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Original Article

# Association between L-α glycerylphosphorylcholine use and delayed dementia conversion: A nationwide longitudinal study in South Korea

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ABSTRACT

*Background:* Alzheimer's disease and vascular dementia are two of the most common causes of dementia. While early diagnosis and intervention are crucial, available treatments and research concerning the mild cognitive impairment stage remain limited. This study aimed to evaluate the real-world effectiveness and safety of L-α glycerylphosphorylcholine in this context.
*Objectives:* To investigate the impact of L-α glycerylphosphorylcholine on the risk of conversion from mild cognitive impairment to Alzheimer's disease dementia and vascular dementia, as well as its influence on stroke risk
*Design:* A nationwide, population-based cohort study
*Setting:* Data from South Korea's National Health Insurance Service
*Participants:* Overall, 508,107 patients newly diagnosed with mild cognitive impairment between 2013 and 2016 were included.
*Intervention:* Patients were classified as users or non-users of L-α glycerylphosphorylcholine based on prescription records.
*Measurements:* The primary outcomes were the risk of progression to Alzheimer's disease dementia and vascular dementia. Stroke risk was examined as a secondary outcome. A time-dependent Cox regression analysis was used to adjust for demographic and clinical factors.
*Results:* Compared to non-users, L-α glycerylphosphorylcholine users had a lower risk of progression to Alzheimer's disease dementia (hazard ratio = 0.899, 95 % confidence interval: 0.882–0.918) and vascular dementia (hazard ratio = 0.832, 95 % confidence interval: 0.801–0.865) within 2,435,924 and 662,281.6 person-years, respectively. In patients under 65, L-α glycerylphosphorylcholine significantly reduced the risk of progression to Alzheimer's and vascular dementia. Stroke risk significantly decreased in patients who did not progress to dementia but not in those who did.
*Conclusions:* L-α Glycerylphosphorylcholine reduces dementia conversion and stroke risk in patients with mild cognitive impairment, making it a viable early intervention. Future large-scale randomized controlled studies should examine its effects on other dementia subtypes and long-term cognitive outcomes.

## 1. Background

Alzheimer's disease (AD) is the most common cause of dementia, accounting for over 50 % of dementia cases, followed by vascular dementia (VaD) [1,2]. Once dementia progresses, altering its course becomes challenging, making early diagnosis and intervention before the mild cognitive impairment (MCI) stage critical. While there are various management guidelines for cognitive impairment, acetylcholine esterase inhibitors (AchEIs) and *N*-methyl-*D*-aspartic acid receptor antagonist comprise the standard treatments for AD. However, except for anti-amyloid

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therapies for amyloid-positive MCI due to AD, there are currently no United States Food and Drug Administration (FDA)-approved medications available for MCI.

In some countries, L-α glycerylphosphorylcholine (α-GPC, choline alfoscerate), *Gingko biloba* (EGb71), and nicergoline are used [3]. α-GPC is a choline precursor widely prescribed or taken without a prescription by many patients with MCI [4]. The mechanism of this drug is based on the cholinergic hypothesis. In patients with AD and VaD, neurodegeneration leads to reduced acetylcholine secretion from the cholinergic neurons in the basal forebrain [5,6]. α-GPC, similar to AchEIs, helps preserve cognitive function by counteracting reduced acetylcholine secretion [7]. Additionally, α-GPC has been shown to increase free choline in the body, cross the blood-brain barrier, and boost acetylcholine production [8–10].

However, although some clinical trials have demonstrated cognitive improvement benefits [11–13], large-scale studies are lacking. Thus, α-GPC is not currently included in treatment guidelines for MCI. Additionally, the risk of concurrent ischemic or hemorrhagic stroke in the general population requires further investigation to clarify the effective indication of this medication. Unlike in other countries, α-GPC is classified as an ethical drug in South Korea, which optimizes the ability to track its usage for research. Therefore, this study aimed to assess the real-world efficacy and safety of α-GPC in patients with MCI. We longitudinally evaluated patients diagnosed with MCI between 2013 and 2016 to determine whether α-GPC use prevented conversion to dementia and increased stroke risk.

## 2. Methods

### 2.1. Study design and data source

This nationwide, population-based cohort study utilized data from the National Health Insurance Service (NHIS) database. Briefly, the Korean NHIS is a mandatory insurance system in the Republic of Korea that covers 97 % of the Korean population through national health insurance and provides medical aid to the remaining 3 % at the lowest income level. The NHIS database includes all medical claims covered by these insurance and aid programs, thus providing comprehensive medical utilization information. The database contains demographic records; date of death; and healthcare utilization data such as diagnostic codes, prescription records, medical procedures, treatments, and costs. Data from January 2012 to December 2021 were used for the analysis, focusing on patients with MCI who were identified between January 2013 and December 2016.

