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Association of regular glucosamine use with incident dementia: evidence from a longitudinal cohort and Mendelian randomization study

Jiazhen Zheng[1], Can Ni[1], Yingchai Zhang[2], Jinghan Huang[3,4], Daniel Nyarko Hukportie[5], Buwen Liang[1] and Shaojun Tang[1,6*]

Abstract

Background Emerging data suggests the neuroprotective and anti-neuroinflammatory effects of glucosamine. We aimed to examine the association between regular glucosamine use and risk of incident dementia, including dementia subtypes.

Methods We conducted large-scale observational and two-sample Mendelian randomization (MR) analyses. Participants in UK Biobank having accessible data for dementia incidence and who did not have dementia at baseline were included in the prospective cohort. Through the Cox proportional hazard model, we examined the risks of incident all-cause dementia, Alzheimer's disease (AD), and vascular dementia among glucosamine users and non-users. To further test the causal association between glucosamine use and dementia, we conducted a 2-sample MR utilizing summary statistics from genome-wide association studies (GWAS). The GWAS data were obtained from observational cohort participants of mostly European ancestry.

Results During a median follow-up of 8.9 years, there were 2458 cases of all-cause dementia, 924 cases of AD, and 491 cases of vascular dementia. In multivariable analysis, the hazard ratios (HR) of glucosamine users for all-cause dementia, AD, and vascular dementia were 0.84 (95% CI 0.75–0.93), 0.83 (95% CI 0.71–0.98), and 0.74 (95% CI 0.58–0.95), respectively. The inverse associations between glucosamine use and AD appeared to be stronger among participants aged below 60 years than those aged above 60 years ($p = 0.04$ for interaction). The *APOE* genotype did not modify this association ($p > 0.05$ for interaction). Single-variable MR suggested a causal relationship between glucosamine use and lower dementia risk. Multivariable MR showed that taking glucosamine continued to protect against dementia after controlling for vitamin, chondroitin supplement use and osteoarthritis (all-cause dementia HR 0.88, 95% CI 0.81–0.95; AD HR 0.78, 95% CI 0.72–0.85; vascular dementia HR 0.73, 95% CI 0.57–0.94). Single and multivariable inverse variance weighted (MV-IVW) and MR-Egger sensitivity analyses produced similar results for these estimations.

Conclusions The findings of this large-scale cohort and MR analysis provide evidence for potential causal associations between the glucosamine use and lower risk for dementia. These findings require further validation through randomized controlled trials.

*Correspondence:
Shaojun Tang
shaojuntang@ust.hk
Full list of author information is available at the end of the article

Keywords Glucosamine, Dementia, Alzheimer's disease, APOE

Background

Dementia is characterized by an inexorably progressive impairment of cognition and the capacity to carry out activities of daily life. It is a heterogeneous syndrome posing a substantial burden on patients, their proxies, and national health-care systems [1]. In the UK, over 850,000 individuals suffer with dementia [2]. Globally, roughly 50 million individuals have dementia, with this figure expected to rise to 152 million by 2050 [1]. In the absence of effective pharmacological treatments for dementia, the identification and detailed investigation of potentially modifiable protective factors have gained considerable attention in recent years.

Glucosamine is a widely used non-vitamin, non-mineral supplement for relieving both osteoarthritis and joint discomfort [3]. It is an approved osteoarthritis prescription medication in most European nations and is widely used as a nutritional supplement in countries like the USA and Australia, where roughly 20% of adults use it daily [4, 5]. Despite the controversy regarding the efficacy of glucosamine supplements on osteoarthritis and joint discomfort [6, 7], glucosamine has been proved to have anti-inflammatory properties [8] and may prevent a wide range of diseases [9, 10]. In this instance, a variety of epidemiological studies have revealed that glucosamine consumption may protect against colorectal cancer [11, 12], lung cancer, [13], cardiovascular disease [14, 15], diabetes [16], and all-cause death [17]. Importantly, a cross-sectional research recorded the association between glucosamine consumption and better cognitive function [18]. However, research regarding the association between glucosamine use and dementia risk remains scant.

The importance of glucosamine in brain function has been highly supported by previous studies [19, 20]. Glucosamine mimicked the effects of a low-carbohydrate diet in a prior animal research, resulting in increased lifespan [21], and studies consistently showed that a low-carbohydrate diet protects against dementia [22, 23]. An animal study suggested that glucosamine may promote cognitive function by impacting energy metabolism [20]; other animal models have indicated the neuroprotective and anti-neuroinflammatory effects of glucosamine [24]. In addition, glucosamine participates in the O-linked N-acetylglucosaminylation of various proteins, which was verified to be related to many neurological or neurodegenerative diseases [25, 26]. Therefore, we hypothesize that regular use of glucosamine may have a causal influence on incident dementia.

Based on the UK Biobank study of nearly 500,000 British people, we investigated the relationship between regular use of glucosamine and the risk of all-cause dementia, Alzheimer's disease (AD) and vascular dementia. We also explored potential modifying effects by several established risk factors (including *APOE* ε4 genotypes) for dementia.

Traditional observational studies include drawbacks such as residual confounding and/or reverse causation, inadequate adjustment (e.g., healthy lifestyle or other factors), and a focus on correlation rather than causation. By employing genetic variants as proxy for glucosamine use, Mendelian randomization (MR) avoids some of these limitations and provides genetic support for causal associations [27]. Thus, in addition to observational analysis, we performed MR to give additional insights for the assessment of potential causal relationships.

