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Effect of Choline Alfoscerate on the Progression From Mild Cognitive Impairment to Dementia: Distributed Network Analysis of a Multicenter Korean Database Using a Common Data Model

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ABSTRACT

Background and Purpose: Choline alfoscerate (CA) is an acetylcholine precursor known for its beneficial effect on cognition in patient with Alzheimer's disease dementia (ADD). However, there is little evidence of its effects in patients with mild cognitive impairment (MCI). We assessed the influence of CA on the progression from MCI to all-cause dementia or ADD in three observational Korean databases using a Common Data Model (CDM).
Methods: Patients who were diagnosed with MCI and were aged over 60 years were included. After propensity score matching, 3,062 matched pairs patients using CA use and those not using CA were included. The Cox regression model was used to analyze the hazard ratio (HR) of CA use for conversion from MCI to all-cause dementia or ADD. Subgroup analyses were performed based on sex, acetylcholine esterase inhibitor (AchEI) use, and donepezil use.
Results: A meta-analysis across three hospitals revealed that CA use was not associated with the progression from MCI to all-cause dementia (hazard ratio [HR], 0.93; 95% confidence interval [CI], 0.59–1.26) or ADD (HR, 1.05; 95% CI, 0.51–1.59). Subgroup analyses revealed that CA use was not related to progression to all-cause dementia or ADD when stratified by sex, AchEI use, and donepezil use.
Conclusions: In this multicenter cohort study based on the Observational Medical Outcomes Partnership CDM real-world data, no association was noted between CA use and disease progression from MCI to all-cause dementia or ADD.

Keywords: Choline Alfoscerate; Mild Cognitive Impairment; Dementia; Common Data Model; Meta-analysis

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Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

Conceptualization: Pyun JM, Lee I, Lee K, Kim MH, Park C, Yang HJ; Data curation: Pyun JM, Lee I, Lee K, Kim MH, Park C, Yang HJ; Formal analysis: Pyun JM, Lee I, Lee K, Kim MH, Park C, Yang HJ; Methodology: Pyun JM, Lee I, Lee K, Kim MH, Park C, Yang HJ; Software: Pyun JM; Supervision: Pyun JM, Yang HJ; Validation: Pyun JM, Lee I, Lee K, Kim MH, Park C, Yang HJ; Visualization: Pyun JM; Writing - original draft: Pyun JM; Writing - review & editing: Pyun JM, Lee I, Lee K, Kim MH, Park C, Yang HJ.

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of neurodegenerative dementia, accounting for 60%–80% of cases.[1] Patients with Alzheimer's disease dementia (ADD) are in a dependent state for performing activities of daily living because of cognitive impairments involving memory, executive function, language, attention, and visuospatial function.[2] Mild cognitive impairment (MCI) is the stage of preceding dementia, in which patients can independently perform activities of daily living despite cognitive impairment.[3] It is therefore crucial to predict the progression from MCI to dementia and identify the relevant factors and medical treatment options.

The cholinergic hypothesis is one of the known mechanisms of AD.[4] Presynaptic cholinergic deficit,[5] reduced acetylcholine release,[6] and reduced choline acetyltransferase[7] (an enzyme for the synthesis of acetylcholine) has been associated with AD and its early stage, MCI.[8] Based on this theory, acetylcholine esterase inhibitors (AchEIs) such as donepezil, rivastigmine, and galantamine, are currently used as AD therapeutics.

Choline alfoscerate (CA) is an acetylcholine precursor that increases the bioavailability of acetylcholine in the nervous tissue.[9] By enhancing cholinergic transmission, CA in combinational use with AchEIs can exhibit beneficial effects in alleviating cognitive and behavioral impairments in patients with mild-to-moderate AD and concomitant ischemic cerebrovascular disease.[10-12] CA has been widely prescribed in several countries because of its good tolerability and safety profile.[13]

However, the effect of CA in patients with MCI has not been elucidated. As limited treatment options are available in the MCI stage, assessment of the effect of CA on the progression from MCI to dementia and on dementia subtypes, such as ADD and all-cause dementia, would be meaningful.

The Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) is an open community data model that standardizes heterogeneous data sources and integrates CDM-based vocabularies into a common data format. Transforming various observational healthcare data into this CDM enables efficient large-scale network analysis using reliable standardized data.[14] Although CA have been widely prescribed in Korea, studies on the effects of CA in patients with MCI across multiple centers are scarce. A CDM-based study can efficiently integrate multi-center data and provide insights into the effects of CA in MCI patients.