### 2.2. Standard protocol approvals, registrations, and patient consents

The study protocol was approved by the institutional review board of Wonju Severance Christian Hospital (CR321308). The requirement for informed consent was waived due to the secondary analytical study design and the use of de-identified participant data.

### 2.3. Study population

Patients newly diagnosed with MCI between January 1, 2013, and December 31, 2016, were included. MCI was identified using the International Classification of Disease 10th revision (ICD-10) code F067. The exclusion criteria were: [1] MCI diagnosis in 2012, [2] history of dementia (ICD-10 codes F00–F03, G30–G31) before MCI diagnosis, [3] age <40 years, and [4] dementia diagnosis within 1 year of MCI diagnosis. Additional information on the cohort selection process is provided in Supplementary Figure 1.

### 2.4. Assessment of α-GPC use

α-GPC use was evaluated by extracting information from the NHIS database using α-GPC prescription codes (Additional file 2). Participants were categorized into user and non-user groups based on their α-GPC prescription history. The user group included participants who had been prescribed α-GPC at least once after their MCI diagnosis, whereas the non-user group comprised individuals who had never been prescribed α-GPC during the study period.

### 2.5. Covariates

Covariates included age at MCI diagnosis, sex, income level, and several chronic conditions: hypertension, diabetes mellitus, dyslipidemia, heart failure, chronic kidney disease (CKD), cancer, and chronic obstructive pulmonary disease (COPD). Age was recorded at the time of MCI diagnosis. Income levels were classified into three groups using health insurance data divided into 20 percentiles. Hypertension and diabetes mellitus were identified by the presence of diagnostic codes during at least one hospital admission or two outpatient visits (hypertension: I10–I13, I15; diabetes mellitus: E11–E14). Dyslipidemia, heart failure, CKD, and cancer were defined according to the presence of their respective disease codes during at least one hospital admission or outpatient department visit (dyslipidemia: E78; heart failure: I50; CKD: N18; cancer: C00–C97; and rare intractable disease: V193). COPD was identified using the codes J41–J44 during at least one hospital admission. Each of the seven chronic conditions (hypertension, diabetes mellitus, dyslipidemia, heart failure, CKD, cancer, and COPD) was coded as 1 if diagnosed within 1 year before MCI diagnosis; otherwise, it was coded as 0.

Among the entire participants, those with available national health checkup data were assessed for smoking, drinking, and physical activity. Smoking status was defined as being a current smoker. Drinking was defined as consuming alcohol at least once per week. Physical activity was defined as engaging in high-intensity exercise for at least 20 min on three or more days per week or moderate-intensity exercise for at least 20 min on five or more days per week.

### 2.6. Outcomes

The primary outcomes were the incidence of dementia, categorized as AD dementia and VaD. AD dementia was defined by the presence of disease codes F00 or G30, along with a prescription history for dementia medications such as rivastigmine, galantamine, donepezil, or memantine. VaD was defined by the presence of the disease code F01. The study population was followed from MCI diagnosis until the occurrence of dementia, death, or the end of the study period (December 31, 2021), whichever came first. The secondary outcome measures were ischemic stroke and hemorrhagic stroke. Ischemic stroke and hemorrhagic stroke were defined according to the presence of the disease codes I61 and I63, respectively, during at least two hospital admissions.

### 2.7. Statistical analysis

Population characteristics were analyzed using independent *t*-tests for continuous variables and chi-square tests with Yates' continuity correction for categorical variables. Since the proportional hazard assumption was not met, a time-dependent Cox regression was performed, treating α-GPC as a time-dependent variable. This analysis examined the association between α-GPC use and dementia incidence among MCI patients, adjusting for covariates such as sex, age, income level, hypertension, diabetes mellitus, dyslipidemia, heart failure, CKD, cancer, and COPD. Survival time was defined as the period from MCI diagnosis to the occurrence of dementia, death, or the end of the study period (December 31, 2021), whichever came first. Additionally, the relationship between α-GPC use and the incidence of ischemic stroke and hemorrhagic stroke was also examined. Propensity scores were estimated using logistic regression, considering covariates such as age, sex, income level, hypertension, diabetes mellitus, dyslipidemia, heart failure, CKD, cancer, COPD, smoking, alcohol, and physical activity. 1:1 propensity