Methods

Study design

This study analyzed data from UK Biobank (application 55,794), a large prospective cohort study enrolling over 500,000 participants between the ages of 40 and 70 from 22 research centers in the UK (England, Wales, and Scotland) between 2006 and 2010 [28]. Through detailed electronic questionnaires, face-to-face interviews, and physical assessments, participants provided personal data on health-related variables. Participants who dropped out of the study ($n=1298$), had dementia ($n=224$), or lacked data on glucosamine use ($n=6171$) were excluded from the analysis. We also excluded 15,339 participants from further analysis owing to a lack of quality-controlled genotyping data (Fig. 1).

Exposure assessment

At one of 22 assessment sites across the UK, the participants filled out a touch-screen questionnaire. In answer to the question "Do you usually take any of the following?", a list of supplements, which included glucosamine, was given to the participants to choose from. Based on these data, we established a binary classification for regular glucosamine use: 1 = yes, 0 = no. This evaluation method was used in previous studies [16, 29, 30].

Ascertainment of incident dementia

We used participants' baseline survey information, hospital admission diagnosis records, and death registration records to define outcomes, which included all-cause dementia, AD, and vascular dementia. Diagnoses were

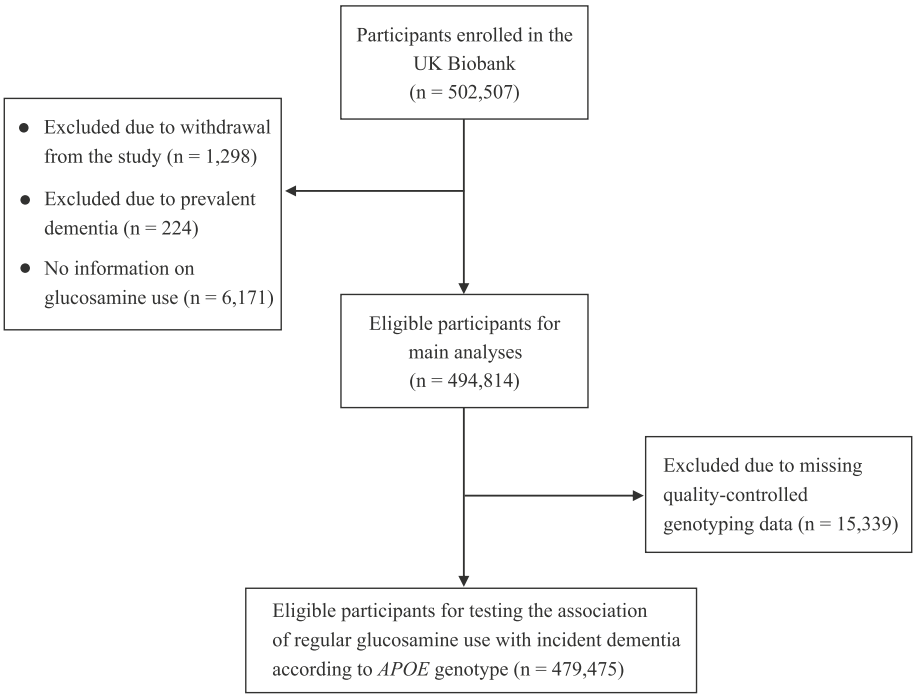

Fig. 1 Flow diagram of the participant selection process

recorded using the International Classification of Diseases (ICD) coding system (Additional file 1: Table S1) [31]. The incident disease in this study was determined by the primary or secondary diagnoses from hospital admission data or primary or secondary causes of inducing death after baseline data collection. A subsample of the population was also retrieved from primary care data using Read Codes (version 2 or 3) in the sensitivity analysis [32]. Participants were followed up from the time of the baseline to the first diagnosis, death, or February 25, 2018, in Wales and England and February 28, 2017, in Scotland, whichever came first. Detailed information on the *APOE* genotyping is presented in the Additional file 1: Supplemental Methods [33–35].

Covariates

Various potential confounders were assessed using a baseline touch-screen questionnaire. Age, gender, ethnicity, the Townsend Deprivation Index (TDI), level of education, and annual household income were included as the sociodemographic factors. Lifestyle behavior included smoking status, alcohol intake, being physically active, body mass index (BMI), vegetable intake and fruit intake. Health-related variables included hypertension, cardiovascular disease, cancer, digestive disease, depression, diabetes, emphysema or chronic bronchitis, high cholesterol, chronic kidney disease, chronic liver disease, and Elixhauser Comorbidity Index. Medication utilization included antihypertensive drugs, insulin treatment, statin, opioids, aspirin, and other non-steroidal anti-inflammatory drugs (NSAIDs). We also included chondroitin, dietary supplements for minerals, vitamins, and other nutrients (fish oil, calcium, iron, zinc, and selenium), memory, and reaction time in the analysis. The details on calculating the Elixhauser Comorbidity Index are shown in the Additional file 1: Supplemental Methods [36, 37]. We calculated participants' BMI by dividing their weight by the square of their height in meters. The TDI is a comprehensive poverty index, which is calculated by the following factors: ownership of a home, ownership of a car, being unemployed or not, and whether there are too many people living together [38]. It shows the socioeconomic status of a participant. According to WHO guidelines on physical activity for health [39], we classified individuals as <150 or ≥ 150 min/week based on total minutes of moderate physical activity per week (collected by touchscreen question, one vigorous physical activity minute equals two moderate physical activity minutes). This assessment method was widely used in prior studies [40, 41]. Patients with any of the following situations are classified as having hypertension: using hypertensive drugs, systolic blood pressure higher than 140 mmHg, diastolic blood pressure higher than 90 mmHg, or self-reported hypertension. Health status was determined through self-reporting combined with ICD-10 codes from hospital records. Memory and