In this multicenter cohort study, we assessed the influence of CA use on the progression from MCI to all-cause dementia or ADD in Korea using a CDM.

METHODS

Data sources

This study was conducted using OMOP CDM data from three hospitals: Soonchunhyang University Seoul Hospital (SCHSH), Ajou University Medical Center (AUMC), and Ewha Womans University Seoul Hospital (EUSH).

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Observational Health Data Sciences and Informatics (OHDSI) is an international collaborative consortium that aims to facilitate the generation of high-quality evidence by developing and applying open-source data analysis solutions to a large network of health databases worldwide.[14,15] Although most Korean hospitals use an electrical health record (EHR) system, numerous Korean diagnoses, medications, and procedural codes are not compatible with the international coding system. Since 2016, data from Ajou University and the Korean nationwide cohort database have been successfully transformed into the OMOP CDM and validated.[16,17] EHR data of 57 million patients from 47 hospitals have recently been integrated into the CDM, which is accessible in Korea by the Federated E-health Big Data for Evidence Renovation Network (FEEDER-NET), a bio-health big data platform supported by the Korean National Project (http://feedernet.com), for collaborating OHDSI networks. FEEDER-NET is connected to each institution's CDM and can domestically conduct multi-institutional CDM research using Atlas, a dedicated CDM analysis tool. This study was approved by the International Review Board (IRB) of SCHSH (IRB No. 2024-02-001). As this was an observational study utilizing de-identified data, the SCHSH IRB waived the requirement for informed consent.

Study design and cohort definitions

This retrospective, observational, and comparative cohort study included all outpatients with MCI aged over 60 years between January 1, 2010 and December 31, 2023. The index date was defined as the date of first MCI diagnosis. The observation period was defined as the period from 180 days to 3 years after the index date. The target cohort consisted of participants continuously exposed to CA for more than 90 days (CA group). Continuous CA exposure was ensured by allowing gaps of <30 days between CA prescriptions. The comparative cohort consisted of participants without CA exposure (non-CA group).

The primary outcome was the incidence of all-cause dementia during observation period, i.e., from at least 180 days to 3 years after the index date. The secondary outcome was the incidence of ADD during the observation period. The OMOP diagnosis codes for primary and secondary outcomes are listed in **Supplementary Table 1**. Primary and secondary outcomes were restricted to cases with gaps of <90 days between the last CA prescription and the outcomes. The cohort definition is presented in **Fig. 1**.

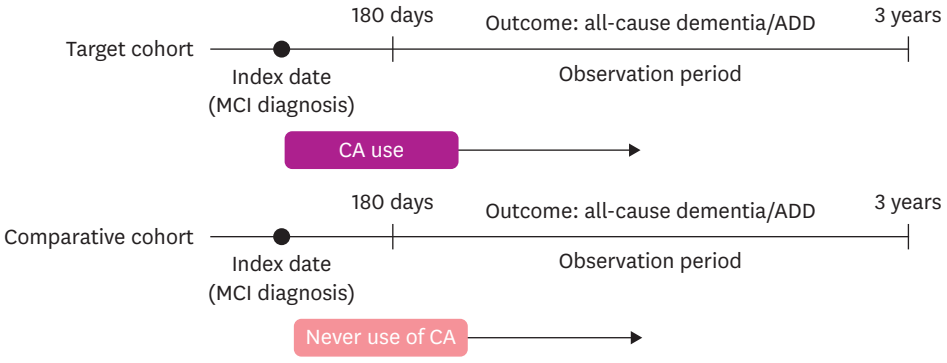

Fig. 1. Scheme presenting cohort definition.
ADD: Alzheimer's disease dementia, MCI: mild cognitive impairment, CA: choline alfoscerate.

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Statistical analysis

Propensity score matching (PSM) was performed to minimize selection bias in baseline characteristics of the target and control cohorts. Propensity scores were calculated through logistic regression with covariates using the MatchIt package in R (version 4.2.3; R Foundation for Statistical Computing, Vienna, Austria). The covariates used for PSM were age, sex, hypertension (HTN), angina pectoris (AP), coronary arteriosclerosis, cerebrovascular disease, diabetes mellitus (DM), dyslipidemia (DL), chronic kidney disease (CKD), hypothyroidism, depression, and AchEI (donepezil, rivastigmine, or galantamine) use. Participants using CA and those not using CA were matched in a 1:1 ratio based on the propensity scores, with a caliper size of 0.2.