**Table 1**
Baseline patient characteristics.

| | Total MCI | | Non-user group | | User group | | *P* value* |
|---|---|---|---|---|---|---|---|
| | No. | (%) | No. | (%) | No. | (%) | |
| Total | 508,107 | | 114,778 | (22.59) | 393,329 | (77.41) | |
| Age (years), mean (SD) | 67.61 | (10.71) | 66.87 | (11.92) | 67.83 | (10.32) | <0.0001 |
| Age groups (years) | | | | | | | <0.0001 |
| 40–49 | 27,082 | (5.33) | 9827 | (8.56) | 17,255 | (4.39) | |
| 50–59 | 95,571 | (18.81) | 23,580 | (20.54) | 71,991 | (18.30) | |
| 60–69 | 149,482 | (29.42) | 29,925 | (26.07) | 119,557 | (30.40) | |
| 70–79 | 169,160 | (33.29) | 34,098 | (29.71) | 135,062 | (34.34) | |
| ≥80 | 66,812 | (13.15) | 17,348 | (15.11) | 49,464 | (12.58) | |
| Sex | | | | | | | <0.0001 |
| Male | 168,903 | (33.24) | 44,337 | (38.63) | 124,566 | (31.67) | |
| Female | 339,204 | (66.76) | 70,441 | (61.37) | 268,763 | (68.33) | |
| Income | | | | | | | <0.0001 |
| Low | 130,638 | (25.71) | 28,683 | (24.99) | 101,955 | (25.92) | |
| Middle | 290,883 | (57.25) | 66,189 | (57.67) | 224,694 | (57.13) | |
| High | 86,586 | (17.04) | 19,906 | (17.34) | 66,680 | (16.95) | |
| Hypertension | 268,663 | (52.88) | 57,162 | (49.80) | 211,501 | (53.77) | <0.0001 |
| DM | 133,830 | (26.34) | 29,421 | (25.63) | 104,409 | (26.54) | <0.0001 |
| Dyslipidemia | 265,073 | (52.17) | 54,838 | (47.78) | 210,235 | (53.45) | <0.0001 |
| Heart failure | 22,335 | (4.40) | 5692 | (4.96) | 16,643 | (4.23) | <0.0001 |
| CKD | 8303 | (1.63) | 2733 | (2.38) | 5570 | (1.42) | <0.0001 |
| Cancer | 21,933 | (4.32) | 6369 | (5.55) | 15,564 | (3.96) | <0.0001 |
| COPD | 8463 | (1.67) | 2916 | (2.54) | 5547 | (1.41) | <0.0001 |

* Chi-square test with the Yates continuity correction.*Abbreviations*: MCI, mild cognitive impairment; DM, diabetes mellitus; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

score matching (PSM) was conducted to pair α-GPC users with non-users. Stratified Cox proportional hazards model was performed to evaluated the incidence of dementia and stroke from MCI diagnosis. All statistical analyses were performed using the SAS software version 9.4 (SAS Institute, Cary, North Carolina). A *P* value of <0.05 was considered statistically significant.

## 3. Results

### 3.1. Baseline characteristics of the study population

A total of 508,107 patients with MCI were included in the analysis, of whom 393,329 (77.41 %) used α-GPC. Table 1 summarizes the baseline demographics and clinical characteristics. The mean age in the user group was higher at 67.83 years. The proportion of females was greater in both the overall population and the user group, at 66.76 % and 68.33 %, respectively. Hypertension, diabetes mellitus, and dyslipidemia were more prevalent in the user group, while heart failure, CKD, cancer, and COPD were more common in the non-user group. Among participants with available data on smoking, drinking, and physical activity, the proportion of smokers was higher in the user group (Supplementary Table 1).

### 3.2. Dementia conversion risk

Conversion to AD dementia and VaD occurred in 8656 (7.54 %) and 2688 (2.34 %) non-users, respectively, within a follow-up of 3098,205.6 person-years. Among users, MCI converted to AD dementia and VaD in 30,662 (7.80 %) and 7982 (2.03 %) patients, respectively. In time-dependent Cox analysis, α-GPC users had a lower risk of conversion to AD dementia (hazard ratio [HR] = 0.899, 95 % confidence interval [CI]: 0.882–0.918) and to VaD (HR = 0.832, 95 % CI: 0.801–0.865), adjusting for age, sex, and chronic diseases (Table 2). Even among participants analyzed through 1:1 PSM considering age, sex, income level, chronic diseases, smoking, drinking, and physical activity, α-GPC users exhibited a lower risk of AD dementia (HR = 0.938, 95 % CI: 0.896–0.981) and VaD (HR = 0.767, 95 % CI: 0.708–0.830; Supplementary Table 2).

