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RESEARCH

Regular glucosamine supplementation and risk of age-related chronic diseases: evidence from a propensity score-matched cohort study

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Abstract

Background Glucosamine is a widely used dietary supplement, particularly among middle-aged and older adults, with potential health benefits beyond joint health. However, its potential role in the prevention of chronic diseases remains uncertain.

Aims To investigate the association between regular glucosamine use and the risk of age-related non-communicable diseases (NCDs) in a large prospective cohort.

Methods 269,033 participants in the large prospective cohort (UK Biobank) without NCDs at baseline were included. 1:1 propensity-score matching (PSM) was used to match glucosamine users with non-users. Cox proportional hazard regression was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs).

Results During a median follow-up of 13.8 years, 52,556 participants reported regular glucosamine use. After PSM, 52,525 users and 52,525 non-users were included in the matched cohort. After false discovery rate correction, regular glucosamine use was associated with a significantly lower risk of seven NCDs: esophageal cancer (HR, 0.73; 95% CI, 0.58–0.92), gout (HR, 0.81; 95% CI, 0.72–0.91), chronic obstructive pulmonary disease (HR, 0.86; 95% CI, 0.80–0.93), colorectal cancer (HR, 0.86; 95% CI, 0.78–0.94), chronic liver disease (HR, 0.87; 95% CI, 0.80–0.94), heart failure (HR, 0.88; 95% CI, 0.81–0.96), and coronary heart disease (HR, 0.92; 95% CI, 0.88–0.96).

Conclusions Regular use of glucosamine was associated with a reduced risk of several age-related chronic diseases. Further studies are needed to confirm these findings and to clarify its potential role in supporting healthy aging.

Keywords Glucosamine · Non-communicable chronic diseases · Propensity score matching · Cohort

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Introduction

Non-communicable chronic diseases (NCDs), encompassing conditions such as cardiovascular disease (CVD), cancer, chronic respiratory diseases, type 2 diabetes (T2D), and neurological disorders, have emerged as the leading global health burden, accounting for approximately 41 million deaths each year [1]. NCDs account for 74% of all deaths worldwide and impose a substantial economic burden [2]. Preventing and controlling these pathologies is therefore a public health imperative.

Glucosamine, an amine-assisted sugar utilized for the alleviation of osteoarthritis and joint discomfort, is commonly used or recommended to support cartilage health [3]. Nearly 20% of middle-aged adults in the U.S., U.K., and Australia are estimated to use glucosamine supplements [4]. Glucosamine is believed to modulate inflammatory responses, particularly through the inhibition of nuclear factor-κB (NF-κB), a pivotal regulator of inflammatory cytokine production and cell survival [5]. Recently, glucosamine has gathered attention for its potential role in reducing the risk of CVD, T2D, and lung cancer [4, 6, 7]. Additionally, glucosamine use may reduce the risk of all-cause mortality [8], perhaps because glucosamine has the ability to extend the lifespan of species that are evolutionarily distinct species by mimicking the effects of a low-carbohydrate diet [9].

The impact of glucosamine supplementation on the incidence of NCDs has not been comprehensively investigated. Given its widespread use and plausible biological mechanisms, it is important to examine whether regular glucosamine use is associated with the risk of major NCDs. Findings from such investigations may offer preliminary evidence to inform future public health research and hypothesis development. In this prospective cohort study, we utilized data from the large, population-based UK Biobank to provide a more detailed understanding of the association between regular glucosamine use and the risk of NCDs, with the aim of generating new insights into its potential public health relevance.

Methods

Study design and populations

The UK Biobank (UKB) recruited over 500,000 adults aged 40–70 years between 2006 and 2010, all of whom were registered with the UK National Health Service. Participants attended one of 22 assessment centers across England, Scotland, and Wales. At the recruitment visit, they completed a nurse-led electronic questionnaire on sociodemographic characteristics, lifestyle exposures, medical history, medication use, and underwent physical measurements. Biological samples were collected to measure various biomarkers. The ethics of the UKB study was approved by the North West Multicenter Research Ethics Committee, and all participants had provided written informed consent. Ethical approval for the UKB is specified in UKB Supplemental Material (further details can be found on the UKB official website https://biobank.ctsu.ox.ac.uk/).

Inclusion and exclusion criteria

We included participants from the UK Biobank cohort who had complete baseline information on medication use and were free of NCDs at baseline. For this study, we excluded participants who withdraw or were lost to follow-up (n = 1,393) and participants with missing medication information (n = 838). To further mitigate the potential influence of pre-existing conditions on both glucosamine use and disease outcomes, we explicitly excluded participants with any diagnosed non-communicable diseases (NCDs) at baseline (n = 231,243). These steps minimized reverse causation. Finally, a total of 269,033 participants were included in the analysis (Fig. 1).

Assessment of regular glucosamine use

Information on glucosamine use was collected via a baseline touch-screen questionnaire. Participants were asked, "Do you regularly take any of the following?" Participants could select more than one answer from a list of supplements, which included glucosamine. From this information, we defined glucosamine use as 0 = no and 1 = yes.

Ascertainment of outcomes

The study outcome was incident NCDs. A total of 49 common NCDs were involved in this study, including 24 cancer and 25 non-cancer illnesses. The diagnoses of cancer were identified through record linkage to the National Health Service (NHS) Digital (England and Wales) and the NHS Central Register (Scotland). The following is a list of 24 site-specific cancers: oral cancer, esophageal cancer, stomach cancer, small intestine cancer, colorectal cancer, liver cancer, gallbladder/ biliary tract cancer, pancreatic cancer, lung cancer, malignant melanoma, mesothelioma, soft tissue cancer, breast cancer, cervical cancer, uterine/endometrial cancer, ovarian cancer, prostate cancer, kidney cancer, bladder cancer, brain cancer, thyroid cancer, non-Hodgkin lymphoma, multiple myeloma, and leukemia. The 25 non-cancer illnesses include sleep disorders, depression, migraine, diverticular disease, multiple sclerosis, stroke, atrial fibrillation (AF), asthma, anxiety disorder, chronic

