

Association of Circulating Caprylic Acid with Risk of Mild Cognitive Impairment and Alzheimer's Disease in the Alzheimer's Disease Neuroimaging Initiative (ADNI) Cohort

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Abstract

OBJECTIVE: Medium-chain fatty acids (MCFAs) can rapidly cross the blood-brain barrier and provide an alternative energy source for the brain. This study aims to determine 1) whether plasma caprylic acid (C8:0) is associated with risk of incident mild cognitive impairment (MCI) among baseline cognitively normal (CN) participants, and incident Alzheimer's Disease (AD) among baseline MCI participants; and 2) whether these associations differ by sex, comorbidity of cardiometabolic diseases, apolipoprotein E (APOE) ϵ 4 alleles, and ADAS-Cog 13.

METHODS: Within the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort, plasma C8:0 was measured at baseline in 618 AD-free participants aged 55 to 91. Logistic regression models were used to estimate odds ratios (ORs) and 95% CIs with incident MCI and AD as dependent variables, separately.

RESULTS: The inverse association between circulating C8:0 and risk of incident MCI was of borderline significance. The inverse association between circulating levels of C8:0 and risk of incident MCI was significant among CN participants with ≥ 1 cardiometabolic diseases [OR (95% CI): 0.75 (0.58-0.98) (P=0.03)], those with one copy of APOE ϵ 4 alleles [OR (95% CI): 0.43 (0.21-0.89) (P=0.02)], female [OR (95% CI): 0.60 (0.38-0.94) (P=0.02)], and ADAS-Cog 13 above the median [OR (95%CI): 0.69 (0.50-0.97)(P=0.03)] after adjusting for all covariates.

CONCLUSION: The inverse associations were present only among subgroups of CN participants, including female individuals, those with one or more cardiometabolic diseases, or one APOE ϵ 4 allele, or higher ADAS-Cog 13 scores. If confirmed, this finding will facilitate precision prevention of MCI, in turn, AD among CN older adults.

Key words: Medium-chain fatty acids, caprylic acid, mild cognitive impairment, Alzheimer's Disease, cardiometabolic diseases, APOE ϵ 4 allele, ADAS-Cog 13.

Introduction

Over the past two decades, mortality rates due to Alzheimer's disease (AD) increased by 110% in the U.S., and 13.8 millions of Americans

are expected to be affected by 2050 (1). To date, no FDA-approved drugs, including aducanumab have confirmed effects to stop or slow the damage to neurons that cause the progression of AD (2). A delay of five years in the expression of AD would reduce the incidence rate by 50% (3) and prevalence by 41% (4). Thus, the need to develop preventive strategies for AD cannot be overstated. A well-established characteristic of AD is brain glucose hypometabolism, which can appear decades before the manifestation of AD symptoms (5, 6). While the improvement in brain energy metabolism through a classic ketogenic diet with ultra-low-carbohydrate intake is associated with better cognitive outcomes in patients with AD or mild cognitive impairment (MCI) (7), the classic ketogenic diet is too strict to maintain long-term (8) and can lead to side effects (9–11). However, previous studies indicate that it produces ketone bodies, which in turn, rescue brain energy (12–16) and improve cognition (7, 17, 18).

Medium-chain fatty acids (MCFAs) are saturated fatty acids of 6-12 carbons in chain length. The main source of MCFAs are mammalian milk and tropical plant oils, such as coconut and palm kernel oils (19). In a precision-based randomized controlled trial, we recently found that in addition to dietary intake, MCFAs (i.e., C7:0 and C8:0) can also be produced by gut microbiota in humans through optimizing calcium: magnesium ratio by magnesium supplementation (20). In contrast to long-chain fatty acids, MCFAs can rapidly cross the blood-brain barrier (8), directly enter the mitochondrial matrix, have intramitochondrial conversion to acyl-CoA thioesters and be directly metabolized by the brain (21). Unlike other MCFAs (22), C12:0, i.e., lauric acid is structurally closer to saturated long-chain fatty acids and may increase blood levels of low-density lipoprotein (LDL) cholesterol (23). The 'medium chain triglyceride (MCT) ketogenic diet', designed as an alternative dietary approach comprising 60% caprylic acid (C8:0) and 40% capric acid (C10:0), has a more flexible carbohydrate restriction to treat drug-

resistant epilepsy (8). Recent evidence has shown that an MCT ketogenic diet improved cognition in patients with AD or MCI (7, 8, 24). Three randomized, double-blind, placebo-controlled trials (25–27) and a retrospective case study (28) conducted in patients with mild cognitive impairment (MCI), or mild-to-moderate AD found that supplementation of MCT containing C8:0 regardless of C10:0 without any dietary restriction, significantly improved cognition. Although promising, these previous studies were short-term and were conducted among individuals with AD or MCI. It remains unclear whether C8:0 can prospectively prevent or predict the development of MCI and the progression from MCI to AD.