### 3.3. Subgroup analysis of dementia conversion risk

To identify factors influencing the risk of dementia conversion, differences in the time-dependent Cox model between subgroups were analyzed. In younger patients (<65 years) and older patients (≥65 years), α-GPC users had a lower risk of AD dementia conversion (HR = 0.779, 95 % CI: 0.729–0.834 and HR = 0.901, 95 % CI: 0.882–0.920, respectively; P for interaction <0.0001). In patients with heart failure, CKD, cancer, and COPD, α-GPC use did not affect the AD dementia conversion rate. However, among patients with other comorbidities, α-GPC use substantially reduced the risk of AD dementia conversion (Fig. 1). The risk of VaD conversion was also lower in younger (<65 years) and older (≥65 years) patients (HR = 0.713, 95 % CI: 0.660–0.770 and HR = 0.873, 95 % CI: 0.835–0.912, respectively; *P* for interaction<0.0001). In males and in females, α-GPC users had a lower risk of VaD conversion (HR = 0.784, 95 % CI: 0.737–0.834 and HR = 0.865, 95 % CI: 0.824–0.908, respectively; *P* for interaction = 0.0443). In patients with heart failure, CKD, and cancer, α-GPC use did not influence VaD conversion. However, in all patients with other comorbidities, α-GPC substantially reduced the risk of VaD conversion (Fig. 2).

To explore age-related differences in dementia conversion risk, we reanalyzed AD dementia and VaD risk in younger and older subgroups. α-GPC use reduced AD dementia conversion risk in the younger subgroup. The risk of AD dementia conversion was lower in those with dyslipidemia and in those without dyslipidemia (HR = 0.870, 95 % CI: 0.792–0.955 and HR = 0.646, 95 % CI: 0.586–0.712, respectively; P for interaction <0.0001). Additionally, VaD conversion risk was lower in those without cancer (HR = 0.695, 95 % CI: 0.643–0.752), while in those with cancer, the risk was not significant (HR = 1.100, 95 % CI: 0.704–1.717; P for interaction = 0.0387). In the older subgroup, there were no covariates causing differences (Supplementary Table 3 and 4).

### 3.4. Stroke risk

In the overall study population, α-GPC consumption was associated with a lower risk of both ischemic stroke (HR = 0.833, 95 % CI: 0.794–0.874) and hemorrhagic stroke (HR = 0.847, 95 % CI: 0.831–0.863). However, in patients whose MCI converted to AD dementia or VaD, α-GPC consumption was not significantly associated with stroke risk.

**Table 2**
Comparison of risk of Alzheimer's disease dementia and vascular dementia between α-GPC users and non-users.

| | Total | Event | | IR | Crude | | | Model 1 | | | Model 2 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. | No. | (%) | | HR | 95 % CI | | HR | 95 % CI | | HR | 95 % CI | |
| Alzheimer's disease dementia | | | | | | | | | | | | | |
| Non-user | 114,778 | 8656 | (7.54) | 12.89 | 1 | | | 1 | | | 1 | | |
| User | 393,329 | 30,662 | (7.80) | 12.45 | 0.889 | 0.871 | 0.907 | 0.897 | 0.879 | 0.915 | 0.899 | 0.882 | 0.918 |
| Vascular dementia | | | | | | | | | | | | | |
| Non-user | 114,778 | 2688 | (2.34) | 3.90 | 1 | | | 1 | | | 1 | | |
| User | 393,329 | 7982 | (2.04) | 3.17 | 0.833 | 0.802 | 0.866 | 0.841 | 0.809 | 0.874 | 0.832 | 0.801 | 0.865 |

Model 1 is adjusted for age and sex. Model 2 is adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, heart failure, chronic kidney disease, cancer, and chronic obstructive pulmonary disease.

