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# Habitual glucosamine use, APOE genotypes, and risk of incident cause-specific dementia in the older population

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## Abstract

**Background** The relationship of glucosamine use with incident dementia in the older population remains uncertain. We aimed to evaluate the longitudinal association between habitual glucosamine supplement and the risk of cause-specific dementia and examine the possible effect modifiers on this association.

**Methods** The study included 214,945 participants over the age of 60 who had available information on glucosamine use and did not have dementia at baseline in the UK Biobank. The APOE genotypes were determined by a combination variant of rs429358 and rs7412. The primary outcome was incident vascular dementia, incident Alzheimer's disease, and incident frontotemporal dementia, respectively.

**Results** Over a median follow-up duration of 12 years, 1039, 1774, and 122 participants developed vascular dementia, Alzheimer's disease, and frontotemporal dementia, respectively. Overall, habitual glucosamine use was significantly associated with a lower risk of incident vascular dementia (adjusted HR, 0.82; 95%CI, 0.70–0.96), but not significantly associated with incident Alzheimer's disease (adjusted HR, 1.02; 95%CI, 0.92–1.14) and incident frontotemporal dementia (adjusted HR, 0.95; 95%CI, 0.63–1.43). Moreover, the inverse association between habitual glucosamine use and incident vascular dementia was more pronounced in participants with concomitant supplement of calcium (*P*-interaction = 0.011), and those without concomitant supplement of zinc (*P*-interaction = 0.018). However, APOE ε4 dosage and baseline cognitive function did not significantly modify the relationships of glucosamine use with incident vascular dementia or Alzheimer's disease (All *P*-interactions > 0.05).

**Conclusions** Regardless of APOE genotypes and baseline cognitive function, habitual glucosamine use was significantly inversely associated with incident vascular dementia in the older population.

**Keywords** Glucosamine supplement, Vascular dementia, Alzheimer's disease, APOE genotypes

## Introduction

Glucosamine is sold as a prescription drug in most European countries. In other countries, including the USA, Australia, and the UK, approximately 20% of the population may choose to take glucosamine supplements instead of being prescribed by a healthcare professional [1–3].

In addition to the possible symptomatic benefits of glucosamine use on painful osteoarthritis [4–8], recent

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evidence suggests that glucosamine may modulate inflammation status [9–11], and may therefore be associated with improvements in a range of chronic metabolic disorders, particularly obesity, type 2 diabetes, and cardiovascular disease (CVD) [12, 13]. Furthermore, studies in animal models have linked the use of glucosamine with better cognitive function [14, 15]. A previous cross-sectional study in the UK also found that participants with glucosamine supplementation showed better cognitive performance [16]. Since inflammation, CVD, and impaired cognitive function are all closely related to dementia, especially vascular dementia, we speculate that glucosamine use may be associated with the reduction of dementia, especially vascular dementia. However, only a few studies [17, 18] have investigated the longitudinal association of habitual glucosamine use with incident dementia in the general population and have reported inconsistent results. In addition, despite older adults are at high risk for dementia, no studies have specifically examined the association of glucosamine use with dementia risk in older adults and explored the possible effect modifies on this association, particularly nutrients such as fish oil, minerals, and vitamins that are commonly used in older adults. More importantly, although Apolipoprotein E (APOE) gene polymorphic alleles are a major determinant for Alzheimer disease and play an important role in the risk of vascular dementia [19, 20], whether the APOE genotypes may modify the association glucosamine use and dementia risk has not been examined in the older population. At the same time, none of the previous studies have evaluated whether baseline cognitive function may modify the association between glucosamine use and the risk of dementia.

To address the aforementioned knowledge gaps, we aimed to evaluate the longitudinal association between habitual glucosamine supplement and the risk of cause-specific dementia, especially vascular dementia, and examine the possible effect modifiers on this association.

## Materials and methods

### Study population

The UK biobank is a large-scale, long-term prospective health research study designed to provide in-depth information on the effects of comprehensive exposures on a wide range of health conditions to further promote human health. The UK Biobank included 500,000 residents in the UK, aged between 40 and 69 years at the time of recruitment from 2006 to 2010. Participants were asked to complete a touch-screen questionnaire, a face-to-face nurse interview, and a series of physical measurements, as well as to provide biological samples for genotype and biomarker analysis. Details of the study design have been described in the official website (https://www.ukbiobank.ac.uk/) and previous studies [21]. The study protocol conforms to the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008, as reflected in the approval by the North West Multi-Center Research Ethics Committee (06/MRE08/65), and all participants were informed and gave written informed consent prior to the study.