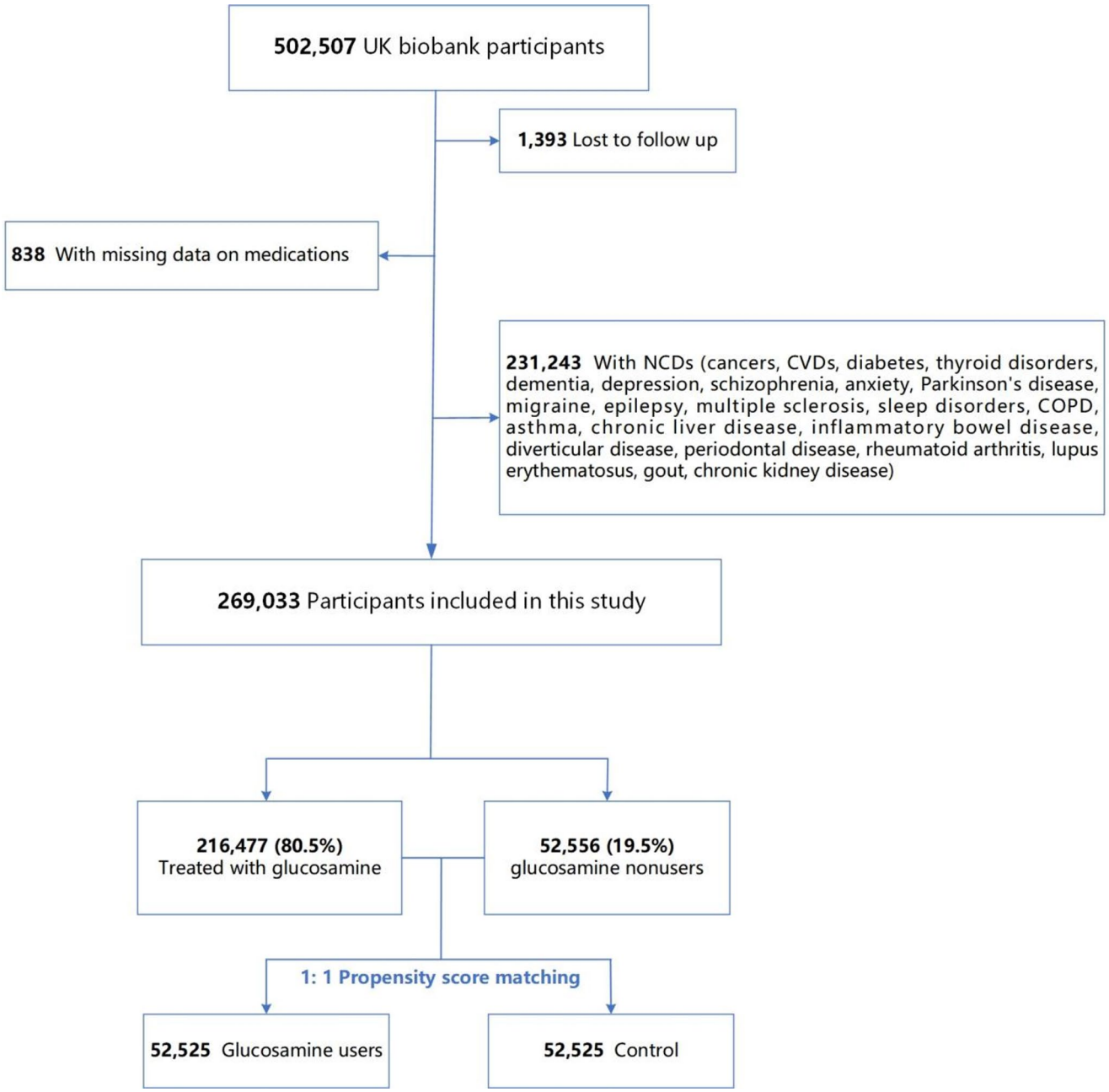

Fig. 1 Flowchart of study participants screening

kidney disease, thyroid disorders, dementia, diabetes, coronary heart disease (CHD), inflammatory bowel disease, Parkinson's disease, epilepsy, heart failure (HF), chronic liver disease (CLD), osteoarthritis, chronic obstructive pulmonary disease (COPD), periodontal disease, gout, lupus erythematosus, and schizophrenia. Information on these outcomes was obtained from self-reported data at baseline and medical records (Supplementary Table S2). Medical records were obtained from the Hospital Episode Statistics for England (HES), the Scottish Morbidity Record (SMR), and the Patient Episode Database for Wales (PEDW). Person-time was calculated from baseline until the occurrence of study outcomes or the end of follow-up, whichever came first (31 May 2022 for PEDW, 31 August 2022 for SMR, and 31 October 2022 for HES).

Statistical analysis

Baseline characteristics of the included participants were summarized as percentages for categorical variables and as means with standard deviations for continuous variables. Missing information on covariates was coded as unknown

category for categorical variables or imputed with mean values for continuous variables.

Propensity score matching (PSM) was used to control potential confounding factors. Various potential confounders were assessed using a baseline touch-screen questionnaire. Specifically, sociodemographic factors included age, gender, race, and the Townsend deprivation index (TDI). Lifestyle behavior included dietary pattern, smoking status, alcohol consumption, physical activity (Definitions of detailed lifestyle factors are provided in Table S1). Health-related measurements included body mass index (BMI), waist-to-hip ratio (WHR), glucose, glycosylated hemoglobin (HbA1c), C-reactive protein (CRP), and estimated glomerular filtration rate (eGFR) (Table S2). Comorbidities included arthritis, neuropathic pain, hypertension, and hyperlipidemia. Medication use included antihypertensive drugs, statins, aspirin, and other non-steroidal anti-inflammatory drugs (NSAIDs). The Townsend Deprivation Index is a composite measure of deprivation based on non-home ownership, non-car ownership, unemployment and household overcrowding, which represents the participant's socioeconomic status. BMI was calculated by dividing a participant's weight by the square of his or her height in metres (kg/m^2). WHR was calculated as the ratio of waist circumference (cm) to hip circumference (cm). Data on antihypertensive drugs, statins, aspirin and NSAIDs were obtained from participant self-reports in combination with the information on treatment/medication received at baseline from the interview. Additional details on these variables are available on the UK Biobank website (www.ukbiobank.ac.uk). All of the above covariates were included in the propensity score matching (PSM) model to adjust for potential confounding through 1:1 nearest neighbor matching, with a caliper of 0.2, no substitution was allowed, and the patient was matched only once. The balances of the matched covariates were evaluated by standardized mean difference (SMD), and < 10% differences were considered to be sufficiently matched [10]. After matching, Cox proportional hazards models were applied to the matched cohort to calculate the hazard ratios (HR) and 95% confidence intervals (CIs) for the relationship between glucosamine use and NCDs without additional covariate adjustment, as covariate balance has achieved through PSM (SMD < 0.1). To quantify the contribution of glucosamine on reducing the burden of individual NCDs, we calculated the population attributable fraction (PAF). The PAF can be interpreted as the proportional reduction in population incidence that would have occurred during follow-up if all participants were glucosamine non-users.