The Cox proportional hazards model was used to calculate the hazard ratios (HRs) for all-cause dementia and ADD with relevant covariates in both groups. The covariates in the Cox model included age, sex, HTN, AP, coronary arteriosclerosis, cerebrovascular disease, DM, DL, CKD, hypothyroidism, depression, and AchEIs use. Covariates less than 10 events were excluded from the analysis. Survival analyses were performed using Kaplan–Meier curves and log-rank test. Then, a meta-analysis was performed to assess the pooled estimated HRs of the three hospitals. The meta-analysis was performed using a random effects (REs) model, with heterogeneity analysis performed using the I^2 index. Subgroup analyses were performed according to sex, AchEI use, and donepezil use. All analyses were performed using R (version 4.2.3) and Atlas (version 2.7.6) provided by the OHDSI collaboration.

RESULTS

Characteristics of study participants

From SCHSH, 882 individuals who had continuously received CA and 834 individuals who had never been prescribed CA were identified. From AUMC, 1,770 and 2,008 individuals were identified in the CA and non-CA groups, respectively. From EUSH, 458 and 1,360 individuals were identified in the CA and non-CA groups, respectively. The baseline characteristics of the target and control groups across three hospitals after 1:1 PSM are described in **Table 1**.

Table 1. Baseline characteristics of the 3 cohorts after 1:1 propensity score matching

Characteristics	SCHSH			AUMC			EUSH		
	CA	Non-CA	SMD	CA	Non-CA	SMD	CA	Non-CA	SMD
No. of patients	834	834		1,770	1,770		458	458	
Age (yr)	72.4±7.6	74.2±7.8	0.232	73.1±7.0	73.3±7.0	0.024	73.4±7.5	73.6±7.7	0.021
Female	569 (68.2)	562 (67.4)	0.018	1,006 (56.8)	1,054 (59.5)	0.055	292 (63.8)	278 (60.7)	0.063
Hypertension	367 (44.0)	271 (32.5)	0.239	724 (40.9)	577 (32.6)	0.173	88 (19.2)	67 (14.6)	0.123
Angina pectoris	87 (10.4)	76 (9.1)	0.044	199 (11.2)	147 (8.3)	0.099	33 (7.2)	28 (6.1)	0.044
Coronary arteriosclerosis	54 (6.5)	35 (4.2)	0.101	254 (14.4)	153 (8.6)	0.180	15 (3.3)	18 (3.9)	0.035
Cerebrovascular disease	190 (22.8)	110 (13.2)	0.252	190 (10.7)	171 (9.7)	0.035	54 (11.8)	48 (10.5)	0.042
Diabetes mellitus	243 (29.1)	185 (22.2)	0.160	396 (22.4)	274 (15.5)	0.177	39 (8.5)	39 (8.5)	<0.001
Dyslipidemia	425 (51.0)	227 (27.2)	0.502	235 (13.3)	161 (9.1)	0.133	55 (12.0)	52 (11.4)	0.020
Chronic kidney disease	54 (6.5)	47 (5.6)	0.035	76 (4.3)	57 (3.2)	0.056	20 (4.4)	22 (4.8)	0.021
Hypothyroidism	96 (11.5)	67 (8.0)	0.117	66 (3.7)	63 (3.6)	0.009	20 (4.4)	16 (3.5)	0.045
Depression	111 (13.3)	109 (13.1)	0.007	115 (6.5)	109 (6.2)	0.014	31 (6.8)	34 (7.4)	0.026
Donepezil use	66 (7.9)	94 (11.3)	0.114	588 (33.2)	303 (17.1)	0.378	151 (33.0)	143 (31.2)	0.037
Rivastigmine use	11 (1.3)	11 (1.3)	<0.001	144 (8.1)	90 (5.1)	0.123	44 (9.6)	45 (9.8)	0.007
Galantamine use	4 (0.5)	1 (0.1)	0.066	16 (0.9)	5 (0.3)	0.081	8 (1.7)	2 (0.4)	0.126

Data are presented as the mean ± standard deviation or number (%), as appropriate.
SCHSH: Soonchunhyang University Seoul Hospital, AUMC: Ajou University Medical Center, EUSH: Ewha Womans University Seoul Hospital, CA: choline alfoscerate, SMD: standardized mean difference.