Of the 502,461 participants in the UK Biobank, a total of 214,945 participants were included in the final analysis after excluding participants who withdrew data ($N=47$), had missing data on glucosamine use ($N=6194$), reported dementia at baseline ($N=587$), or were younger than 60 years of age at recruitment ($N=280{,}688$) (Supplementary Fig. 1).

### Exposure assessment

The information on habitual glucosamine use was collected from a touchscreen questionnaire. Each participant was asked, "Do you regularly take any of the following supplements?", and then could select more than one answer from a list of dietary supplements. Habitual glucosamine use was defined as: 1 = yes, 0 = no.

### Covariates assessment

The APOE genotypes were determined by a combination variant of rs429358 and rs7412 [22]. Based on the number of APOE Ɛ4 allele, participants were further divided into the high-risk group (APOE ε4 dosage = 2, ε4/ε4), medium-risk group (APOE ε4 dosage = 1, ε3/ε4), and low-risk group (APOE ε4 dosage = 0, ε2/ε2, ε2/ε3, ε3/ε3) [23] in this analysis.

Information on demographic, lifestyle factors drug use and nutrient supplementation was collected through a touchscreen questionnaire at baseline. The following covariates were included: age, sex, ethnicity, body mass index (BMI), education levels, household incomes, Townsend deprivation index, smoking status, alcohol consumption, physical activity, family history of dementia, self-reported diseases (diabetes, hypertension, arthritis, CVD), and use of drugs (antihypertensive drugs, lipid-lowering drugs, aspirin, non-aspirin non-steroidal anti-inflammatory drug [NSAID], insulin), dietary intakes (cereal, fish, fruit, red meat, vegetables), vitamin supplements (vitamin A, vitamin B, vitamin C, vitamin D, vitamin E, and folic acid), mineral and other supplements (calcium, selenium, iron, zinc and fish oil), and healthy diet scores. BMI was calculated by dividing weight (kg) by the square of standing height (m) for each participant. Optimal physical activity was defined as more than 4 days of vigorous/moderate physical activity in a typical week [24]. The healthy diet score consisted of following

dietary goals for ideal cardiovascular health [25, 26]: fruit intake ≥ 3 servings/day, vegetable intake ≥ 3 servings/day, whole grain intake ≥ 3 servings/day, fish intake ≥ 2 servings/day, dairy intake ≥ 2 servings/day, vegetable oil ≥ 2 servings/day, refined grain intake ≤ 2 servings/day, processed meat ≤ 1 serving/day, unprocessed meat ≤ 2 servings/day, and sugar-sweetened beverages intake = 0. If participants achieved one of 10 dietary goals, they will get one point. The range of healthy diet score is 0–10.

The cognitive tests were developed specifically for UK Biobank to enable large-scale computerized administration without staff involvement and are therefore non-standardized. The UK Biobank cognitive tests show a range of validity coefficients that coexist with well-validated standard tests of cognitive ability, and most of the tests tend to have moderate to good retest reliability [27]. Baseline cognitive function tests include verbal and numerical reasoning ('Reasoning'), processing speed ('Reaction Time'), attention/working memory ('Numeric Memory"), visuospatial memory ('Pairs Matching'), and prospective memory ('Prospective Memory') [28]. Except that prospective Memory is a binary variable, the raw scores for all tests were converted to *z*-scores for easy interpretation, and standardized within 5-year age bands [29]. Therefore, the average score is approximately zero and the standard deviation is approximately 1. The signs of the *z*-scores for Reaction Time and Pairs Matching were reversed, so a higher *z*-score for each cognitive function test represents a better performance. In addition, a composite measure of global cognitive function was then calculated by averaging the available z-scores for each participant [30].

### Ascertainment of study outcomes

The study outcome was incident vascular dementia, incident Alzheimer's disease, and incident frontotemporal dementia, respectively.

Incident vascular dementia, Alzheimer's disease, and frontotemporal dementia were ascertained from the International Classification of Disease version 10 (ICD-10), ICD-9 coding system. Vascular dementia was defined as ICD-9 codes 290.4, ICD-10 codes F01 and I67.3; Alzheimer's disease was defined as ICD-9 codes 331.0, ICD-10 codes F00 and G30; frontotemporal dementia was defined as ICD-9 codes 331.1, ICD-10 codes F02.0 and G31.0. The accuracy of dementia ascertainment has been validated previously [31, 32].

The follow-up for each participant was calculated from the date of the first assessment until the first diagnosis date of study outcome, date of death, date of loss to follow-up, or the end of follow-up, whichever came first (February 28, 2018, for Wales, March 31, 2021, for England and Scotland).