We further performed subgroup analyses to assess the potential impact of factors such as age (< 65 years and ≥ 65 years), gender (female and male) on the association between glucosamine and NCDs. We tested interaction effects between glucosamine use and the stratifying variables using the Wald test, and reported the corresponding *P*-interaction values.

Several sensitivity analyses were performed to assess the robustness of the findings. First, cox proportional regression analysis in the total population without propensity score matching. Second, reanalysis of the effect of glucosamine on the NCDs after multiple interpolations for the missing covariates. Third, participants who had developed any types of NCDs within two years of follow-up were excluded in order to minimise the potential for reverse causation. Fourth, we also performed a sensitivity analysis categorizing participants into four groups (non-users, glucosamine only, chondroitin only, both) to evaluate the independent and joint effects of glucosamine and chondroitin on NCDs risk. All analyses were performed using R (version 4.1.0).

To account for the large number of statistical tests performed, *p*-values were adjusted using the Benjamini-Hochberg procedure to control the false discovery rate (FDR).

Results

Baseline characteristics

Baseline characteristics of participants in the total, unmatched, and matched cohort are illustrated in Table 1, stratified by glucosamine users and non-users. Among 269,033 included participants, 52,556 (19.5%) were regular users of glucosamine and 216,477 (80.5%) were non-users. 1:1 PSM was used to match glucosamine users with non-users, which ultimately included 52,525 glucosamine users and 52,525 controls (Fig. 1). In the unmatched cohort, compared with non-users, glucosamine users were older, more likely to be female, and had a lower level of socioeconomic deprivation. They were also more likely to be current or former smokers. Additionally, glucosamine users tended to engage in excessive alcohol consumption, exhibit unhealthy dietary patterns, and participate in irregular physical activity. After 1:1 PSM, the characteristics of the participants in these two groups were comparable (SMD<0.1, Table 1). The histograms of the propensity score distributions after matching were showed overlap, and improved balance (Supplementary Figure S1 and Figure S2).

Effects of regular glucosamine use on the risk of NCDs

During a median follow-up of 13.78 years, we found that regular use of glucosamine was related to significant lower risk of several health outcomes (Fig. 2), including a 50%

Table 1 Participants characteristics of the unmatched and matched overall cohorts