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Conversion from MCI to all-cause dementia or ADD

The mean follow-up times of the three hospitals and the number of outcome events are listed in **Supplementary Table 2**. The incidence rate ratios (IRRs) of all-cause dementia were 1.06 (95% confidence interval [CI], 0.72–1.55) in SCHSH, 1.90 (95% CI, 1.53–2.36) in AUMC, and 0.79 (95% CI, 0.57–1.10) in EUSH. IRRs of ADD were 1.10 (95% CI, 0.74–1.64) in SCHSH, 2.45 (95% CI, 1.91–3.13) in AUMC, and 0.80 (95% CI, 0.55–1.15) in EUSH.

Association of CA use with risk of all-cause dementia and ADD

In the Cox regression analysis, CA use was not associated with progression to all-cause dementia in SCHSH and AUMC (**Supplementary Table 3**). However, in EUSH, CA use was related to slow progression to all-cause dementia (HR, 0.62; 95% CI, 0.44–0.87; p=0.006). Regarding the secondary outcome, CA use was not associated with progression to ADD in SCHSH (**Supplementary Table 4**). However, CA use was related to fast progression to ADD in AUMC (HR, 1.54; 95% CI, 1.19–1.98; p<0.001) and slow progression to ADD in EUSH (HR, 0.63; 95% CI, 0.43–0.92; p=0.018). Kaplan–Meier curves of the CA and non-CA groups are presented in **Fig. 2**.

In the meta-analysis across 3 hospitals, CA use was not associated with the progression from MCI to all-cause dementia (HR, 0.93; 95% CI, 0.59–1.26; I^2=70%) or ADD (HR, 1.05; 95% CI, 0.51–1.59; I^2=86%) (**Fig. 3**).