In addition to providing an alternative energy source, C8:0 is the precursor for the biosynthesis of alpha (α)-lipoic acid, which is essential in energy metabolism (29) and may delay AD development (30). Previous studies found that, while C10:0 prefers glycolysis, C8:0 undergoes β -oxidation to readily produce ketones in brain cells (8). Herein, we hypothesize that low circulating levels of C8:0 are associated with an increased risk for MCI (development from cognitively normal to MCI) or AD (progression from MCI to AD). We test our hypothesis in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort, a cohort with up to 13.4 years of follow-up among AD-free older adults. Since cardiometabolic diseases are a major risk factor for MCI and AD (31–33), and the MCT ketogenic diet improves insulin resistance in patients with cardiometabolic diseases (8, 34), we examined whether the associations between levels of C8:0 and risk of incident MCI and AD were stronger among high risk populations, i.e., those with cardiometabolic diseases and APOE ϵ 4 alleles.

Methods

Study Cohort

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. The initial phase (ADNI-1) of ADNI was launched in 2003 and subsequent phases (ADNI-GO, ADNI-2, and ADNI-3) were conducted for follow-up of existing participants and additional new enrollments. The detailed design of ADNI has been described elsewhere (35, 36). Volunteer participants between ages 55 and 90 are recruited at 63 sites across the USA and Canada. For this analysis, 829 eligible participants had data on plasma MCFAs and were enrolled in ADNI-1, ADNI-GO, ADNI-2, or ADNI-

3 between September 30th 2005 and March 4th 2019. We excluded 20 duplicate records, 1 participant with a missing diagnosis, and 190 participants with AD at baseline, leaving 618 participants for analysis. Among these, 226 were cognitively normal (CN) and 392 were MCI at baseline. Consent forms were approved by each participating site's Institutional Review Board (IRB) and all participants provided written informed consent at the time of enrollment.

Assay of Metabolomics

The metabolomics database for plasma biospecimens was obtained from the Alzheimer Disease Metabolomics Consortium (ADMC) funded by the National Institute on Aging (37). Details of sample preparation, data generation, quality control (QC), data filtering and normalization have been described elsewhere (38). In brief, the NIH-West Coast Metabolomics Center used a gas chromatography time of flight mass spectrometry (GCTOFMS) to measure the lipid metabolite profile of blood specimens from individuals from ADNI at baseline (39–41). Metabolomics lab staff were blinded to diagnostic data. After unblinding and data release, metabolite profiles went through QC checks and data preprocessing including batch-effect adjustment, missing value imputation, and log-transformation (37).

Outcome ascertainment

The ADNI diagnostic criteria for determining CN, MCI and AD were previously reported (42). In brief, ADNI investigators used conventional Petersen/Winblad criteria to categorize participants into CN, MCI or AD (42). Endpoints were measured using categorical response variables: any incident MCI among CN participants at baseline, or any incident AD among MCI participants at baseline. In the current study, we only included AD-related dementia as the outcome. Those participants with dementias from other causes were excluded from eligible participants and those who developed non-AD dementias during follow-up were treated as non-cases in the logistic regression models.

Measurement of Covariates

Covariates were determined based on a priori review of AD-related factors from previous publications. Demographic characteristics were obtained from the ADNI data repository (43). During baseline interviews, self-identified demographic characteristics including age (date of birth), sex (male/female), race (American Indian or Alaskan Native/Asian/Native Hawaiian or Other Pacific Islander/Black or African American/White/More than one race), ethnicity (Hispanic or Latino/Not Hispanic or Latino), and years of education (years) were collected in the case report form. A self-