reaction time assessments were conducted through touch screen [42–44]. A pair matching test was used to measure memory, in which participants had to recall six pairs of shapes and their positions in 5 s. The number of mistakes made during matching was used to evaluate performance. The test method of reaction time is shown below: a series of figures will be displayed on the screen; the participant was asked to press the button as rapidly as possible when two identical figures appear. The mean response time (ms) across eight rounds for properly selected matching groups was used to measure performance. The UK Biobank website has further information on these variables (www.ukbiobank.ac.uk).

Statistical analysis

Observational analysis

For continuous variables, the mean (SD) is used, and for categorical variables, the number (%) is used. We performed multiple imputation with chained equations to cope with missing variables to reduce the possibility of inferential bias [45, 46]. There were five datasets imputed. The imputation model contained all variables used in the analysis. Additional file 1: Table S2 provides detailed data on missing variables.

Cox proportional hazard models were used to calculate the hazard ratios (HR) and 95% confidence intervals (CIs) for the relationships between regular glucosamine use and all-cause dementia, AD, and vascular dementia. We tested the proportional hazards assumption by Schoenfeld residual tests [47], and no violations of this assumption were identified. Two models were used. We only included sex and age in Model 1. Additional factors, such as ethnicity, education, TDI, annual household income, BMI, fruit intake, vegetable intake, smoking status, alcohol intake, being physically active, medical conditions, drug use, other supplement use, memory, and reaction time were adjusted in Model 2.

In order to evaluate potential effect modifiers, subgroup analyses based on sex (female or male), age (<60 or ≥ 60 years), obesity (BMI ≥ 30 kg/m^2, no or yes), current smoking status (no or yes), diabetes (no or yes), hypertension (no or yes), aspirin use (no or yes), use of non-aspirin NSAIDs (no or yes), use of vitamin supplementation (no or yes), use of other non-vitamin supplementation (no or yes) and *APOE* ε4 carrier (no or yes) were performed. To investigate the differential effects of glucosamine on the likelihood of dementia in subgroups, we calculated the p-value for interaction by including the cross-product term of the stratifying variables with glucosamine use in the fully adjusted model.

We evaluated the robustness of our findings by a sequence of sensitivity analyses (Additional file 1: Table S3). Firstly, we conducted an analysis of competing risks which considered all-cause mortality as a competing event for dementia. Secondly, since individuals who took glucosamine were more likely to take chondroitin than those who did not, we conducted sensitivity analyses by removing chondroitin users. Thirdly, to minimize the possibility of reverse causality, we excluded people who died within the first 2 years after baseline assessment. Fourthly, we excluded individuals who had missing covariate values. Fifthly, we calculated a propensity score for each participant and further adjusted for the score in the fully adjusted model. The multivariate logistic regression model was applied to estimate propensity scores taking all covariates into account. Sixthly, we added a subsample of the population retrieved from primary care data using Read Codes (version 2 or 3) in the analysis. We performed all analyses using R version 4.0.3, and p less than 0.05 (two-sided) was deemed significant.

Mendelian randomization

We performed a two-sample MR design using summary-level data. Single-nucleotide polymorphisms (SNPs) served as risk factor instruments. The analysis relied on public summary-level data. All original studies received ethical approval. A detailed description of the data sources, the selection of genetic instrumental variables, and the test on instrument strength and statistical power are shown in the Additional file 1: Supplemental Methods [48–56]. Data sources and instruments are listed in Additional file 1: Table S4-12. The GWAS from Ben Neale Lab round 2 used a linear regression model in Hail for large-scale phenotypes in the UK Biobank, even for binary variables. As a workaround, we used BOLT-LMM, a software package widely used to deal UK Biobank data, to calibrate the effect. The detailed information on BOLT-LMM is shown in the Additional file 1: Supplemental Methods [57].

The "MendelianRandomization" and "TwoSampleMR" R packages were used for all statistical analyses. Inverse variance-weighted (IVW) MR was the major analysis we applied for single-variable MR analysis. In order to deal with the issue of the robustness of the IVW result, we used the MR-Egger and weighted median-based regression, both of which assume distinct instrumental variables assumptions [54, 58]. When all genetic variants are invalid instrumental variables, the MR-Egger regression produces consistent results; the weighted median needs valid IVs to contribute 50% of the weight. The accuracy of weighted median estimates and IVW estimates are almost the same, which are much higher than that of MR-Egger estimates because the accuracy of MR-Egger estimates is particularly imprecise when all the IVs are about the same strength [59]. To assess potential IV violations, we carried out the MR-Egger intercept test [60],

MR pleiotropy residual sum and outlier (MR-PRESSO) test [61], and Cochran Q heterogeneity test [62]. To identify high-influence points, we used a leave-one-out validation [63]. The MR Steiger test was also performed to assess the potential reverse causal effect of glucosamine on dementia (Additional file 1: Table S13) [64].