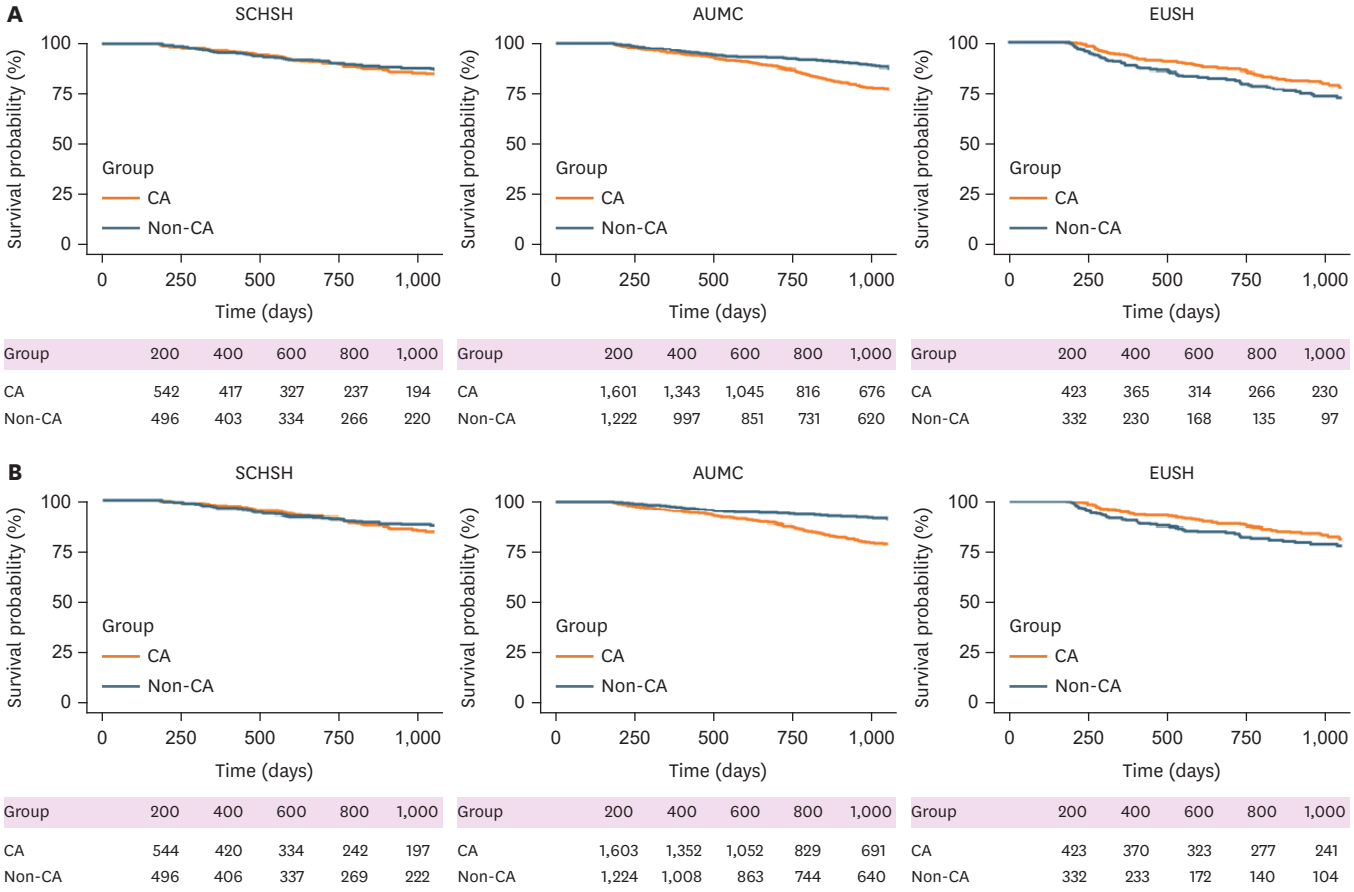

Fig. 2. Kaplan–Meier curves for the risk of all-cause dementia and ADD between the CA group and non-CA groups.
Survival data are described using Kaplan–Meier curves for all-cause dementia (A) and ADD (B).
ADD: Alzheimer's disease dementia, CA: choline alfoscerate, SCHSH: Soonchunhyang University Seoul Hospital, AUMC: Ajou University Medical Center, EUSH: Ewha Womans University Seoul Hospital.

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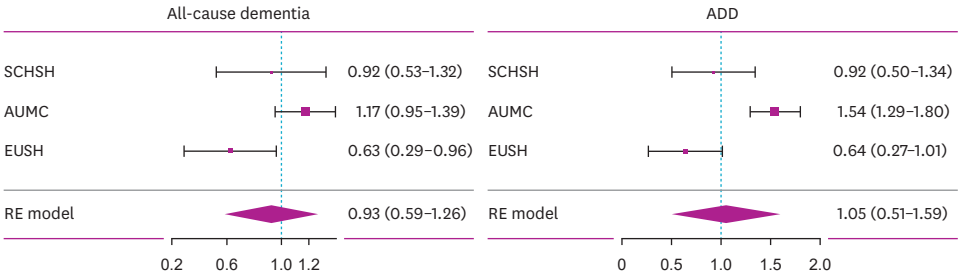

Fig. 3. Meta-analysis of all-cause dementia and ADD between the CA and non-CA groups.
ADD: Alzheimer's disease dementia, CA: choline alfoscerate, SCHSH: Soonchunhyang University Seoul Hospital, AUMC: Ajou University Medical Center, EUSH: Ewha Womans University Seoul Hospital, RE: random effect.

Subgroup analysis

Subgroup analysis was performed to assess the influence of sex, AchEI use, and donepezil use on the primary and secondary outcomes. In the female group, CA use was not associated with progression to all-cause dementia (HR, 0.89; 95% CI, 0.54–1.25; I^2=59%) or ADD (HR, 1.02; 95% CI, 0.41–1.63; I^2=83%) (**Fig. 4**). Similarly, in the male group, CA use was not related to progression to all-cause dementia (HR, 0.96; 95% CI, 0.59–1.34; I^2=29%) or ADD (HR, 1.10; 95% CI, 0.61–1.60; I^2=44%).

In the group prescribed AchEIs (donepezil, rivastigmine, or galantamine), CA use was not associated with the progression from MCI to all-cause dementia (HR, 0.96; 95% CI, 0.59–1.34; I^2=72%) or ADD (HR, 1.08; 95% CI, 0.49–1.66; I^2=87%). Similarly, in the AchEI non-user group, CA use was not related to the progression from MCI to all-cause dementia (HR, 2.44; 95% CI, 0.15–4.73; I^2=89%) or ADD (HR, 3.18; 95% CI, 0.83–5.52; I^2=84%). SCHSH was not