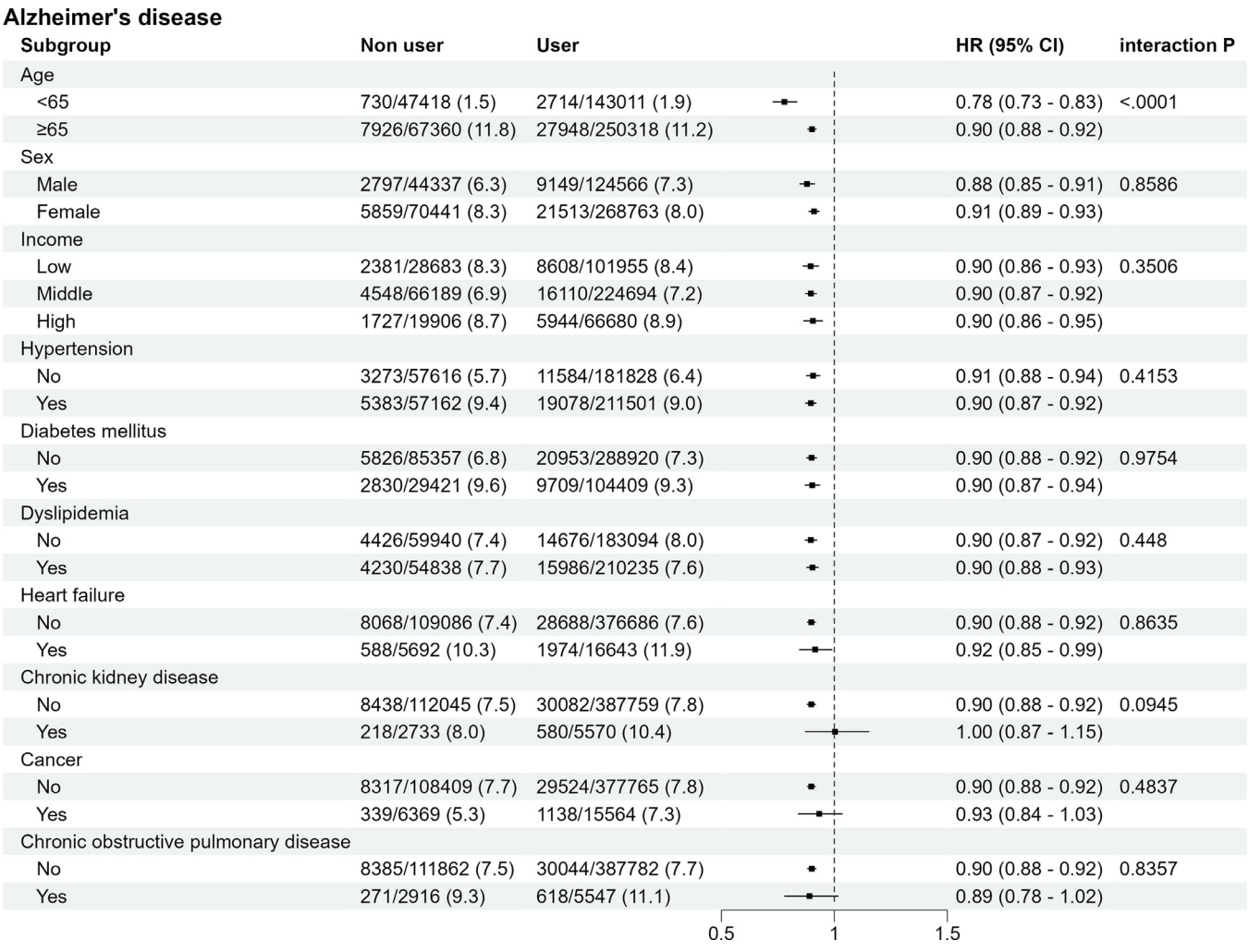


**Fig. 1.** Time-dependent Cox model.
This figure shows the time-dependent Cox model for conversion to Alzheimer's disease dementia in the subgroup analysis.

In contrast, in patients whose MCI did not convert to AD dementia or VaD, α-GPC consumption significantly reduced the risk of both ischemic stroke (HR = 0.813, 95 % CI: 0.771–0.859) and hemorrhagic stroke (HR = 0.837, 95 % CI: 0.819–0.856; Table 3). However, in the 1:1 PSM analysis considering age, sex, income level, chronic diseases, smoking, drinking, and physical activity, no significant differences were observed for both ischemic and hemorrhagic stroke (Supplementary Table 5).

## 4. Discussion

The usefulness of α-GPC in improving cognitive impairment has not been firmly established. In this study, α-GPC users exhibited a substantially lower risk of developing both AD dementia and VaD. Subgroup analysis showed that the risk of conversion to AD dementia and VaD was lower in younger patients (<65 years) than in older patients, with a greater reduction in VaD conversion risk observed among males than among females. Additionally, α-GPC consumption did not increase the risk of ischemic or hemorrhagic stroke in the overall population and it notably reduced such risks in patients in whom MCI did not convert to AD dementia and VaD. Collectively, these findings support that α-GPC is beneficial in reducing the risks of both dementia and stroke. This study provides a comprehensive assessment of the incidence and preventive effects of dementia and stroke in an unbiased cohort of newly diagnosed MCI patients.