### Statistical analysis

Baseline characteristics of study participants were summarized and stratified by glucosamine use status at baseline. Continuous and categorical variables were presented as means (standard deviation: SD) and numbers (proportion), respectively. Differences between groups were determined by *t* tests and chi-square tests, accordingly.

Cox proportional hazard models were applied to calculate the hazard ratios (HRs) and 95% confidence intervals (95%CIs) for associations of glucosamine use with incident risk of vascular dementia, Alzheimer's disease, and frontotemporal dementia, respectively. The proportional hazards assumption was checked using Schoenfeld residuals, and no violation of this assumption was detected. Basic model was adjusted for age and sex (female or male). Model 1 included the adjustments for age, sex (female or male), ethnicity (white, others), centers, BMI, household incomes (< 18,000, 18,000–30,999, 31,000–51,999, 52,000–10,000, > 100,000 £/year), Townsend deprivation index, smoking status (never, former, current), alcohol consumption (daily or almost daily, 3–4 times a week, once or twice a week, 1–3 times a month, never or special occasions only), optimal physical activity (yes or no), family history of dementia (yes or no), APOE ε4 dosage (0,1,2), self-reported diabetes (yes or no), self-reported hypertension (yes or no), self-reported arthritis (yes or no), history of cardiovascular disease (yes or no), antihypertensive drugs (yes or no), lipid treatment (yes or no), aspirin use (yes or no), non-aspirin NSAID use (yes or no), and insulin treatment (yes or no). Model 2 included the adjustments for covariates in Model 1, plus several dietary factors, including cereal intake, fish intake, fruit intake, red meat intake, vegetable intake, vitamin supplements, mineral and fish oil supplements, and healthy diet score. For covariates with a missing rate > 5% (7.8% for optimal physical activity), we imputed mean values for continuous variables or created an additional category for categorical variables.

Furthermore, stratified analyses were performed to explore the potential modifying effects of APOE ε4 dosage, baseline cognitive function, and a range of covariates on the association of glucosamine use with risk of vascular dementia, Alzheimer's disease.

We conducted all analysis using R version 4.0.1. In all statistical tests, the two-sided *P* value < 0.05 was considered to be statistically significant.

## Results

### Baseline characteristics of study participants

Of the 214,945 participants included, the mean age was 64.1 (SD: 2.9) years, 113,476 (52.8%) participants were