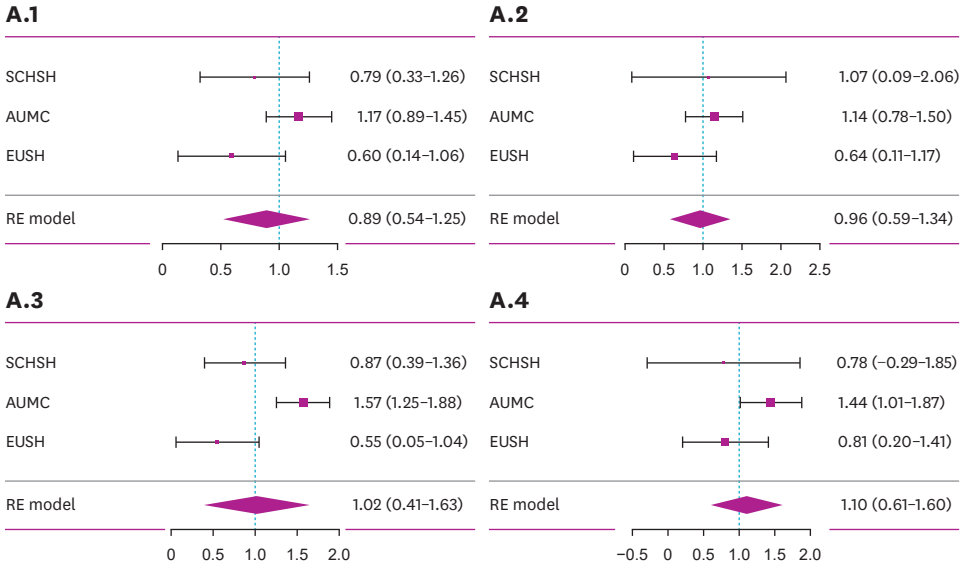

Fig. 4. Meta-analysis of Cox regression models to determine the association between CA use and progression to all-cause dementia or ADD depending on sex, AchEI use, and donepezil use.
Meta-analysis of Cox regression models was performed to determine the association between CA use and the progression from mild cognitive impairment to all-cause dementia or ADD across SCHSH, AUMC, and EUSH depending on sex, AchEI use, and donepezil use. Hazard ratios of CA use for all-cause dementia in females (A.1) and males (A.2) and for ADD in females (A.3) and males (A.4). Hazard ratios of CA use for all-cause dementia in AchEI users (B.1) and AchEI non-users (B.2) and for ADD in AchEI users (B.3) and AchEI non-users (B.4). Hazard ratios of CA use for all-cause dementia in donepezil users (C.1) and donepezil non-users (C.2) and for ADD in donepezil users (C.3) and donepezil non-users (C.4).
CA: choline alfoscerate, ADD: Alzheimer's disease dementia, AchEI: acetylcholine esterase inhibitors, SCHSH: Soonchunhyang University Seoul Hospital, AUMC: Ajou University Medical Center, EUSH: Ewha Womans University Seoul Hospital, RE: random effect.