Characteristics (%)	Total (N=269033)	Unmatched cohorts		SMD	Matched cohorts		SMD
		glucosamine non-users (n=216477)	glucosamine users (n=52556)		Controls (n=52525)	Glucosamine users (n=52525)	
Age, years, mean±SD	69.08 (8.12)	68.37 (8.17)	72.04 (7.23)	0.476	72.14 (7.51)	72.03 (7.23)	0.014
Sex - No. (%)							
Male	122,083 (45.3)	102,232 (47.2)	19,851 (37.8)	0.192	20,076 (38.2)	19,850 (37.8)	0.009
Female	146,950 (54.6)	114,245 (52.8)	32,705 (62.2)		32,449 (61.8)	32,675 (62.2)	
BMI, kg/m^2, mean±SD	26.81 (4.34)	26.81 (4.35)	26.81 (4.26)	0.993	26.83 (4.34)	26.81 (4.26)	0.005
Race - No. (%)							
White	252,926 (94.0)	202,478 (93.5)	50,448 (96.0)	0.112	50,452 (96.1)	50,419 (96.0)	0.009
Asian	7,645 (2.8)	6,708 (3.1)	937 (1.8)		912 (1.7)	937 (1.8)	
Black	3,471 (1.2)	2,986 (1.4)	485 (0.9)		504 (1.0)	484 (0.9)	
Mixed	3,742 (1.3)	3,218 (1.5)	524 (1.0)		514 (1.0)	523 (1.0)	
Unknown	1,249 (0.4)	1,087 (0.5)	162 (0.3)		143 (0.3)	162 (0.3)	
TDI, mean±SD	-1.45 (3.00)	-1.35 (3.06)	-1.89 (2.73)	0.185	-1.88 (2.75)	-1.89 (2.73)	0.001
WHR, mean±SD							
Normal	150,830 (56.0)	119,665 (55.3)	31,165 (59.3)	0.083	31,024 (59.1)	31,142 (59.3)	0.005
Elevated	117,605 (43.7)	96,294 (44.5)	21,311 (40.5)		21,424 (40.8)	21,303 (40.6)	
Unknown	598 (0.2)	518 (0.2)	80 (0.2)		77 (0.1)	80 (0.2)	
CRP, mean±SD	2.20 (3.58)	2.21 (3.58)	2.19 (3.55)	0.003	2.21 (3.42)	2.19 (3.55)	0.005
Glucose, mean±SD	4.95 (0.58)	4.95 (0.58)	4.98 (0.58)	0.054	4.98 (0.60)	4.98 (0.58)	0.007
HbA1c, mean±SD	34.72 (3.45)	34.66 (3.46)	34.98 (3.37)	0.093	35.00 (3.39)	34.98 (3.37)	0.004
eGFR, mean±SD	92.12 (16.18)	92.13 (16.42)	92.09 (15.14)	0.002	91.90 (15.55)	92.09 (15.15)	0.012
					(Table 1 continues on next page)		
Smoking status - No. (%)							
Never smoke	26,557 (9.8)	23,310 (10.8)	3,247 (6.2)	0.17	3,296 (6.3)	3,247 (6.2)	0.006
Previous/Current smoke	241,200 (89.6)	192,048 (88.7)	49,152 (93.5)		49,085 (93.5)	49,121 (93.5)	
Diet pattern - No. (%)							
Healthy	213,894 (79.5)	173,267 (80.0)	40,627 (77.3)	0.115	40,602 (77.3)	40,610 (77.3)	0.001
Unhealthy	49,688 (18.4)	38,418 (17.7)	11,270 (21.4)		11,268 (21.5)	11,256 (21.4)	
Alcohol drink status- No. (%)							
None/moderate	74,737 (27.7)	59,732 (27.6)	15,005 (28.6)	0.041	14,967 (28.5)	14,992 (28.5)	0.003
Excessive	158,562 (58.9)	127,430 (58.9)	31,132 (59.2)		31,178 (59.4)	31,115 (59.2)	
Physical activity - No. (%)							
Regular	63,530 (23.6)	53,055 (24.5)	10,475 (19.9)	0.132	10,472 (19.9)	10,474 (19.9)	0.002
Irregular	200,238 (74.4)	158,829 (73.4)	41,409 (78.8)		41,391 (78.8)	41,379 (78.8)	
Arthritis - No. (%)							
No	251,880 (93.6)	204,427 (94.4)	47,453 (90.3)	0.156	47,695 (90.8)	47,453 (90.3)	0.016
Yes	17,153 (6.3)	12,050 (5.6)	5,103 (9.7)		4,830 (9.2)	5,072 (9.7)	
Hypertension - No. (%)							
No	129,192 (48.0)	105,808 (48.9)	23,384 (44.5)	0.088	23,285 (44.3)	23,375 (44.5)	0.003
Yes	139,841 (51.9)	110,669 (51.1)	29,172 (55.5)		29,240 (55.7)	29,150 (55.5)	
Hyperlipidemia - No. (%)							
No	237,804 (88.3)	192,202 (88.8)	45,602 (86.8)	0.062	45,535 (86.7)	45,575 (86.8)	0.002
Yes	31,229 (11.6)	24,275 (11.2)	6,954 (13.2)		6,990 (13.3)	6,950 (13.2)	
Neuropathic pain - No. (%)							
No	253,406 (94.1)	204,810 (94.6)	48,596 (92.5)	0.087	48,669 (92.7)	48,583 (92.5)	0.006
Yes	15,627 (5.8)	11,667 (5.4)	3,960 (7.5)		3,856 (7.3)	3,942 (7.5)	
					(Table 1 continues on next page)		
Antihypertensive drugs - No. (%)							
No	230,962 (85.8)	186,607 (86.2)	44,355 (84.4)	0.051	44,205 (84.2)	44,328 (84.4)	0.006
Yes	38,071 (14.1)	29,870 (13.8)	8,201 (15.6)		8,320 (15.8)	8,197 (15.6)	
Lipid treatment - No. (%)							
No	252,619 (93.8)	203,779 (94.1)	48,840 (92.9)	0.049	48,795 (92.9)	48,812 (92.9)	0.001
Yes	16,414 (6.1)	12,698 (5.9)	3,716 (7.1)		3,730 (7.1)	3,713 (7.1)	

Table 1 (continued)

Characteristics (%)	Total (N=269033)	Unmatched cohorts		SMD	Matched cohorts		SMD
		glucosamine non-users (n=216477)	glucosamine users (n=52556)		Controls (n=52525)	Glucosamine users (n=52525)	
Aspirin - No. (%)							
No	247,909 (92.1)	200,361 (92.6)	47,548 (90.5)	0.075	47,442 (90.3)	47,520 (90.5)	0.005
Yes	21,124 (7.8)	16,116 (7.4)	5,008 (9.5)		5,083 (9.7)	5,005 (9.5)	
Non-aspirin-NSAIDs - No. (%)							
No	207,197 (77.0)	169,087 (78.1)	38,110 (72.5)	0.13	38,440 (73.2)	38,105 (72.5)	0.014
Yes	61,836 (22.9)	47,390 (21.9)	14,446 (27.5)		14,085 (26.8)	14,420 (27.5)	

Values are mean ± SD, n (%), or median ± IQR (range). BMI, Body Mass Index. TDI, Townsend Deprivation Index. WHR, Waist-Hip Ratio. CRP, C-Reactive Protein. HbA1c, Glycosylated Hemoglobin. eGFR, estimated glomerular filtration rate. NSAID, Non-Steroidal Anti-Inflammatory Drug

reduction in the risk of schizophrenia (HR = 0.50, 95%CI: 0.28–0.88, P = 0.017), a 27% decreased risk of esophageal cancer (HR = 0.73, 95%CI: 0.58–0.92, P = 0.007), a 19% lower risk of gout (HR = 0.81, 95%CI: 0.72–0.91, P < 0.001), a 14% lower risk of COPD (HR = 0.86, 95%CI: 0.80–0.93, P < 0.001), a 14% lower risk of colorectal cancer (HR = 0.86, 95%CI: 0.78–0.94, P = 0.001), a 13% lower risk of CLD (HR = 0.87, 95%CI: 0.80–0.94, P = 0.001), a 13% lower risk of rheumatoid arthritis (HR = 0.87, 95%CI: 0.78–0.97, P = 0.011), a 12% reduced risk of HF (HR = 0.88, 95%CI: 0.81–0.96, P = 0.003), and an 8% lower risk of diabetes (HR = 0.92, 95%CI: 0.86–0.99, P = 0.018), and an 8% decreased risk of CHD (HR = 0.92, 95%CI: 0.88–0.96, P < 0.001, Fig. 2). After FDR correction, significant associations remained for esophageal cancer, gout, COPD, colorectal cancer, CLD, HF and CHD.