The likelihood of using additional supplements is higher among glucosamine users than in non-glucosamine users. Taking these associations into account, we conducted multivariable MR to assess the direct effect of regular use of glucosamine on dementia under the condition of controlling vitamin, chondroitin supplements intake, and osteoarthritis. We aggregated the genetic instruments used in the related GWASs—glucosamine, vitamin, chondroitin supplements, and osteoarthritis. SNPs were clumped by linkage disequilibrium within a window of 10,000 kb ($R^2 < 0.001$) to confirm their independence. Then we derived SNP effects and standard errors from the GWAS summary statistics and harmonized them with GWAS data on dementia. Measured and unmeasured pleiotropy were taken into account by using multivariable MR extension of the IVW MR approach [65] and the MR-Egger method [66].

Results

The mean age of the 494,814 participants was 56.5 years (SD 8.1) and the proportion of female was 54.4%. At baseline, 94,259 (19.0%) of participants reported using glucosamine. There was a higher percentage of older, female, non-smoking, and physically active glucosamine users than nonusers. In addition, glucosamine users had a lower TDI, higher prevalence of comorbidities such as cancer, hypertension, arthritis, and depression, but less cardiovascular disease, emphysema or chronic bronchitis, diabetes, high cholesterol, chronic kidney disease, and chronic liver disease. The percentage of using statin, opioids, non-aspirin NSAIDs, chondroitin, vitamins, minerals, and other dietary supplements was higher in glucosamine users than non-users (Table 1).

Associations of glucosamine use with incident dementia

During the 8.9-year (IQR 8.3–9.7 years) median follow-up, we recorded 2458 cases of all-cause dementia, 924 cases of AD, and 491 cases of vascular dementia. Table 2 shows the associations of regular use of glucosamine with the outcomes. A statistically significant inverse relationship was found between glucosamine use and risk for all-cause dementia (HR 0.81; 95% CI 0.73–0.90), AD (HR 0.78; 95% CI 0.65–0.92), and vascular dementia (HR 0.68; 95% CI 0.54–0.87). The hazard ratios of glucosamine users in multivariable-adjusted models were 0.84 (95% CI 0.75 to 0.93) for all-cause dementia; 0.83 (95% CI 0.71 to 0.98) for AD; and 0.74 (95% CI 0.58 to 0.95) for vascular dementia (Table 2).

Subgroup and sensitivity analyses

To investigate potential subgroup effects, we conducted several specified subgroup analyses (Fig. 2). We found that the protective effect of glucosamine on AD was stronger among participants aged below 60 years, compared with those above 60 years ($p = 0.04$ for interaction). Other stratifying variables have not modified the association of glucosamine use with incident dementia (p for interaction > 0.05).

When we excluded participants who had outcomes within 2 years of follow-up, participants who used chondroitin, and participants with missing values for variables, the relationships of glucosamine use with all-cause dementia, AD, and vascular dementia persisted. After adding cases that were retrieved from the primary care data using Read Codes, the results did not alter. During the follow-up in participants without dementia, 19,082, 19,654, and 19,763 deaths were documented as competing events for all-cause dementia, AD, and vascular dementia, respectively. The competing risks analysis produced results which were consistent with the Cox proportional hazards model (Additional file 1: Table S2).

Mendelian randomization

According to Univariable MR analysis, genetically determined regular glucosamine use was associated with a decreased risk for all-cause dementia (IVW odds ratio, 0.85; 95% CI 0.76 to 0.95), AD (IVW odds ratio, 0.85; 95% CI 0.78 to 0.93) and vascular dementia (IVW odds ratio, 0.64; 95% CI 0.42 to 0.96) (Table 3). Weighted median and the MR-Egger provided similar estimates to those of IVW. The accuracy of the MR-Egger estimations was much lower. We use forest plots to display the MR results for the impacts of SNPs related to glucosamine use on dementia risk (Additional file 1: Fig. S1). No pleiotropy across instruments has been found by the Cochran's Q statistic. We did not find directional pleiotropy by MR-Egger intercept analysis. No potential outliers were found by MR-PRESSO. No high leverage, high impact points were found using conventional IVW leave-one-out analysis (Additional file 1: Fig. S2). Absence of weak instrument bias is shown by F statistics for genetic instruments (Additional file 1: Table S5). Using the MR Steiger test, we detected no evidence of reverse causality (Additional file 1: Table S13).

In MVMR, the genetic liabilities for regular glucosamine, vitamin, chondroitin use, and osteoarthritis were evaluated. Use of glucosamine continued to have a significant effect on all-cause dementia (IVW odds ratio, 0.88; 95% CI, 0.81–0.95; $P < 0.001$), AD (IVW odds ratio,