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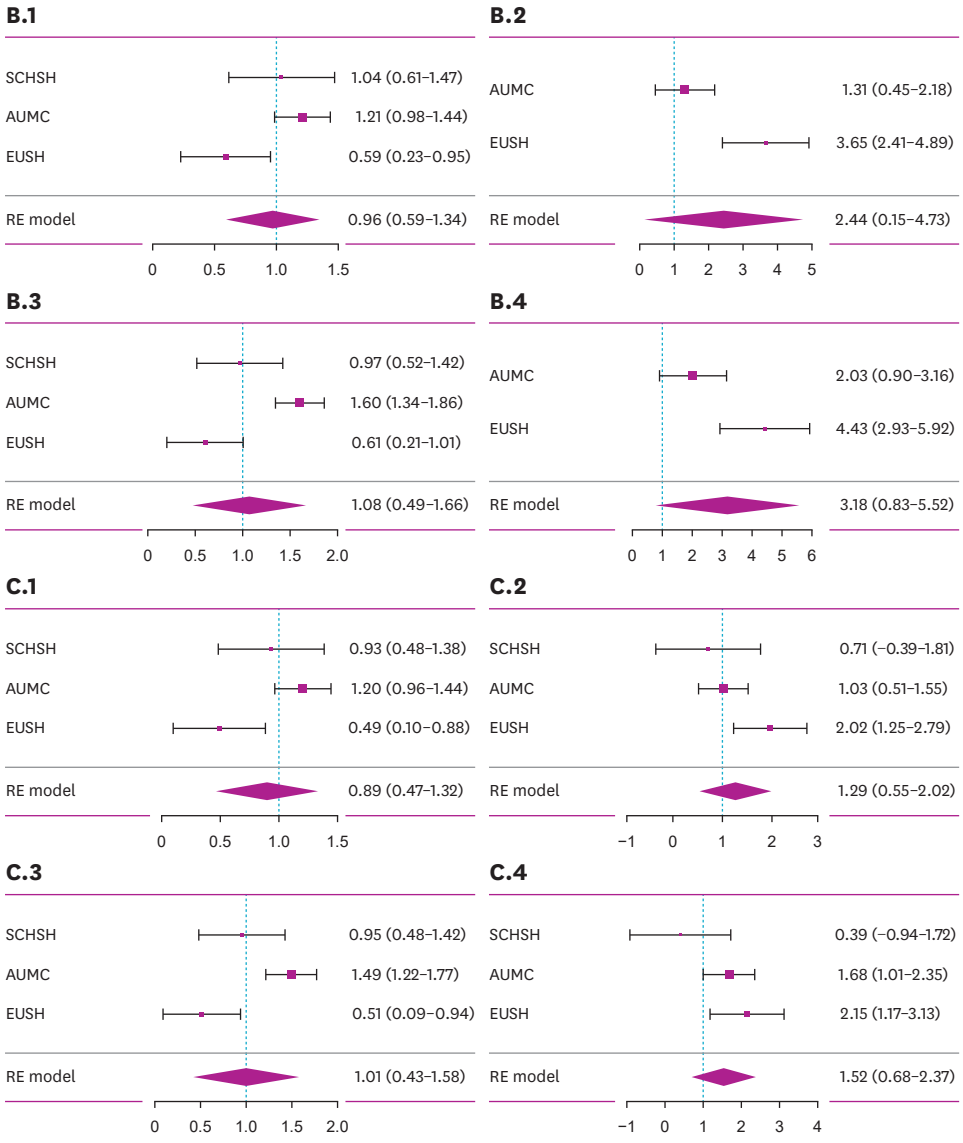

Fig. 4. (Continued) Meta-analysis of Cox regression models to determine the association between CA use and progression to all-cause dementia or ADD depending on sex, AchEI use, and donepezil use.
Meta-analysis of Cox regression models was performed to determine the association between CA use and the progression from mild cognitive impairment to all-cause dementia or ADD across SCHSH, AUMC, and EUSH depending on sex, AchEI use, and donepezil use. Hazard ratios of CA use for all-cause dementia in females (A.1) and males (A.2) and for ADD in females (A.3) and males (A.4). Hazard ratios of CA use for all-cause dementia in AchEI users (B.1) and AchEI non-users (B.2) and for ADD in AchEI users (B.3) and AchEI non-users (B.4). Hazard ratios of CA use for all-cause dementia in donepezil users (C.1) and donepezil non-users (C.2) and for ADD in donepezil users (C.3) and donepezil non-users (C.4).
CA: choline alfoscerate, ADD: Alzheimer's disease dementia, AchEI: acetylcholine esterase inhibitors, SCHSH: Soonchunhyang University Seoul Hospital, AUMC: Ajou University Medical Center, EUSH: Ewha Womans University Seoul Hospital, RE: random effect.

included in the meta-analysis of the AchEI non-user group because of less than 10 events of all-cause dementia and ADD.

In the donepezil user group, CA use was not associated with progression to all-cause dementia (HR, 0.89; 95% CI, 0.47–1.32; I^2=77%) or ADD (HR, 1.01; 95% CI, 0.43–1.58; I^2=85%). In the donepezil non-user group, CA use was also not related to progression to all-cause dementia (HR, 1.29; 95% CI, 0.55–2.02; I^2=64%) or ADD (HR, 1.52; 95% CI, 0.68–2.37; I^2=57%).

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DISCUSSION

In this study, the risk of progression from MCI to all-cause dementia or ADD was compared between the CA and non-CA groups across three hospitals using OMOP CDM data. No significant difference was noted in the risk of progression to all-cause dementia or ADD between the CA and non-CA groups. Moreover, subgroup analysis according to sex, AchEI use, and donepezil use revealed no difference in the risk of all-cause dementia or ADD events between the CA and non-CA groups.