Population attributable fraction

In this study, PAF was used to perform a counterfactual analysis to compare changes in the risk of NCDs in the study population between the current exposure levels and an ideal scenario in which exposure is perfectly controlled. Specifically, regular glucosamine use is associated with significant PAF levels. The attributable fractions were 32.30% for schizophrenia, 12.84% for esophageal cancer, 11.14% for gout, 6.53% for colorectal cancer, 5.67% for COPD, 6.54% for CLD, 6.86% for rheumatoid arthritis, 6.09% for HF, 4.01% for diabetes, and 4.16% for CHD (Fig. 3).

Subgroup analyses

Subgroup analyses were conducted to assess whether the relationship between regular glucosamine use and the risk of NCDs varied by age or gender. After Bonferroni's correction, results stratified by gender showed that there was an interaction between regular glucosamine use and gender on the risk of HF ($P_{interaction}$=0.001, Fig. 4). Regular glucosamine use was related to a 22% lower risk of HF in men (HR = 0.78, 95%CI: 0.69–0.87, P < 0.001), but no significant associations in women (Fig. 4).

In addition, results stratified by age showed that there was an interaction between regular glucosamine use and age on the risk of AF ($P_{interaction}$<0.001, Fig. 4). Regular glucosamine use was related to a 51% higher risk of AF among the participants younger than 65 years old (HR = 1.51, 95%CI: 1.19–1.91, P < 0.001).

Sensitivity analyses

Sensitivity analyses confirmed the robustness of these findings. The observed associations remained materially unchanged after analyzing the association between regular glucosamine use and NCDs risk using Cox Proportional Hazards Model (Table S4), multiple interpolation of missing data (Table S5), excluding cases diagnosed within first two years of follow-up (Table S6) and combined associations of glucosamine and chondroitin use with the risk of NCDs (Table S7).

Discussion

In this propensity score-matched, prospective, outcome-wide analysis, regular glucosamine use was associated with a reduced risk of esophageal cancer, gout, COPD, colorectal cancer, CLD, HF, and CHD, after adjustment for multiple confounding factors and correction for multiple testing. These associations were independent of age and gender. Causality cannot be inferred from this observational study. Nevertheless, population attributable fraction estimates suggest that, assuming a causal relationship, differences in glucosamine use could be responsible for 4.16–32.30% of NCD cases.

To our knowledge, this is the first study to investigate the associations between regular glucosamine use and a wide

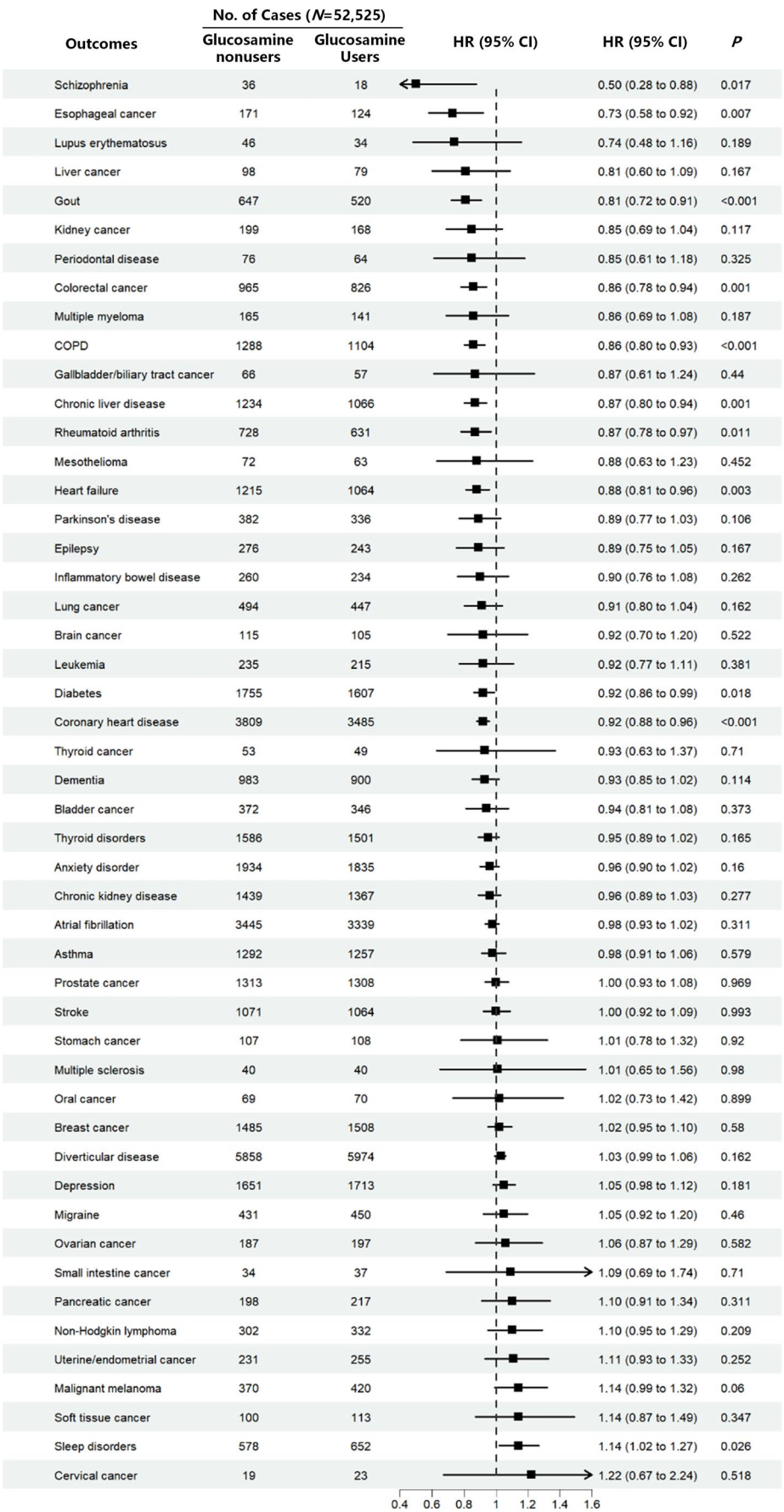

Fig. 2 Associations between regular glucosamine use and the risk of 49 types of non-communicable diseases (NCDs) compared with nonusers after 1:1 propensity score matching (PSM). The PSM were used to adjust age, gender, race, Townsend deprivation index (TDI), dietary pattern, smoking status, alcohol consumption, physical activity, body mass index (BMI), waist-to-hip ratio (WHR), glucose, glycosylated hemoglobin (HbA1c), C-reactive protein (CRP), estimated glomerular filtration rate (eGFR), arthritis, neuropathic pain, hypertension, hyperlipidemia, antihypertensive drugs, statins, aspirin, and other non-steroidal anti-inflammatory drugs (NSAIDs). Specific disorders for female (breast, cervix, endometrium and ovary cancer) were additionally adjusted for menopause status and hormone replacement therapy. COPD, chronic obstructive pulmonary disease