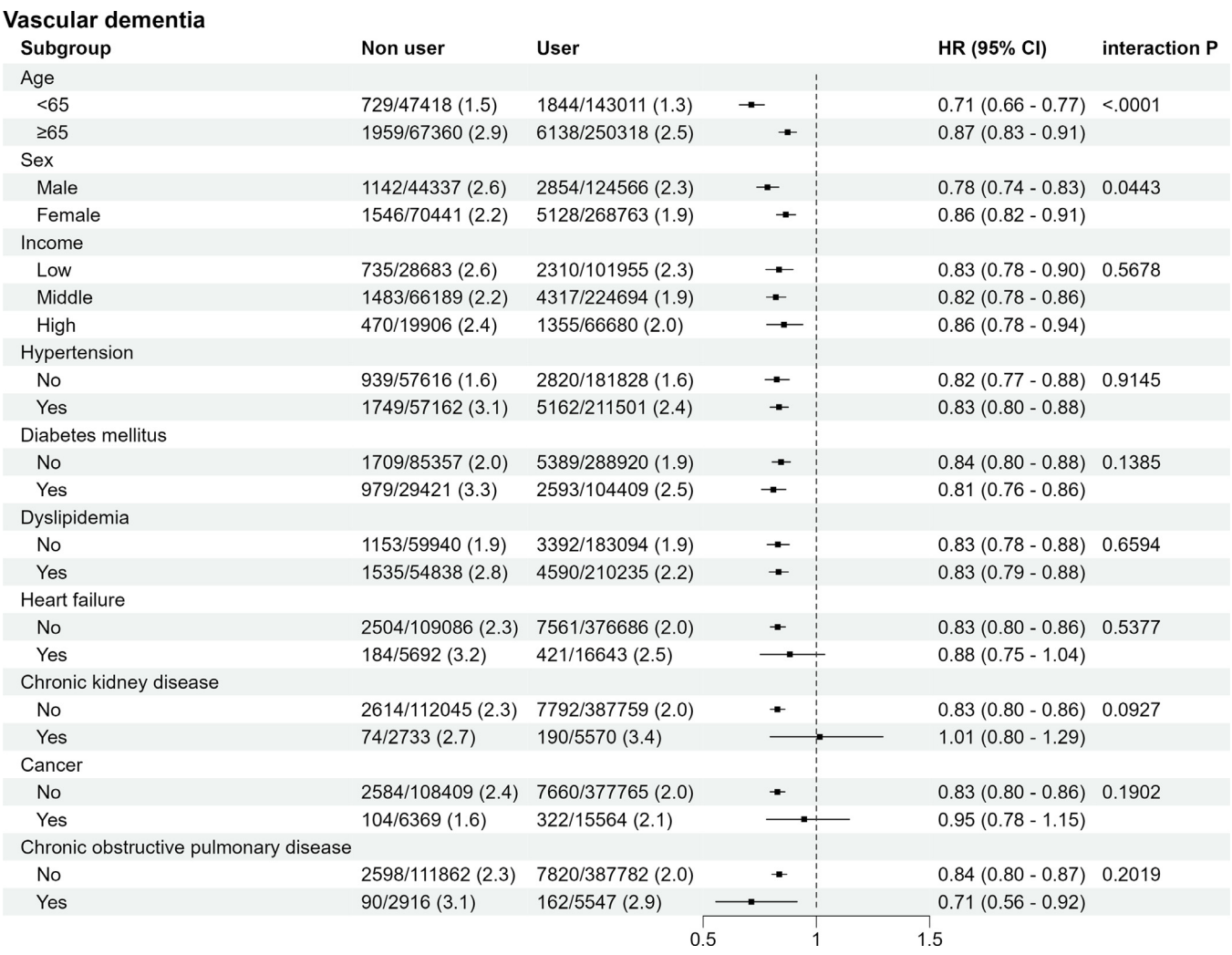


**Fig. 2.** Time-dependent Cox model.
This figure shows the time-dependent Cox model for conversion to vascular dementia in the subgroup analysis.

Neuropathologic studies have shown that cholinergic neuronal activity, particularly in the hippocampus, is reduced by up to 70 % in patients with AD and by 40 % in patients with VaD compared to that in controls [5,14,15]. Acetylcholine is a key neurotransmitter involved in learning and memory, especially in regions such as the entorhinal cortex, one of the most vulnerable areas in AD. Thus, acetylcholine levels are closely linked to memory impairment symptoms [16]. Additionally, core pathologies of AD, such as amyloid-beta and phosphorylated tau increase acetylcholinesterase concentration [17–19]. Choline supplements not only directly elevate acetylcholine levels in the synaptic cleft [8–10] but also exhibit neuroprotective effects. In an APP/PS1 mouse model of AD, choline supplementation modulated microglial activation, slowing AD progression [20]. Choline inhibits the production of reactive oxygen species within cells, thereby protecting neurons from oxidative damage. It also influences epigenetic processes such as DNA methylation, regulating gene expression and maintaining neuronal stability [21]. Furthermore, choline serves as a precursor to phosphatidylcholine, which is essential for cell membrane synthesis and contributes to the prevention of cognitive decline [22].

In our study, $\alpha$-GPC reduced the risk of stroke among the overall MCI population and in those whose MCI did not convert to AD dementia or VaD. There were no substantial differences in stroke risk for those whose MCI converted to AD dementia or VaD. The association between the cholinesterase inhibitor donepezil and the cholinergic precursor choline alfoscerate in Alzheimer's disease (ASCOMALVA) trial found that adding $\alpha$-GPC to AchEI in patients with AD with vascular burden not only prevented cognitive decline, but also reduced the severity of behavioral and psychological symptoms in dementia and brain volume loss [13,23–27]. Furthermore, a pooled analysis of several studies consistently demonstrated that $\alpha$-GPC, either alone or combined with donepezil, improved cognitive, functional, and behavioral outcomes in individuals with cognitive decline associated with cardiovascular disorders [12].

