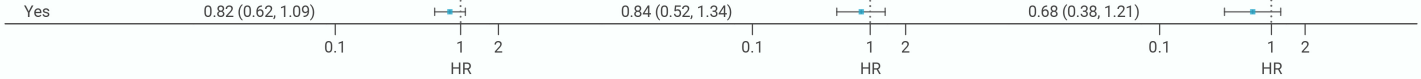

Figure 1. Subgroup analyses of the associations between habitual glucosamine use and mortality All models were adjusted for the full set of covariates, excluding the stratification variables themselves. The vertical dashed line corresponds to a hazard ratio (HR) of 1; horizontal bars represent 95% CI. BMI, body mass index; CI, confidence interval; HR, hazard ratio.

using Fine–Gray subdistribution hazard models (Table S10).

DISCUSSION

Principal findings

In this prospective cohort study, glucosamine use was associated with lower risks of all-cause, cancer, and cardiovascular disease mortality among individuals with type 2 diabetes. These associations persisted after adjustment for potential confounders, including diabetes-related factors (HbA_{1c} level, diabetes duration and diabetes medication use), and were generally robust across sensitivity analyses. Moreover, blood biomarkers collectively explained 13.61% of the observed association between glucosamine use and all-cause mortality.

Comparison with other studies

Recent epidemiological studies have suggested that regular glucosamine use is associated with lower risks of chronic diseases and mortality in the general population.[5,16,32] For example, during a median follow-up of 8.9 years, a previous cohort study among over 450000 participants found glucosamine use was significantly associated with a lower risk of all-cause mortality (15%), cancer mortality (6%), cardiovascular mortality (18%), digestive mortality (26%) and respiratory mortality (27%).[16] However, subgroup analyses showed no significant inverse associations between glucosamine use and mortality outcomes among individuals with diabetes.[5,16] One plausible explanation is that the secondary analysis did not account for important diabetes-related confounding factors (e.g., diabetes duration). With nearly five additional years of follow-up, our findings suggest that habitual glucosamine use was associated with a 23% lower risk of all-cause mortality among individuals with type 2 diabetes. Furthermore, our findings provide new evidence that glucosamine use was significantly associated with lower risks of cancer, cardiovascular, and respiratory mortality. Despite reporting a null association with digestive disease mortality, this finding may be attributed to the fact that digestive diseases are less frequent causes of death among individuals with

type 2 diabetes, in contrast to more prevalent fatal conditions such as cancer or cardiovascular disease.[33] Nevertheless, it should be noted that glucosamine use was only assessed once at baseline, and the association should not be interpreted as evidence of sustained pharmacologic effects or treatment effects. Moreover, glucosamine use may reflect a broader health-related behavior rather than an isolated supplement exposure; the moderate E-values suggest that moderate unmeasured confounding could plausibly have influenced the results.

Safety concerns surrounding glucosamine supplementation in individuals with type 2 diabetes continue to warrant attention, yet these issues remain insufficiently addressed in the existing evidence.[34] In line with previous studies,[5,35] our study observed that individuals with type 2 diabetes had a higher prevalence of osteoarthritis but were less likely to use glucosamine. This pattern may stem from clinical concerns among healthcare providers regarding potential detrimental impacts of glucosamine on glycemic regulation. Existing research has suggested that short-term administration of high-dose glucosamine may exert unfavorable effects on insulin sensitivity and disrupt glucose tolerance in humans,[7-10] but the reliability of these findings is constrained by small sample sizes, post hoc analyses, and the absence of randomization. Elucidating the role of glucosamine throughout the course of diabetes is clinically relevant, given the higher prevalence of osteoarthritis in this population.[35]

Previous prospective studies have suggested that the association of glucosamine with chronic diseases may vary by lifestyle factors or blood biomarker levels.[5,32] For instance, a more pronounced inverse relationship was detected among participants with elevated baseline C-reactive protein levels, implying that glucosamine may lower the risk of type 2 diabetes partly through its anti-inflammatory properties.[32] In this study, a lower risk of all-cause mortality was consistently observed among glucosamine users with type 2 diabetes, independent of demographic characteristics, lifestyle, and medication-related factors. More importantly, the current study added evidence that these associations were not modified by diabetes-related factors, including years lived with diabetes, glycemic control, and diabetes medication use. However, given the limited statistical power in some cause-specific mortality outcomes and subgroup analyses, confirmation in large studies is warranted.