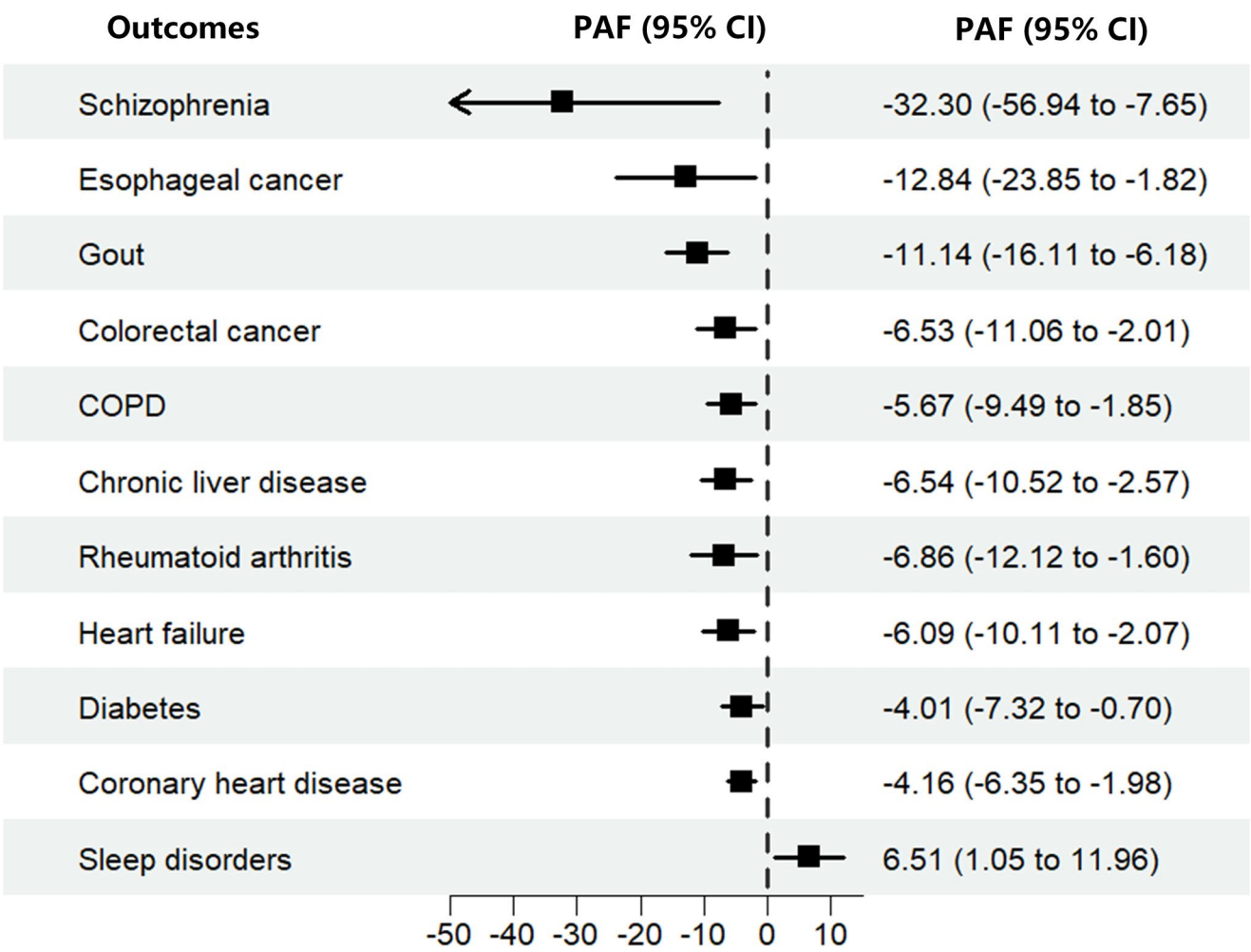

Fig. 3 Population attributable fraction (PAF) for regular glucosamine use on the risk of NCDs in matched cohorts

spectrum of NCDs, as well as the corresponding population attributable fractions (PAFs), within a population-based longitudinal cohort. Our findings align with previous studies on glucosamine use and specific chronic diseases, such as those from the Nurses' Health Study and Health Professionals' Follow-up Study, which indicated a protective association with colorectal cancer [11]. In the Vitamins and Lifestyle (VITAL) study, glucosamine use was significantly associated with a 27% lower risk of colorectal cancer [12]. In addition, a previous UKB study with a median follow-up of seven years supported our findings that glucosamine use was associated with a lower risk of CHD events and not associated with the risk of stroke [6]. For CLD, a previous UKB study supports our observation that glucosamine use is associated with a reduced risk of digestive mortality [8]. Another UKB study of 18,753 patients with T2D and metabolic steatotic liver disease suggested that regular glucosamine use was associated with a reduced risk of major liver disease [13]. Moreover, previous UKB studies with a median follow-up of eight years suggested glucosamine use was related to a lower risk of COPD, and gout [14, 15]. A UKB study with a median follow-up of 8.9 years indicated that glucosamine use was related to a lower risk of dementia [16]. However, a recent UKB study with a median follow-up of 10 years suggested that there is no relationship between glucosamine use and dementia or Parkinson's disease, which is in line with our findings [17]. The findings of our study did not indicate a notable correlation between the use of glucosamine and a decreased risk of lung cancer, a result that differs from previously observed [7]. The longer follow-up period and the exclusion of participants with pre-existing NCDs at the baseline may have resulted in a more favorable health status among this study population, thereby attenuating the observable effects of glucosamine.