**Table 1** Characteristics of the UK Biobank participants by glucosamine use

| Characteristics | Total<br>*N* = 214,945 | Glucosamine non-users<br>*N* = 162,052 | Glucosamine users<br>*N* = 52,893 | *P* value |
|---|---|---|---|---|
| Female, *n* (%) | 113,476 (52.8) | 80,613 (49.7) | 32,863 (62.1) | < 0.001 |
| Age, years | 64.1 (2.9) | 64.1 (2.9) | 64.2 (2.8) | < 0.001 |
| White race, *n* (%) | 207,923 (97.1) | 156,539 (97.0) | 51,384 (97.4) | < 0.001 |
| Household income, £ | | | | < 0.001 |
| < 18,000 | 59,429 (27.8) | 46,816 (29) | 12,613 (23.9) | |
| 18,000–30,999 | 56,958 (26.6) | 41,803 (25.9) | 15,155 (28.7) | |
| 31,000–51,999 | 36,426 (17.0) | 26,517 (16.5) | 9909 (18.8) | |
| 52,000–100,000 | 17,539 (8.2) | 13,040 (8.1) | 4499 (8.5) | |
| > 100 000 | 4182 (2.0) | 3177 (2.0) | 1005 (1.9) | |
| Townsend deprivation index | −1.6 (3.0) | −1.4 (3.0) | −2 (2.7) | < 0.001 |
| Body mass index, kg/m$^2$ | 27.6 (4.6) | 27.6 (4.6) | 27.4 (4.5) | < 0.001 |
| Optimal physical activity | 118,718 (59.9) | 87,525 (58.9) | 31,193 (63) | < 0.001 |
| Smoking status, *n* (%) | | | | < 0.001 |
| Never | 106,920 (49.7) | 79,245 (48.9) | 27,675 (52.3) | |
| Former | 89,309 (41.5) | 67,034 (41.4) | 22,275 (42.1) | |
| Current | 17,655 (8.2) | 14,924 (9.2) | 2731 (5.2) | |
| Alcohol consumption, *n* (%) | | | | < 0.001 |
| Daily or almost daily | 50,181 (23.3) | 36,951 (22.8) | 13,230 (25.0) | |
| 3–4 times a week | 47,371 (22) | 34,796 (21.5) | 12,575 (23.8) | |
| Once or twice a week | 51,283 (23.9) | 38,799 (23.9) | 12,484 (23.6) | |
| 1–3 times a month | 21,258 (9.9) | 16,118 (9.9) | 5140 (9.7) | |
| Never or special occasions only | 44,700 (20.8) | 35,256 (21.8) | 9444 (17.9) | |
| Healthy diet score | 3.2 (1.4) | 3.2 (1.4) | 3.4 (1.4) | < 0.001 |
| Family history of dementia, *n* (%) | 32,271 (15.0) | 23,823 (14.7) | 8448 (16.0) | < 0.001 |
| APOE ε4 dosage | | | | 0.290 |
| 0 | 151,036 (73.7) | 113,815 (73.7) | 37,221 (73.7) | |
| 1 | 49,098 (23.9) | 37,051 (24.0) | 12,047 (23.8) | |
| 2 | 4904 (2.4) | 3651 (2.4) | 1253 (2.5) | |
| Global cognitive function (z-score) | 0.00 (0.73) | −0.02 (0.74) | 0.04 (0.67) | < 0.001 |
| **Self-reported disease history, *n* (%)** | | | | |
| Diabetes | 15,076 (7.0) | 12,749 (7.9) | 2327 (4.4) | < 0.001 |
| Hypertension | 77,998 (36.3) | 61,097 (37.7) | 16,901 (32.0) | < 0.001 |
| Arthritis | 29,344 (13.7) | 17,813 (11.0) | 11,531 (21.8) | < 0.001 |
| History of cardiovascular disease | 27,694 (12.9) | 22,995 (14.2) | 4699 (8.9) | < 0.001 |
| **Drug use, *n* (%)** | | | | |
| Anti-hypertensive | 68,098 (31.9) | 53,976 (33.5) | 14,122 (26.8) | < 0.001 |
| Lowering cholesterol | 59,983 (28.1) | 47,578 (29.5) | 12,405 (23.5) | < 0.001 |
| Insulin treatment | 2955 (1.4) | 2541 (1.6) | 414 (0.8) | < 0.001 |
| Aspirin | 45,315 (21.3) | 35,662 (22.3) | 9653 (18.4) | < 0.001 |
| Non-aspirin NSAID | 22,514 (10.6) | 14,571 (9.1) | 7943 (15.1) | < 0.001 |
| **Supplement use, *n* (%)** | | | | |
| Vitamin | 36,008 (16.8) | 22,521 (14) | 13,487 (25.6) | < 0.001 |
| Mineral and fish oil | 96,999 (45.1) | 59,005 (36.4) | 37,994 (71.8) | < 0.001 |

Variables are presented as mean (SD) or *n* (%)

*NASID* non-steroidal anti-inflammatory drug

female, and 52,893 (24.6%) participants were habitual glucosamine users.

The characteristics of the participants by using glucosamine supplement or not are showed in Table 1. Compared with glucosamine non-users, habitual glucosamine users were older, more likely to be female and non-smokers, and less likely to take anti-hypertensive, lowering cholesterol drugs, insulin treatment, and aspirin; had higher physical activity levels and lower levels of deprivation; consumed more alcohol and a healthier diet; and tended to take non-aspirin NSAID and supplements of vitamins, minerals, and fish oil. Moreover, glucosamine users had higher prevalence of family history of dementia and self-reported arthritis, and lower prevalence of diabetes, hypertension, and CVD (Table 1).

### Associations of glucosamine use with risk of incident cause-specific dementia

During a median follow-up duration of 12 years, 1039, 1774, and 122 participants developed incident vascular dementia, Alzheimer's disease cases, and frontotemporal dementia, respectively.

Overall, habitual glucosamine use was significantly associated with a lower risk of incident vascular dementia (adjusted HR, 0.83; 95% CI, 0.70–0.97), but not significantly associated with the risk of incident Alzheimer's disease (adjusted HR, 1.00; 95% CI, 0.89–1.11) and incident frontotemporal dementia (adjusted HR, 1.20; 95% CI, 0.78–1.85) (Table 2).

Excluding participants with follow-up duration of less than 5 years (Supplementary table 1, Sensitivity analysis 1), or including baseline cognitive function scores in the adjustment (Supplementary table 1, Sensitivity analysis 2), did not materially alter the findings.

### Stratified analyses

Stratified analyses were performed to assess the possible modifying factors on the association of glucosamine use with incident vascular dementia and incident Alzheimer's disease (Figs. 1 and 2, and Supplementary Fig. 2).