A large-scale population-based study in Korea found that $\alpha$-GPC intake increased stroke risk in the general population in a dose-dependent manner [28]. In contrast, our study, despite evaluating a similar population, yielded opposite results of protective effect of $\alpha$-GPC against both ischemic and hemorrhagic strokes. However, the PSM analysis of stroke risk resulted in a reduced number of participants, which led to a substantial decrease in the number of stroke events. Furthermore, the period from MCI diagnosis to the initiation of medication was included as part of the "medication duration," potentially introducing immortal time bias. Therefore, the primary findings from the original data analyzed using a time-dependent Cox model are considered to be more reliable. Although the relationship between choline and stroke risk remains unclear, previous studies have suggested that increased trimethylamine N-oxide (TMAO) levels from choline precursors could elevate stroke risk [29–31]. Dietary choline is metabolized by the gut microbiota into trimethylamine, which is subsequently converted to TMAO [32,33].

**Table 3**
Time-dependent Cox proportional hazard model for stroke risk.

| | Total | Event | | IR | Crude | | | Model 1 | | | Model 2 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. | No. | (%) | | HR | 95 % CI | | HR | 95 % CI | | HR | 95 % CI | |
| **All MCI participants** | | | | | | | | | | | | | |
| Ischemic stroke | | | | | | | | | | | | | |
| Non-user | 114,778 | 1569 | (1.37) | 2.26 | 1 | | | 1 | | | 1 | | |
| User | 393,329 | 5315 | (1.35) | 2.10 | 0.803 | 0.766 | 0.842 | 0.831 | 0.792 | 0.871 | 0.833 | 0.794 | 0.874 |
| Hemorrhagic stroke | | | | | | | | | | | | | |
| Non-user | 114,778 | 9076 | (7.91) | 13.57 | 1 | | | 1 | | | 1 | | |
| User | 393,329 | 32,393 | (8.24) | 13.26 | 0.83 | 0.814 | 0.847 | 0.849 | 0.833 | 0.866 | 0.847 | 0.831 | 0.863 |
| **Conversion to Alzheimer's disease dementia** | | | | | | | | | | | | | |
| Ischemic stroke | | | | | | | | | | | | | |
| Non-user | 8656 | 184 | (2.13) | 3.42 | 1 | | | 1 | | | 1 | | |
| User | 30,662 | 655 | (2.14) | 3.35 | 0.959 | 0.837 | 1.099 | 0.996 | 0.869 | 1.142 | 0.996 | 0.869 | 1.142 |
| Hemorrhagic stroke | | | | | | | | | | | | | |
| Non-user | 8656 | 1426 | (16.47) | 28.45 | 1 | | | 1 | | | 1 | | |
| User | 30,662 | 5012 | (16.35) | 27.51 | 0.957 | 0.911 | 1.006 | 0.966 | 0.919 | 1.015 | 0.962 | 0.915 | 1.01 |
| **Conversion to vascular dementia** | | | | | | | | | | | | | |
| Ischemic stroke | | | | | | | | | | | | | |
| Non-user | 2688 | 180 | (6.70) | 10.92 | 1 | | | 1 | | | 1 | | |
| User | 7982 | 541 | (6.78) | 10.83 | 1.009 | 0.871 | 1.169 | 1.08 | 0.932 | 1.252 | 1.083 | 0.934 | 1.255 |
| Hemorrhagic stroke | | | | | | | | | | | | | |
| Non-use | 2688 | 755 | (28.09) | 52.34 | 1 | | | 1 | | | 1 | | |
| User | 7982 | 2222 | (27.84) | 50.55 | 0.935 | 0.87 | 1.005 | 0.94 | 0.875 | 1.011 | 0.939 | 0.873 | 1.009 |
| **Non-conversion to Alzheimer's disease dementia and vascular dementia** | | | | | | | | | | | | | |
| Ischemic stroke | | | | | | | | | | | | | |
| Non-user | 103,434 | 1205 | (1.16) | 1.93 | 1 | | | 1 | | | 1 | | |
| User | 354,685 | 4119 | (1.16) | 1.80 | 0.780 | 0.739 | 0.823 | 0.811 | 0.768 | 0.856 | 0.813 | 0.771 | 0.859 |
| Hemorrhagic stroke | | | | | | | | | | | | | |
| Non-user | 103,434 | 6895 | (6.67) | 11.41 | 1 | | | 1 | | | 1 | | |
| User | 354,685 | 25,159 | (7.09) | 11.35 | 0.820 | 0.802 | 0.838 | 0.839 | 0.821 | 0.858 | 0.837 | 0.819 | 0.856 |

Model 1 is adjusted for age and sex. Model 2 is adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, heart failure, chronic kidney disease, cancer, and chronic obstructive pulmonary disease.