Several biological mechanisms may underlie the potential protective effects of glucosamine against NCDs. One area of research has focused on its role in reducing the risk of CVD. Although specific preclinical models of osteoarthritis-induced atherosclerosis are limited, studies using hypercholesterolemic rabbit models of chronic arthritis

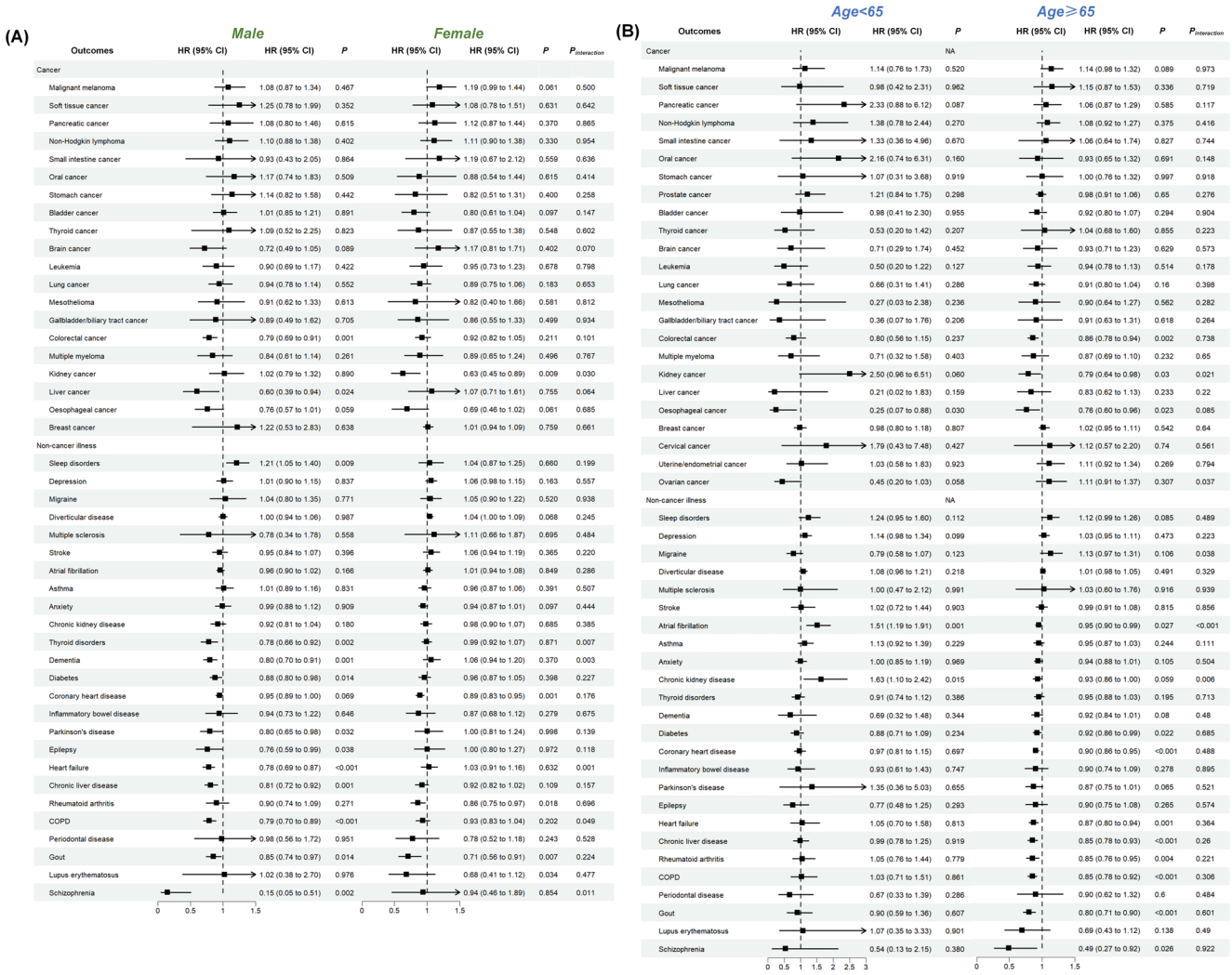

Fig. 4 Stratified analysis of regular glucosamine use and the risk of NCDs by age and gender

have demonstrated that severe arthritis accompanied by vascular injury can increase plaque instability and promote spontaneous plaque formation [18]. Notably, high-dose oral glucosamine at levels comparable to those used in human treatments significantly reduced atherosclerotic lesion formation, decreased circulating inflammatory markers, and inhibited NF-κB activation in mononuclear cells [19]. While the ability of glucosamine to inhibit of NF-κB has been recognized [20, 21]. Additionally, glucosamine may exert protective effects against systemic inflammation and cardiovascular dysfunction by enhancing O-GlcNAcylation of the NF-κB p65 subunit, as supported by evidence of reduced joint damage and inflammation in osteoarthritis rabbit models [22]. Data from the National Health and Nutrition Examination Survey (NHANES) indicated that individuals who reported glucosamine use had significantly lower levels of CRP, a biomarker of systemic inflammation, compared to non-users [23]. The anti-inflammatory properties of glucosamine may be attributable to its capacity to regulate the hexosamine pathway, which integrates pivotal cellular molecules, including lipids, amino acids, and carbohydrates, to modulate the inflammatory response [24]. Given the central role of inflammation in the pathogenesis of NCDs, the anti-inflammatory properties of glucosamine may partly account for its observed protective effects.

Furthermore, glucosamine may also mimic the metabolic effects of a low-carbohydrate diet, as demonstrated in animal studies that it reduced glycolysis, increased amino acid catabolism, improved blood sugar levels, and extended lifespan [25]. The antioxidant properties of glucosamine, including its capacity to scavenge superoxide and hydroxyl radicals, contribute to the protection of macromolecules from oxidative damage, is essential in the prevention of NCDs [26, 27]. Glucosamine has also been shown to modulate key cellular processes, including proliferation, apoptosis, angiogenesis, migration, and invasion, which may

contribute to its broader protective effects against NCDs [28]. In addition, glucosamine may promote mitochondrial biogenesis, thereby improving cellular energy metabolism and potentially contributing to its protective effects [29].