A significantly stronger inverse association between glucosamine use and incident vascular dementia was found in participants with concomitant supplement of calcium (yes, adjusted HR, 0.46; 95% CI, 0.28–0.75; *vs.* no, adjusted HR, 0.87; 95% CI, 0.74–1.03; *P* for interaction = 0.011), and those without concomitant supplement of zinc (no, adjusted HR, 0.79; 95% CI, 0.67–0.93; *vs.* yes, adjusted HR, 1.74; 95% CI, 0.91–3.31; *P* for

**Table 2** Associations of glucosamine use with incident cause-specific dementia

| Categories of dementia | Glucosamine non-users<br>*N* = 162,052 | Glucosamine users<br>*N* = 52,893 | *P* value |
|---|---|---|---|
| **Vascular dementia** | | | |
| No. of case | 1039 | 229 | - |
| Person-years | 1,853,990 | 613,980 | - |
| Age- and sex-adjusted model | 1 [Reference] | 0.68 (0.59, 0.78) | < 0.001 |
| Model 1 | 1 [Reference] | 0.82 (0.70, 0.96) | 0.014 |
| Model 2 | 1 [Reference] | 0.83 (0.70, 0.97) | 0.023 |
| **Alzheimer's disease** | | | |
| No. of case (%) | 1774 | 581 | |
| Person-years | 1,852,132 | 613,119 | |
| Age- and sex-adjusted model | 1 [Reference] | 0.97 (0.88, 1.07) | 0.553 |
| Model 1 | 1 [Reference] | 1.02 (0.92, 1.14) | 0.648 |
| Model 2 | 1 [Reference] | 1.00 (0.89, 1.11) | 0.929 |
| **Frontotemporal dementia** | | | |
| No. of case (%) | 122 | 32 | - |
| Person-years | 1,855,706 | 614,363 | - |
| Age- and sex-adjusted model | 1 [Reference] | 0.83 (0.56, 1.23) | 0.348 |
| Model 1 | 1 [Reference] | 0.95 (0.63, 1.43) | 0.804 |
| Model 2 | 1 [Reference] | 1.20 (0.78, 1.85) | 0.401 |

Model 1: adjusted for age, sex (female or male), ethnicity (white, others), centers, body mass index, household income (< 18,000, 18,000–30,999, 31,000–51,999, 52,000–10,000, > 100,000 £/yr), Townsend deprivation index, smoking status (never, former, current), alcohol consumption (daily or almost daily, 3–4 times a week, once or twice a week, 1–3 times a month, never or special occasions only), optimal physical activity (yes or no), family history of dementia (yes or no), APOE ε4 dosage (0, 1, 2), self-reported diabetes (yes or no), self-reported hypertension (yes or no), self-reported arthritis (yes or no), history of cardiovascular disease (yes or no), antihypertensive drugs (yes or no), lipid treatment (yes or no), aspirin use (yes or no), non-aspirin NSAID use (yes or no), insulin treatment (yes or no)

Model 2: covariates in Model 1 plus cereal intake, fish intake, fruit intake, red meat intake, vegetable intake, vitamin supplements, mineral and other supplements, healthy diet score