The underlying biological mechanisms for the inverse association between glucosamine use and mortality remain unclear. Glucosamine has been reported to extend lifespan in mice by increasing amino acid catabolism and decreasing glycolysis, resembling the effects of a low-carbohydrate diet.[36] Low-carbohydrate diets have been linked to lower risks of all-cause, cancer and cardiovascular mortality among individuals with type 2 diabetes.[37] Moreover, glucosamine may exert an anti-inflammatory effect by inhibiting nuclear factor-κB activity.[38] Consistent with a previous study,[19] we observed significantly lower circulating concentrations of C-reactive protein in glucosamine users relative to non-users. Our exploratory mediation analyses suggested a potential role of C-reactive protein in the association between glucosamine use and mortality. In addition, our findings suggested a potential role of blood biomarkers related to renal function, liver function, and lipid profiles in the observed associations. However, it should be noted that these exploratory analyses provide only a plausible mechanistic explanation rather than evidence of causal pathways; further experimental studies are required to elucidate the underlying biological mechanisms.

Strengths and limitations

This study has several strengths, including its prospective cohort design, extensive collection of data on covariates and well-validated blood biomarkers, allowing detailed investigation of the association between glucosamine use and mortality, as well as exploration of potential mediating pathways. Nevertheless, several limitations should be acknowledged. First, glucosamine use was self-reported and assessed only once at baseline, which may introduce measurement error and limit the ability to capture dynamic changes in glucosamine use over time. Although previous evidence suggested that glucosamine use may be relatively stable, with over 93% of baseline users continuing use after 4 years,[39] this does not fully address potential changes in use during the long follow-up period. Second, detailed information on glucosamine exposure, including dose, duration, frequency, and formulation, was not available in the UK Biobank, warranting consideration of these factors in future studies. Third, given the baseline differences between glucosamine users and non-users, glucosamine use in this study may reflect a broader health-related behavioral profile rather than an isolated supplement exposure. Although we adjusted for a wide range of covariates and conducted propensity score matching analyses, residual confounding cannot be ruled out. Fourth, mediation results should be interpreted as exploratory and hypothesis-generating since glucosamine use and blood biomarkers were both measured at recruitment, which limited our ability to establish the exposure-mediator temporal sequence. Fifth, because of the limited number of cause-specific deaths among individuals with type 2 diabetes, we were unable to examine more detailed subtypes of cause-specific mortality, despite potential heterogeneity across disease subtypes. In addition, relatively wide confidence intervals in subgroup and mediation analyses indicate limited statistical precision, highlighting the need for confirmation in larger studies. Sixth, because UK Biobank had a low response rate (approximately 5.5%), participants may be more health-conscious than the general population, and the cohort was predominantly white, potentially affecting the generalizability of our findings. Seventh, while the main associations remained unchanged after excluding individuals who died within the initial two years of follow-up, reverse causality may still exist. Consequently, further rigorously designed clinical trials are warranted to confirm these findings.

CONCLUSIONS

Among individuals with type 2 diabetes, glucosamine use was associated with lower all-cause, cancer and cardiovascular mortality risks. In the mediation analyses, a panel of blood biomarkers reflecting liver function, renal function, systemic inflammation, and lipid metabolism partly explained the observed associations. Further rigorously designed randomized controlled trials are needed to clarify the safety and potential implications of glucosamine use in individuals with type 2 diabetes.

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AUTHOR CONTRIBUTIONS

A.P. and Y.W. designed the study. Y.W. and R.L. conducted the data analysis. G.L., Y.W., R.L. and M.X. drafted the manuscript. A.P., G.L., R.L., M.X., S.W., S.L., T.G., J.X., H.Y. and J.Z. reviewed and revised the manuscript. The final manuscript was approved by all authors.

DECLARATION OF INTERESTS

An Pan is a member of the journal's editorial board but was not involved in the peer review or decision process for this manuscript. All other authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

Written informed consent was obtained from all participants. Ethical approval for the UK Biobank was granted by the North West Multi-Centre Research Ethics Committee, and the current study was conducted under application number 109546.

DATA AND CODE AVAILABILITY

UK Biobank data are available on application at www.ukbiobank.ac.uk/register-apply