Table 1 Baseline characteristics of study participants by glucosamine use

	All participants (*n* = 494,814)	Use of glucosamine	
		Yes (*n* = 94,259)	No (*n* = 400,555)
Age, mean (SD), years	56.54 (8.09)	59.08 (7.07)	55.95 (8.20)
Female	269,380 (54.4)	58,996 (62.6)	210,384 (52.5)
White ethnicity	466,252 (94.2)	90,306 (95.8)	375,946 (93.9)
With college or university degree	160,409 (32.4)	31,119 (33.0)	129,290 (32.3)
TDI, mean (SD)	-1.31 (3.09)	-1.79 (2.79)	-1.20 (3.14)
Household income (£)			
18,000	116,776 (23.6)	21,044 (22.3)	95,732 (23.9)
≥ 18,000	378,038 (76.4)	73,215 (77.7)	304,823 (76.1)
BMI, mean (SD), kg/m^2	27.43 (4.80)	27.36 (4.65)	27.45 (4.83)
Physical activity (min/week)			
150	228,109 (46.1)	38,269 (40.6)	189,840 (47.4)
≥ 150	266,705 (53.9)	55,990 (59.4)	210,715 (52.6)
Fruit intake (servings/day)			
4	337,958 (68.3)	56,085 (59.5)	281,873 (70.4)
≥ 4	156,856 (31.7)	38,174 (40.5)	118,682 (29.6)
Vegetable intake(servings/day)			
4	320,640 (34.8)	57,027 (60.5)	263,613 (65.8)
≥ 4	174,174 (35.2)	37,232 (39.5)	136,942 (34.2)
Alcohol consumption frequency			
3 times a week	280,147 (56.6)	49,736 (52.8)	230,411 (57.5)
≥ 3 times a week	214,667 (43.4)	44,523 (47.2)	170,144 (42.5)
Smoking status			
Never smoker	271,869 (54.9)	52,132 (55.3)	219,737 (54.9)
Ex-smoker	170,903 (34.5)	36,013 (38.2)	134,890 (33.7)
Current smoker	52,042 (10.5)	6114 (6.5)	45,928 (11.5)
Personal medical condition			
Hypertension	279,569 (56.5)	54,670 (58.0)	224,899 (56.1)
CVD	28,699 (5.8)	4147 (4.4)	24,552 (6.1)
Cancer	39,090 (7.9)	7823 (8.3)	31,267 (7.8)
Arthritis	23,256 (4.7)	7729 (8.2)	15,527 (3.9)
Emphysema or chronic bronchitis	8262 (1.7)	1325 (1.4)	6937 (1.7)
Diabetes	25,945 (5.2)	3450 (3.7)	22,495 (5.6)
High cholesterol	86,314 (17.4)	15,972 (16.9)	70,342 (17.6)
Digestive disease	1484 (0.3)	188 (0.2)	1296 (0.3)
Chronic kidney disease	10,391 (2.1)	1885 (2.0)	8506 (2.1)
Chronic liver disease	7422 (1.5)	1225 (1.3)	6197 (1.5)
Depression	75,706 (15.3)	14,704 (15.6)	61,002 (15.2)
Elixhauser Comorbidity Index, mean (SD)	2.1 (1.7)	2.3 (1.8)	2.0 (1.7)
Medication or supplementation			
Antihypertensive drugs	88,208 (17.8)	16,897 (17.9)	71,311 (17.8)
Insulin treatment	4839 (1.0)	594 (0.6)	4245 (1.1)
Use of statin	55,913 (11.3)	10,839 (11.5)	45,074 (11.3)
Use of opioids	26,719 (5.4)	5372 (5.7)	21,347 (5.3)
Use of aspirin	69,216 (14.0)	13,299 (14.1)	55,917 (14.0)
Use of non-aspirin NSAIDs	72,939 (14.7)	17,713 (18.8)	55,226 (13.8)
Use of chondroitin	6432 (1.3)	5844 (6.2)	588 (0.1)
Use of vitamin supplementation	157,109 (31.8)	52,388 (55.6)	104,721 (26.1)
Use of minerals and other dietary supplementation	184,233 (37.2)	65,352 (69.3)	118,881 (29.7)
Memory, mean (SD), no. of errors	4.25 (3.32)	4.28 (3.45)	4.23 (3.34)
Reaction time, mean (SD), ms	558 (118)	562 (125)	557 (120)
APOE*E4 carrier	135,883 (28.3)	25,609 (28.0)	110,274 (28.4)

Values are numbers (%) unless stated otherwise. *TDI*, Townsend Deprivation Index; *BMI*, body mass index; *CVD*, cardiovascular disease; *NSAID*, non-steroidal anti-inflammatory drug; *APOE*, apolipoprotein E. All variables globally significantly different between groups at $P < 0.001$, except for BMI, digestive disease and use of aspirin ($P > 0.05$). *P*-values are derived using either Student's t-test, Wilcoxon rank sum test, or chi-square test

0.78; 95% CI, 0.72–0.85; $P < 0.001$) and vascular dementia (IVW odds ratio, 0.73; 95% CI, 0.57–0.94; $P < 0.001$). These results align with those derived from the MVMR-Egger sensitivity analyses. Again, no horizontal pleiotropy was found in the MR-Egger intercept analysis. Details on the instruments used in MVMR can be found in Additional file 1: Table S14-15.