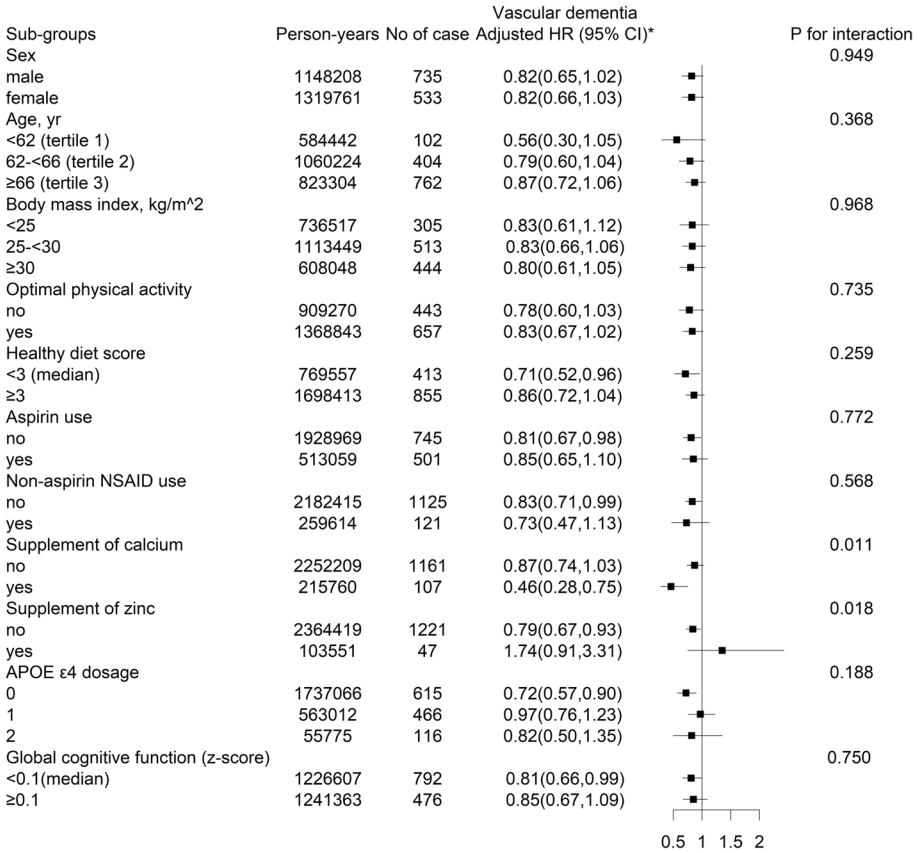


**Fig. 1** Stratified analyses of the association between glucosamine use and incident vascular dementia. *Adjusted for age, sex (female or male), ethnicity (white, others), centers, body mass index, household income (< 18,000, 18,000–30,999, 31,000–51,999, 52,000–10,000, > 100,000 £/yr), Townsend deprivation index, smoking status (never, former, current), alcohol consumption (daily or almost daily, 3–4 times a week, once or twice a week, 1–3 times a month, never or special occasions only), optimal physical activity (yes or no), family history of dementia (yes or no), APOE ε4 dosage (0, 1, 2), self-reported diabetes (yes or no), self-reported hypertension (yes or no), self-reported arthritis (yes or no), history of cardiovascular disease (yes or no), antihypertensive drugs (yes or no), lipid treatment (yes or no), aspirin use (yes or no), non-aspirin NSAID use (yes or no), and insulin treatment (yes or no)

interaction = 0.018). Moreover, supplement of calcium and zinc did not significantly modify the association between glucosamine use and incident Alzheimer's disease (both *P* for interactions ≥ 0.05) (Figs. 1 and 2, Supplementary Fig. 2).

As expected, APOE Ɛ4 dosage was significantly and positively associated with the risk of incident vascular dementia (2 *vs.* 0; adjusted HR: 5.81; 95%CI: 4.72, 7.15), and incident Alzheimer's disease (2 *vs.* 0; adjusted HR: 12.05; 95%CI: 10.54, 13.77) (Supplementary Table 2). However, APOE ε4 dosage did not show significant modifying effects on the relationship of glucosamine use with incident vascular dementia (*P* for interaction = 0.188) and Alzheimer's disease (*P* for interaction = 0.375). Other variables, including cognitive function, sex, age, BMI, physical activity, healthy diet score, self-reported arthritis, aspirin use, non-aspirin NSAID use, diabetes, hypertension, history of CVD, supplement of vitamin A, vitamin B, vitamin C, vitamin D, vitamin E, folate, selenium, iron, and fish oil, also did not significantly modify the associations of glucosamine use with risks of incident vascular dementia or Alzheimer's disease associations (all *P* for interactions > 0.05) (Figs. 1 and 2, Supplementary Fig. 2).

## Discussion

Our study showed that in the older population, habitual supplement of glucosamine was significantly associated with a lower risk of incident vascular dementia, but not significantly associated with the risk of incident Alzheimer's disease and frontotemporal dementia. APOE genetic variations and baseline cognitive function did not significantly modify this association.

A few studies [17, 18] have investigated the longitudinal association of habitual glucosamine use with incident dementia in the general population and have reported inconsistent results. Ai et al. [17] found that habitual