CA has been reported to increase the effectiveness of donepezil in a clinical trial of AD with concomitant cerebral ischemia.[11] However, the evidence of CA use in the MCI stage is limited. Several studies have evaluated the effect of CA in the MCI stage using neurophysiological biomarkers. In a study using quantitative electroencephalography, the MCI group treated with CA for 2 months exhibited decreased low-frequency band (delta and theta) power in the parietal and temporal lobes, increased high-frequency band (alpha) power in the occipital lobe, and default mode network enhancement compared with the controls.[18] As increased low-frequency band power and decreased high-frequency band power are observed in MCI and are related to cognitive impairment, this result suggests a beneficial effect of CA in patients with MCI.[19,20] In another study based on P300 event-related evoked potentials, which reflect cognitive functions involving attention, short-term memory, and neuron processing speed, the MCI group using CA tended to exhibit improved P300 latency.[21] In our study, CA use was related to slow progression to all-cause dementia in 1 hospital (EUSH); however, no significant association was noted between CA use and disease progression in the other two hospitals (SCHSH and AUMC). This discrepancy between hospitals may have resulted from differences in CA prescription patterns of physicians because of a lack of clear consensus on CA prescriptions in the MCI stage. Moreover, the discrepancy could be attributed to differences in the number of patients or characteristics of patients despite PSM. Regarding the secondary outcome, a significant association was noted between CA use and slow progression to ADD in EUSH; however, no such association was noted in SCHSH. In AUMC, CA use was related to fast progression to ADD. In the meta-analysis, no significant association was noted between CA use and all-cause dementia or ADD across 3 hospitals. Consequently, the influence of cohort populations on the results was assessed based on disease severity or drug interactions by performing subgroup analysis.

Subgroup analysis was performed according to sex, AchEI use, and donepezil use. The effect of sex difference was assessed because of the higher incidence of dementia or ADD in females than in males.[22] No association was noted between CA use and disease progression in both females and males. Subgroup analysis depending on AchEI use was performed because of the possibility that patients with MCI treated with AchEIs could have higher disease severity than those not treated with AchEIs. However, no association was noted between CA use and progression in both AchEI user and AchEI non-user groups. In our study, the effect of CA use was also assessed depending on donepezil use, because previous studies have reported that a combination of CA and donepezil has a positive effect on cognition.[11,23] No association was noted between CA use and progression in the donepezil non-user group. Similarly, no beneficial effect was noted in the donepezil user group.

This study revealed substantial heterogeneity in the meta-analysis of the association between CA use and progression from MCI to all-cause dementia, with variability ranging from 70% to 86%. This high heterogeneity may stem from the absence of consistent guidelines for CA prescription in MCI. Additionally, the diverse cognitive severity among study participants and the varying underlying pathologies of MCI could contribute to the observed heterogeneity.

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In clinical practice, CA is recommended for managing cognitive impairment and behavioral disturbances in ADD with concomitant ischemic cerebrovascular disease. However, there is no established guideline for their use in MCI. Our findings suggest that CA use in MCI warrants cautious consideration and a refined therapeutic strategy. The lack of association between CA use and progression to dementia may be attributed to the heterogeneity of patient characteristics and underlying pathologies. Further research is needed to identify the appropriate target population within the MCI group for CA treatment. To achieve this, prospective studies are necessary to evaluate the effects of CAs on MCI patients. Additionally, it is important to consider stratifying groups based on the severity of cognitive impairment. Moreover, the effects of CAs should be investigated across various biological stages of AD, confirmed by biomarkers.

This study has several limitations. First, cognitive assessment measurements, such as neuropsychological test scores or educational levels, could not be used because of their unavailability in the OMOP CDM; these parameters may help understand the effect of CA on cognitive changes more specifically. Second, the dose of CA could not be included because of the lack of a coding system in the OMOP CDM. Third, this is a retrospective study and selection bias may exist. Although we tried to reduce selection bias by performing PSM, several covariates, such as AchEI use, remained unbalanced and could influence the results. Therefore, we tried to minimize this limitation through subgroup analysis. However, a randomized controlled clinical trial is warranted in the future.

In conclusion, no association was noted between CA use and the progression from MCI to all-cause dementia or ADD. Our study is a multicenter cohort study based on standardized methodology to assess real-world evidence.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Definition codes for all-cause dementia and Alzheimer's disease dementia

Supplementary Table 2
Incidence rate ratio and risk of all-cause dementia and ADD between CA and non-CA groups

Supplementary Table 3
Association of CA use with risk of all-cause dementia based on Cox regression model

Supplementary Table 4
Association between CA use and risk of ADD based on Cox regression model

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