Discussion

We observed that regular glucosamine use was related to a 15% decreased risk of all-cause dementia, 17% for AD, and 26% for vascular dementia in this large population-based study including 494,814 participants. These associations remained after adjusting for variables including sociodemographic factors, lifestyle behavior, comorbid conditions, medication, and other dietary conditions. Moreover, the beneficial effect of glucosamine use on AD seemed to be larger in participants aged below 60 years than in those aged above 60 years. The *APOE* genotype

Table 2 Associations of regular glucosamine use with incident dementia

Outcomes	Glucosamine non-user (*n* = 400,555)	Glucosamine user (*n* = 94,259)	Model 1[a]		Model 2[b]		Propensity score adjusted	
			HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
All-cause dementia	1971 (0.5)	487 (0.5)	0.81 (0.73–0.90)	< 0.001	0.84 (0.75–0.93)	0.002	0.82 (0.73–0.92)	< 0.001
Alzheimer's disease	732 (0.2)	192 (0.2)	0.78 (0.65–0.92)	0.018	0.83 (0.71–0.98)	0.029	0.80 (0.68–0.95)	< 0.001
Vascular dementia	408 (0.1)	83 (0.09)	0.68 (0.54–0.87)	0.002	0.74 (0.58–0.95)	0.018	0.72 (0.56–0.93)	0.009

Values are numbers (%) unless stated otherwise

[a] Model 1: adjusted for age and sex

[b] Model 2: additionally adjusted for ethnicity, education, Townsend Deprivation Index, household income, body mass index, fruit consumption, vegetable consumption, smoking status, alcohol consumption, physical activity, health condition, antihypertensive drugs, insulin treatment, statin use, opioids use, chondroitin use, aspirin use, non-aspirin NSAID use, vitamin supplementation, mineral and other dietary supplementation, memory, and reaction time

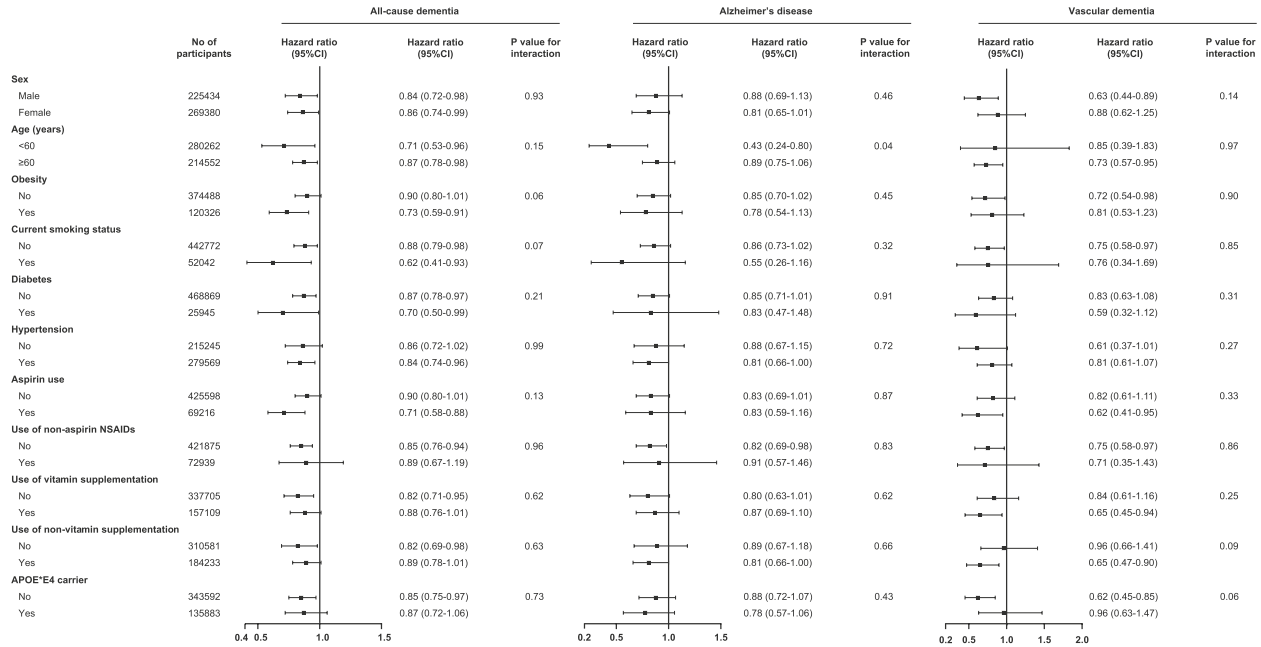

Fig. 2 Relationship between glucosamine use and risk of dementia stratified by potential risk factors. Findings were adjusted for age, sex, ethnicity, education, Townsend Deprivation Index, household income, body mass index, fruit consumption, vegetable consumption, smoking status, alcohol consumption, physical activity, health condition, antihypertensive drugs, insulin treatment, statin use, opioids use, chondroitin use, aspirin use, non-aspirin NSAID use, vitamin supplementation, mineral and other dietary supplementation, memory, and reaction time

did not modify this association. In the MR analysis, we again observed protective causal effects of regular glucosamine use on dementia risk. Our findings were mostly consistent among various MR methods that made various assumptions regarding horizontal pleiotropy, demonstrating that horizontal pleiotropy is not probable to be a sufficient explanation for our findings.

We found that 19.0% of participants used glucosamine; this number is close to the 22.0% of the Australians over 45 who also take glucosamine [5]. Our findings are in line with a prior cross-sectional investigation that found glucosamine intake to be related to better cognitive function [18]. Glucosamine users had a higher reasoning score and faster reaction speed than non-users [18]. Furthermore, in a mouse model, glucosamine exerted a cognition-enhancing function [20], which implicated the beneficial impact of glucosamine use on dementia prevention.