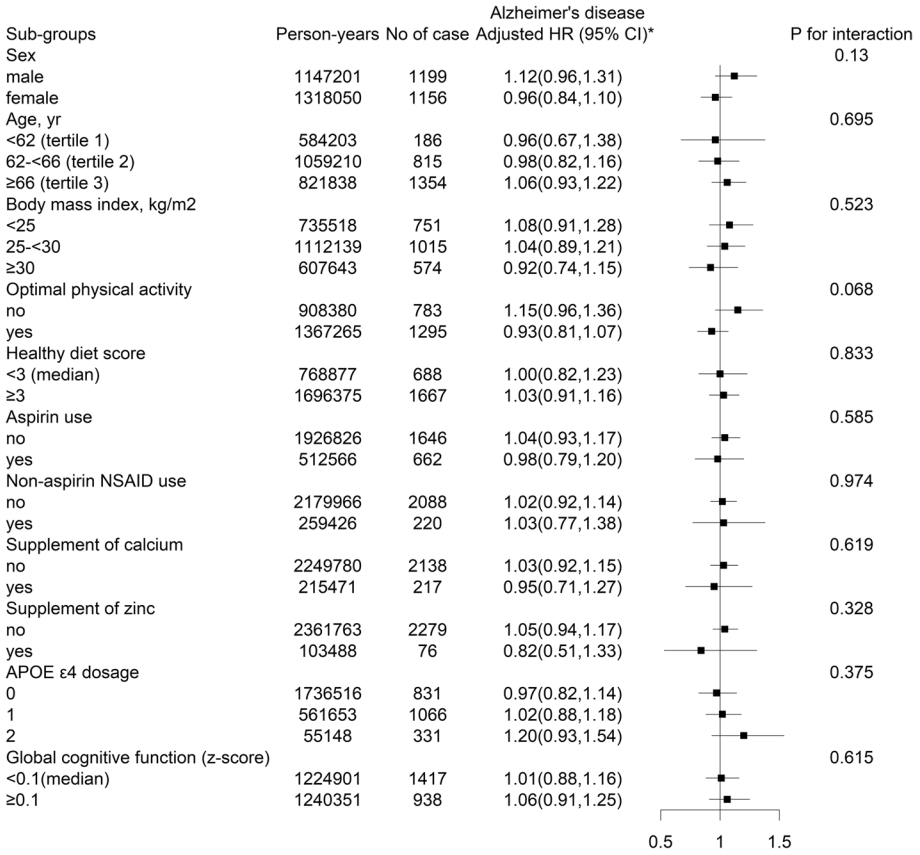


**Fig. 2** Stratified analyses of the association between glucosamine use and incident Alzheimer's disease. *Adjusted for age, sex (female or male), ethnicity (white, others), centers, body mass index, household income (< 18,000, 18,000–30,999, 31,000–51,999, 52,000–10,000, > 100,000 £/yr), Townsend deprivation index, smoking status (never, former, current), alcohol consumption (daily or almost daily, 3–4 times a week, once or twice a week, 1–3 times a month, never or special occasions only), optimal physical activity (yes or no), family history of dementia (yes or no), APOE ε4 dosage (0, 1, 2), self-reported diabetes (yes or no), self-reported hypertension (yes or no), self-reported arthritis (yes or no), history of cardiovascular disease (yes or no), antihypertensive drugs (yes or no), lipid treatment (yes or no), aspirin use (yes or no), non-aspirin NSAID use (yes or no), and insulin treatment (yes or no)

supplementation of glucosamine was not associated with incident all-cause dementia in approximately 290,000 middle- to old-aged participants during a median follow-up of 9.1 years. However, Zheng et al. [18] showed that glucosamine use was associated with a lower risk of all-cause dementia, Alzheimer's disease, and vascular dementia in approximately 490,000 middle- to old-aged participants over a median follow-up of 8.9 years. Of note, none of the previous studies have examined the association between glucosamine use and incident frontotemporal dementia. Moreover, although the high risk of dementia in older adults, no studies have specifically investigated the association between glucosamine use and incident dementia in the older population and fully explored the possible effect modifications on this association, particularly with regard to fish oil, minerals, and vitamins that are commonly used by older adults, and baseline cognitive function. Our current study, which has the longest follow-up duration compared to previous studies [17, 18], addresses the above knowledge gaps in time in the older population, by adjusting for a range of important confounding factors, and taking into account the modifying effect of baseline cognitive function and use of fish oil and a series of minerals and vitamins.

Our study provides some new insights. Firstly, in the older population, there was a significant inverse association of glucosamine use with incident vascular dementia. However, glucosamine use was not significantly associated with incident Alzheimer's disease and frontotemporal dementia. Previous studies have found that glucosamine supplementation was associated with a reduced risk of CVD [5] and type 2 diabetes [13], both of which are associated with an increased risk of dementia, particularly vascular dementia [33, 34]. In addition, a previous randomized trial, including 38 subjects diagnosed with knee osteoarthritis, showed that glucosamine sulfate

supplements could modulate the metabolic and immune activity of the gastrointestinal microbiota [35], thereby affecting the risk of neurodegenerative diseases [36]. All of these results suggest a possible beneficial effect of glucosamine on dementia.

The underlying mechanism for the benefit of glucosamine supplementation in vascular dementia is uncertain, but biologically plausible. First, glucosamine use may provide an anti-inflammation effect by interfering with nuclear factor-κB activity [9], therefore reducing angiogenesis and remodeling [37]. Second, glucosamine treatment could relieve inflammatory atherosclerosis at the femoral wall and aortic [38]. These beneficial effects of glucosamine supplement on vascular functions may play an important in the prevention of vascular dementia [39]. Of note, our data indicate a significant inverse association between glucosamine use and vascular dementia only, not Alzheimer's disease and frontotemporal dementia, in the older population. It could be that different types of dementia have different mechanisms. For example, although vascular dementia is closely related to the biological processes of Alzheimer's disease [40], vascular dementia is primarily due to vascular lesions [41], while the primary cause of Alzheimer's disease is β amyloid deposition [42]. Glucosamine may have a stronger effect on vascular damage and thus a stronger association with vascular dementia. In addition, the hippocampus gradually shrinks and cortical density decreases in the elderly, which leads to a decrease in cell membrane receptors of brain cells, thus weakening the effect of glucosamine on Alzheimer's disease and frontotemporal dementia.