This process has been shown to promote atherosclerosis, thereby increasing the risk of various cardiovascular diseases [34,35]. In mice, choline supplementation raises TMAO levels, leading to the upregulation of macrophage scavenger receptors, which promote atherosclerosis and elevate cardiovascular disease risk [32,36].

However, conflicting findings have also been reported. Subsequent population-based studies found that while high TMAO levels increased stroke risk, TMAO precursors, including carnitine, choline, betaine, and trimethyl lysine, did not elevate such risk [37]. Additionally, plasma choline pathway metabolites, including choline and betaine, were found to reduce the risk of cardiovascular disease and stroke recurrence [38]. Even after ischemic stroke, high choline concentration has been shown to have a protective effect against cognitive decline [39]. While it is well-established that high TMAO levels increase cardiovascular risk, the relationship between choline intake and cardiovascular risk remains unclear, with conflicting results across studies. Furthermore, there is a lack of human studies examining the association between plasma choline levels, stroke risk, and cognitive function.

In this study, non-conversion to AD dementia and VaD demonstrated a protective effect against stroke, suggesting that choline consumption may not increase cardiovascular risks in certain individuals and could instead provide neuroprotective benefits. The conversion of choline to TMAO is significantly influenced by gut microbiota, and variations in microbiome composition can lead to differences in metabolite levels [32,40]. These factors likely contributed to the reduced stroke risk observed in patients who did not experience dementia conversion. Moreover, the reduction in AD dementia risk was less pronounced in younger patients (<65 years) with dyslipidemia, possibly due to choline-induced atherosclerosis impacting vascular burden. Thus, while the efficacy of $\alpha$-GPC may be limited in certain subgroups, there appears to be no reason to avoid $\alpha$-GPC consumption solely to prevent stroke.

This study has some limitations. First, dementia was identified using diagnostic codes and prescriptions for antidementia medications, which reduced but did not completely eliminate the potential for misclassification. Similarly, other comorbid conditions were identified based on diagnostic codes from claims data, which may also introduce the possibility of misclassification. Due to the nature of public registries, which are not limited to memory clinics, there is a possibility of inaccuracies in diagnostic codes. Second, this study lacked data on specific clinical features of dementia, such as the simple cognitive tests (mini-mental state examination or clinical dementia rating), neuropsychological assessments, detailed clinical manifestations, AD biomarker profiles, and non-cognitive symptoms, including behavioral and psychological symptoms. Third, the study focused solely on AD dementia and VaD, excluding other dementia subtypes. Future research should investigate a wider range of dementia subtypes to provide a more comprehensive understanding of the disease and its various manifestations. Fourth, this study did not consider variations in medication dosage or formulation. Only the oral formulation of $\alpha$-GPC itself was investigated. Additionally, there was no analysis based on different dosages; therefore, the effects of high versus low doses or a cumulative dosage could not be assessed.

## 5. Conclusions

$\alpha$-GPC use could effectively reduce the risk of dementia conversion to both AD dementia and VaD in patients with MCI in real-world settings. Additionally, $\alpha$-GPC lowered the risk of both ischemic and hemorrhagic strokes without increasing stroke risk, regardless of dementia conversion to AD dementia and VaD. These findings suggest that $\alpha$-GPC's cognitive protective effects extend beyond preserving cholinergic neuron function, also offering protection against dementia conversion associated with vascular burden.

## Ethics approval and consent to participate

The study protocol was approved by the institutional review board of Wonju Severance Christian Hospital (CR321308). The requirement for

informed consent was formally waived due to the secondary analytical study design and the use of de-identified participant data.

## Consent for publication

Not applicable.

## Availability of data and material

The original anonymized data used in this analysis were obtained from the Korean NHIS. The dataset is not publicly available due to restricted access. However, researchers can request access to the data through a license agreement. Requests can be submitted via the NHIS website (https://nhiss.nhis.or.kr/bd/ab/bdaba000eng.do).

## Declaration of generative AI and AI-assisted technologies in the writing process

Nothing to declare.

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## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Min Seok Baek reports financial support was provided by Korea Ministry of Science and ICT. Han-Kyeol Kim reports financial support was provided by Korea Ministry of Education. Min Seok Baek reports financial support was provided by Korea Ministry of Trade Industry and Energy. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## CRediT authorship contribution statement

**Han-Kyeol Kim:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Sojeong Park:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Sung-Woo Kim:** Investigation, Formal analysis, Conceptualization. **Eun Seok Park:** Resources, Investigation, Conceptualization. **Jin Yong Hong:** Resources, Investigation, Formal analysis, Conceptualization. **Ickpyo Hong:** Writing – review & editing, Methodology, Investigation, Formal analysis, Conceptualization. **Min Seok Baek:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100059.

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