Because glucosamine and chondroitin supplements are typically used simultaneously once daily [6], our observed relationships might be attributed to either of these supplements. To address this concern, a sensitivity analysis was conducted to test whether glucosamine alone (without chondroitin) could prevent dementia. No substantial change occurred in the sensitivity analyses. Thus, we

Table 3 MR results for the relationship between regular glucosamine use and incident dementia

Method	All-cause dementia				Alzheimer's disease				Vascular dementia			
	Number of SNPs	OR (95% CI)	*P* for association	*P* for MR-Egger intercept	Number of SNPs	OR (95% CI)	*P* for association	*P* for MR-Egger intercept	Number of SNPs	OR (95% CI)	*P* for association	*P* for MR-Egger intercept
Univariable MR												
IVW	9	0.85 (0.76–0.95)	0.007	0.542	9	0.85 (0.78–0.93)	< 0.001	0.505	9	0.64 (0.42–0.96)	0.031	0.763
Weighted median		0.83 (0.72–0.96)	0.011			0.85 (0.76–0.96)	0.007			0.44 (0.30–0.65)	< 0.001	
MR-Egger		0.32 (0.03–3.49)	0.378			0.50 (0.08–3.07)	0.481			0.82 (0.05–6.15)	0.762	
Multivariable MR[a]												
IVW	70	0.88 (0.81–0.95)	< 0.001	0.171	67	0.78 (0.72–0.85)	< 0.001	0.202	70	0.73 (0.57–0.94)	< 0.001	0.094
MR-Egger		0.43 (0.09–2.28)	0.386			0.56 (0.11–2.66)	0.502			0.90 (0.12–5.35)	0.915	

[a] Multivariable MR analysis estimating the effect of regular glucosamine use on incident dementia, conditioning on vitamin supplement, chondroitin product intake, and osteoarthritis. All statistical tests were two-sided $P < 0.05$ was considered significant

speculate that glucosamine use might have a preventive role in the development of dementia, independent of chondroitin co-administration.

In our study, a stronger effect was found between glucosamine use and AD among participants aged below 60 years compared with those above 60 years. The weaker effect of glucosamine use in older participants may be related to the gradual atrophy of the hippocampus and the reduction of cortical density as the age increases, resulting in the reduction of brain cell membrane receptors and the decreased sensitivity to drugs [67]. This result underscores the age-modified connection between glucosamine use and dementia and emphasizes the importance of early prevention of dementia.

The protective association between glucosamine use and dementia may be explained by a few different processes. As a popular supplement that can pass through the blood–brain barrier, glucosamine may get to the hippocampus, striatum, and cortex [68, 69]. Meanwhile, several glucosamine transporters were identified in the brain [70]. For instance, glucose transporter 2 (GLUT2) was found in neurons and exhibited the greatest affinity for glucosamine [71, 72]. Intriguing evidence indicates that specific neuronal populations rely on GLUT2 to regulate glucose levels, thereby affecting their vulnerability to pathogenic mechanisms underlying AD [73, 74]. These studies highly support the important role of glucosamine on dementia. C-reactive protein, an indicator of systemic inflammation, was significantly lower in those who regularly took glucosamine, according to data from the National Health and Nutrition Examination Survey (NHANES) [8]. Animal studies also showed that glucosamine might suppress neuroinflammation [75], which is proved to increase the risk of dementia [76]. Furthermore, a prior research discovered that glucosamine might simulate a low-carbohydrate diet in mice through lowering glycolysis and enhancing amino acid catabolism [77]: consequently, glucosamine has been considered a mimicking agent for energy restriction [21]. Recent works demonstrated that a low-carbohydrate diet protects against the development of dementia [78, 79]. In addition, glucosamine could reverse the imbalanced gut microbiota [80]. Through the gut–brain axis, the gut microbiota modulates the brain functioning of the host and plays a significant role in dementia pathogenesis [81, 82]. Thus, glucosamine might have a beneficial effect on dementia pathology by regulating the gut microbiota. Other pathways may possibly be relevant and warrants further studies to explore the functional roles of glucosamine in dementia.

Our research had a number of advantages, such as a large number of participants and abundant data on dietary, health-related behaviors, and various factors that enabled us to examine the robustness of the findings and explore the effects of exposure in several subgroups. Furthermore, the MR analysis offered a superior method of obtaining somewhat less confounded estimates of causal associations that were not impacted by reverse causation or confounding. We admit that our research has limitations. Firstly, the "regular glucosamine use" was defined as self-reported at the baseline only, which might have changed in the follow-up period. Details on glucosamine use, such as dose and use duration, were not collected in the UK Biobank, which may weaken the study findings. Hence, further research that incorporates the glucosamine intake pattern and cross-validates the data on glucosamine for accuracy is required to delve into these connections. Secondly, UK Biobank did not record the adverse side effects participants suffered after using glucosamine. Nonetheless, glucosamine has been proved to be a safe supplementation for individuals with osteoarthritis due to its low risk of side effects including rare allergic reactions and gastrointestinal reactions [3]. Although people at high risk of diabetes showed reduced glucose tolerance after taking glucosamine [83, 84], studies have proved that in healthy people and diabetic patients, any oral dose of glucosamine will not affect the glucose metabolism and lipid status [85, 86]. Thirdly, in general, 20–100 imputed datasets are recommended, while in this study 5 datasets were imputed. Due to rather low proportions of missing data, we consider five imputed datasets to operate well. Fourthly, despite the SNPs we used were significantly correlated with the exposure, the genetic variants reflected only a modest portion of the overall variance in glucosamine intake, limiting them from being precise proxies of exposure. Given that we do not yet know how the genetic instruments work biologically, we cannot totally eliminate out breaches of the independence and exclusion restriction assumptions, especially with regard to pleiotropy [63]. Nevertheless, to infer reliable causal estimates, we used a variety of techniques, including Cochran's Q statistic, MR-PRESSO, weighted median, and MR-Egger. Fifthly, the interpretation of genetic liability of supplement use should be cautious as genetic predictors of glucosamine may capture participants with worse joint health [87]. We further adjusted osteoarthritis in the multivariable MR analysis to reduce bias. Sixthly, MR is a useful option for validating results; nevertheless, genetic variants reflect lifetime exposures rather than brief treatment modalities, which may create a bigger impact than a time-limited intervention [88]. Therefore, our findings should be taken cautiously, since they are hypothesis generating and warrant more clinical data to further investigate the connection between