Secondly, a stronger inverse association between glucosamine use and risk of vascular dementia among those with concomitant supplement of calcium, or those without concomitant supplement of zinc. A recent study in Sweden found that those who received calcium supplementation had a more than threefold risk of developing vascular dementia compared to those who did not [43]. Therefore, participants with concomitant use of calcium may have benefited more from the anti-inflammatory and vascular protective effects of glucosamine use. However, a Mendelian randomization study found that increased serum calcium levels were associated with a reduced risk of Alzheimer's disease [44]. Therefore, more research is needed to confirm our findings and further examine the underlying mechanisms. At the same time, zinc is an essential mineral nutrient that is involved in many important biological processes, including maintaining insulin homeostasis, influencing inflammatory responses [45], and playing key structural roles in thousands of proteins [46]. A recent study has reported that zinc intake was inversely associated with the prevalence of low cognitive performance [47]. We speculate that zinc and glucosamine may share some of the mechanisms that are beneficial to dementia risk, thus diminishing the beneficial effects of glucosamine. However, it must be noted that interactions of calcium supplement or zinc supplement and glucosamine use on incident vascular dementia became non-significant after the Bonferroni correction. As such, due to the chance given multiple testing, our results are just hypotheses, and the clinical implication of these interactions needs to be evaluated with more studies.

Our study has several limitations. First, the UK Biobank did not collect more specific information on glucosamine use, including form, dose, frequency, duration, etc. Moreover, the information on supplement use in the UK Biobank was available at one time point; more frequent assessments could provide more accurate results. Second, although a broad range of covariates were included in the adjustments, possible confounding from other unknown or unmeasured factors could not be excluded. Third, the causation cannot be determined through the observational design in this analysis. Fourth, previous studies have reported different positive predictive values (PPV) for different types of dementia [31, 32], with vascular dementia and frontotemporal dementia in particular having relatively low PPV, which could lead to potential misclassification bias. In addition, dementia cases may have been underestimated due to the ascertainment based on ICD9/10 codes, leading to an underestimation of the true effect size. Fifth, the present study was conducted in UK older people with special socioeconomic status and overall health status, and 97% of the participants were white race [48]; whether the observed results can be extrapolated to other populations will need further investigation.

In summary, our study showed that habitual glucosamine use was significantly associated with a lower risk of incident vascular dementia in the older population, regardless of APOE genotypes and cognitive function. If further confirmed, habitual glucosamine use may act as a dietary supplement for primary prevention of vascular dementia in the elderly.

**Abbreviations**

| | |
|---|---|
| APOE | Apolipoprotein E |
| BMI | Body mass index |
| CVD | Cardiovascular disease |
| HR | Hazard ratio |
| NSAID | Non-steroidal anti-inflammatory drug |
| PPV | Positive predictive values |
| SD | Standard deviation |
| 95%CI | 95% Confidence interval |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13195-023-01295-6.

**Additional file 1: Supplementary figure 1.** Flow chart of the study participants. **Supplementary figure 2.** Stratified analyses of the association between glucosamine use and incident vascular dementia (A), incident Alzheimer's disease (B) in other subgroups. **Supplementary table 1.** Sensitivity analysis for associations of glucosamine use with incident cause-specific dementia*. **Supplementary table 2.** Associations between APOE ε4 dosage and incident vascular dementia, incident Alzheimer's disease*.

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**Authors' contributions**
Chun Zhou and Xianhui Qin designed the research; Chun Zhou, Ziliang Ye and Xianhui Qin conducted the research; Chun Zhou, Yanjun Zhang, Ziliang Ye performed the data management and statistical analyses; Chun Zhou and Xianhui Qin wrote the draft; All authors revised and approved the final manuscript.

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**Availability of data and materials**
Data, analytic methods, and study materials that support the findings of this study will be available from the corresponding authors on request.

## Declarations

**Ethics approval and consent to participate**
The study protocol conforms to the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008, as reflected in the approval by the North West Multi-Center Research Ethics Committee (06/MRE08/65), and all participants were informed and gave written informed consent prior to the study.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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## Publisher's Note