Given its widespread use and accessibility, glucosamine may represent a promising, low-cost intervention for the prevention of chronic diseases, particularly among aging populations. Although traditionally employed for joint health, our findings suggest that its benefits may extend beyond musculoskeletal outcomes to include a reduced risk of several major NCDs. In light of the global burden of NCDs and the limited availability of pharmacological preventive options in many settings, glucosamine could serve as a feasible, accessible, and scalable strategy to promote healthy aging. Nevertheless, it is important to acknowledge that this study is observational in design. While the associations observed are robust and adjusted for multiple confounders, causal relationships cannot be definitively established. Therefore, future researches, including randomized controlled trials and mechanistic investigations, are warranted to confirm these findings and elucidate the underlying biological pathways.

The primary strength of our study is that it is the largest investigation to date examining regular glucosamine use and the risk of a wide range of NCDs. This large sample size provided sufficient statistical power to analyze uncommon and rare NCDs, which together account for the majority of incident cases. Another key strength is the application of propensity score matching (PSM), which effectively controlled for confounding by creating comparable groups with balanced covariates. This approach not only enhances the internal validity of our findings but also improves the robustness and precision of the estimated associations between glucosamine use and NCD risk. Finally, we are the first to apply PAF analysis in this context, enabling quantification of the proportion of NCD risk potentially attributable to glucosamine use at the population level, thereby providing a clearer understanding of its potential public health impact.

Several limitations of our study need to be considered. First, information on glucosamine supplementation was based on self-reported questionnaires, without external validation or detailed information on adherence or treatment duration. Therefore, exposure misclassification is possible. Moreover, the lack of detailed data on glucosamine dosage, formulation, frequency, and duration prevented us from assessing dose-response relationships, which are important for evaluating the strength of causality. This limits our ability to draw more definitive conclusions regarding the magnitude of effect. Second, specific information on forms of glucosamine supplementation (glucosamine sulfate, glucosamine hydrochloride, N-acetyl-glucosamine) was not collected, making it difficult to assess whether the association between different forms of glucosamine supplement and NCD risk might differ. Third, we did not account for the competing risk of death in our primary analyses. Given the older age of the cohort and extended follow-up, this may lead to overestimation of disease incidence. Future studies should consider applying competing risk models, such as Fine and Gray subdistribution hazard models, to provide more accurate estimates of absolute risk in the presence of competing events. Fourth, although we conducted a 2-year lag analysis by excluding events that occurred within the first two years of follow-up, we did not explore longer lag periods such as 3 or 5 years due to concerns about statistical power and reduced event numbers. Therefore, we cannot entirely rule out the possibility that early, undiagnosed conditions or pre-existing symptoms might have influenced both the likelihood of exposure and disease risk. Future studies with larger sample sizes or pooled datasets should further investigate these associations using multiple lag periods. Fifth, although participants with prevalent NCDs were excluded to reduce confounding, the UK Biobank does not provide information on the exact reasons for glucosamine use. It is possible that some participants took glucosamine in response to early symptoms such as joint discomfort or undiagnosed osteoarthritis, which may be associated with overall health status and future disease risk. Therefore, residual confounding by indication cannot be entirely ruled out. Sixth, we acknowledge that immortal time bias remains a general concern in observational studies relying on baseline behaviors. Also, glucosamine users may be more health-conscious, better engaged with the healthcare system, and more likely to undergo routine screenings, introducing a potential "healthy user" bias. Future research is needed to further investigate these associations, ideally through randomized controlled trials or studies that can more effectively account for such biases. Given the observational study design, conclusions regarding causality should be drawn with caution, as residual confounding cannot be completely excluded, even using PSM to control for known confounders. In addition, the participants in this study were predominantly white, who are more likely to have healthier behaviors than the general British population, so it is possible that the findings may not be generalizable to other races and ethnicities. Moreover, given that our analyses were conducted in a single large cohort, validation in independent populations is warranted. Future replication in comparable datasets will help confirm the generalizability of our findings.

It is also worth noting that although UK Biobank includes genetic and some environmental exposure data (e.g., air pollution), these variables were not included in our current analysis due to data complexity, limited availability for all participants, and potential methodological constraints.

Future studies incorporating genetic risk scores and detailed environmental metrics may help further clarify these associations. Nevertheless, we attempted to minimize potential confounding by adjusting for a wide range of sociodemographic, lifestyle, and clinical factors—many of which may partially reflect underlying genetic and environmental influences (e.g., smoking status, BMI, physical activity, CRP levels). Additionally, since the UK Biobank predominantly includes individuals of white European ancestry and relatively similar socioeconomic status, population stratification due to genetic diversity may be reduced.

Conclusion

In conclusion, our findings suggest that regular glucosamine use is associated with a reduced risk of several non-communicable diseases, including esophageal cancer, gout, COPD, colorectal cancer, chronic liver disease, heart failure, and coronary heart disease. These associations were generally consistent across different age and sex groups. Given the observational design of this study, causal interpretations should be made with caution. Further research, particularly randomized controlled trials, is warranted to confirm these associations and to evaluate the potential role of glucosamine in chronic disease prevention.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40520-025-03171-9.

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Author contributions JH and YM designed the study. YM and JH acquired, analyzed, and interpreted the data. YM, JH and YJ drafted the manuscript. YM, JH, and JY completed the statistical analysis. JJ and FS supervised the final manuscript. FS conducted the validation. JJ and FS made critical revision of the manuscript. FS had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. JH and YM contributed equally to the article.

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Data availability UK Biobank data are available in a public, open-access repository. This research has been conducted using the UK Biobank Resource under Application Number 63454. The UK Biobank data are available on the application to the UK Biobank (www.ukbiobank.ac.uk/).

Declarations

Ethics approval and consent to participate UK Biobank has ethics approval from the North West Multi-Centre Research Ethics Committee (11/NW/0382). Appropriate informed consent was obtained from participants and ethical approval was covered by the UK Biobank.

Competing interests The authors declare no competing interests.

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