glucosamine intake and dementia. Seventhly, although the current definition for dementia was widely used in previous studies and the true positive rate for all-cause dementia collected in the UK Biobank was as high as 82.5% [89]; the true positive rates of Alzheimer's disease and vascular dementia were lower than 75%. Thus, the results on the subtypes of dementia should be taken cautiously.

Conclusions

Regular glucosamine use was associated with a lower risk of all-cause dementia, AD, and vascular dementia, based on data from the UK Biobank cohort and a mendelian randomization study. The potential implications of our findings for dementia prevention need additional confirmation in well-powered randomized controlled trials. We also recommend additional basic scientific research to investigate the underlying mechanisms.

Abbreviations

MR	Mendelian randomization
AD	Alzheimer's disease
GWAS	Genome-wide association studies
HR	Hazard ratios
MV-IVW	Multivariable inverse variance weighted
ICD	International Classification of Diseases
TDI	Townsend Deprivation Index
BMI	Body mass index
NSAIDs	Non-steroidal anti-inflammatory drugs
CIs	Confidence intervals
SNPs	Single-nucleotide polymorphisms

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-023-02816-8.

Additional file 1: Table S1. Disease definitions used in the UK Biobank study. **Table S2.** The numbers (percentages) of participants with missing covariates. **Table S3.** Results from sensitivity analyses for the relationship between regular glucosamine use and incident dementia. **Table S4.** GWAS summary statistics: source and description. **Table S5.** Summary information on glucosamine SNPs used as genetic instruments for the Mendelian randomization analyses. **Table S6.** Summary information on chondroitin SNPs used as genetic instruments for the Mendelian randomization analyses. **Table S7.** Summary information on vitamin supplement SNPs used as genetic instruments for the Mendelian randomization analyses. **Table S8.** Summary information on osteoarthritis SNPs used as genetic instruments for the Mendelian randomization analyses. **Table S9.** Potential confounders of exposures SNPs under the condition of $P < 5 \times 10^{-8}$ in the PhenoScanner database. **Table S10.** Summary information on all-cause dementia for the 9 genome-wide significant SNPs associated with glucosamine. **Table S11.** Summary information on Alzheimer' disease for the 9 genome-wide significant SNPs associated with glucosamine. **Table S12.** Summary information on vascular dementia for the 9 genome-wide significant SNPs associated with glucosamine. **Table S13.** Results of MR Steiger direction test for glucosamine on dementia. **Table S14.** Independent instruments used for multivariable MR. Table S15. Summary information on dementia for the genome-wide significant SNPs associated with multivariable Instruments. **Figure S1.** Forest plot for the relationship of regular glucosamine use with incident dementia. **Figure S2.** Leave-one-out analyses for SNPs associated with regular glucosamine use on incident dementia.

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Authors' contributions

JZZ, CN, and SJT designed the study. JZZ and JHH performed the statistical analyses. JZZ, YCZ, and DNH wrote the manuscript. JZZ, CN, and BWL contributed to the interpretation of the data. YCZ and JHH contributed to the replication of the findings. All authors contributed to and approved the final version of the manuscript.

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Availability of data and materials

Data are available in a public, open access repository. Data from the UK Biobank (https://www.ukbiobank.ac.uk/) are available to researchers on application. The application number of this research is 55794.

Declarations

Ethics approval and consent to participate.

All participants provided written informed consent before enrolment in the UK Biobank, which was conducted in accordance with the Declaration of Helsinki. The UK Biobank study, and the sharing of anonymized data with the research community, was approved by the North West Multi-center Research Ethics Committee (REC reference: 12/NW/03820).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Bioscience and Biomedical Engineering Thrust, Systems Hub, The Hong Kong University of Science and Technology (Guangzhou), Guangzhou, Guangdong, China. [2]Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Sha Tin, New Territories, Hong Kong, SAR, China. [3]Biomedical Genetics Section, School of Medicine, Boston University, Boston, USA. [4]Department of Chemical Pathology, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, SAR, China. [5]Department of Epidemiology, School of Public Health, (Guangdong Provincial Key Laboratory of Tropical Disease Research), Southern Medical University, Guangzhou, China. [6]Division of Emerging Interdisciplinary Areas, The Hong Kong University of Science and Technology, Clear Water Bay, Hong Kong, SAR, China.

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