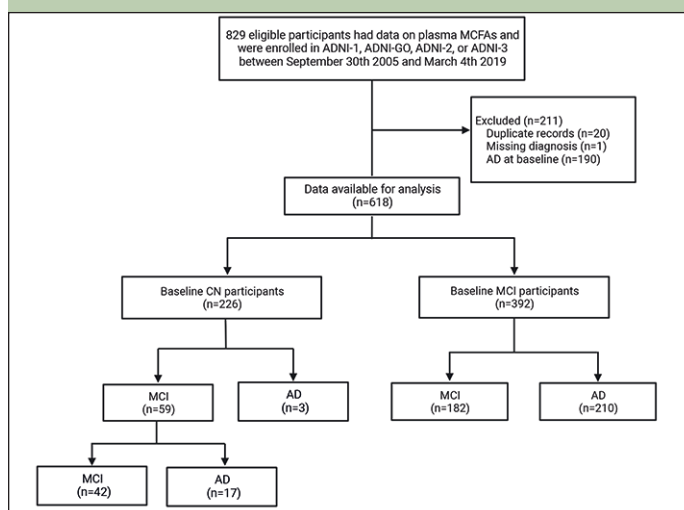
reported physician-diagnosed history of medical conditions including type 2 diabetes, hypertension, stroke, cardiovascular disease, and endocrine-metabolic diseases were also collected in the case report form (yes/no). If yes, additional questions captured information about whether the condition was current and the age at diagnosis as well as details of medication use. APOE $\epsilon 4$ genotyping was performed at the time of participant enrollment. The two SNPs (rs429358, rs7412) that define the epsilon 2, 3, and 4 alleles were genotyped and the copy numbers of APOE $\epsilon 4$ alleles for each individual were calculated based on genotyping data (44).

Statistical analysis

Included in the analysis are 392 participants with MCI at baseline of whom 210 (53.6%) developed incident AD. Also included are 226 CN participants at baseline, of whom 42 (18.6%) of participants converted from CN to MCI only, 17 (7.5%) of participants further converted to incident AD during the follow-up interval, and 3 (1.3%) of participants converted directly from CN to incident AD without an observed MCI phase (Figure 1). Logistic regression models and multinomial logistic regression models were used to estimate odds ratios (ORs) and 95% CIs with incident MCI and AD as dependent variables. Log-transformed circulating levels of C8:0 served as independent variables. Associations between log-transformed circulating levels of C8:0 and risk of incident MCI among CN participants, and risk of incident AD among MCI participants were examined in 3 models, respectively. Model 1 shows crude ORs (95% CIs) without adjustment. In Model 2, we adjust for age, sex, race, ethnicity, years of education, and APOE $\epsilon 4$ alleles. In multivariable-adjusted model 3, we additionally adjust for type 2 diabetes, hypertension, stroke, cardiovascular disease, and metabolic diseases. Since cardiometabolic diseases and APOE $\epsilon 4$ alleles are two major risk factors for MCI and AD (31–33), subgroup analyses were conducted to examine the associations stratified by sex, comorbidity of cardiometabolic diseases, APOE $\epsilon 4$ alleles, and the 13-item Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog 13, range: 0–85, higher scores indicate greater dysfunction), respectively. The significance of multiplicative interactions was evaluated by adding a corresponding interaction terms in the models. We also repeated the analyses using Cox regression models. For exploratory analyses, multinomial logistic regression models were used to predict the risk of incident MCI only and incident AD among baseline CN participants. Sensitivity analysis was conducted by excluding amyloid-negative MCI patients predicted by cerebrospinal fluid (CSF) biomarkers at baseline. Elecsys p-tau/A $\beta 42$ ratio has been shown in previous studies to have >94% overall, positive, and negative agreement with amyloid positron emission tomography (PET) classification (45); thus, we used the CSF p-tau/

A $\beta 42$ ratio to classify amyloid positive and negative MCI participants at baseline. Restricted cubic splines were used to examine possible nonlinear relationships between log-transformed circulating levels of MCFAs and risk of incident MCI and AD, respectively (46). AIC was used for knots selection and three knots for the spline curve achieved the best performance. Multivariable-adjusted analyses with 3 knots were conducted within the values between the 5th and 95th percentile to minimize the impact of potential outliers. Three knots were located at the 10th, 50th, and 90th percentiles of log-transformed circulating levels of MCFAs, respectively. All analyses were conducted using Statistical Analysis Software, version 9.4 (SAS Institute Inc., Cary, North Carolina) and restricted cubic splines were plotted using R 4.2.0 (<https://cran.r-project.org/>). All hypothesis testing was 2-sided with $P < 0.05$ indicating a statistically significant finding.

Figure 1. Flow chart of study participants



Abbreviations: ADNI, the Alzheimer's Disease Neuroimaging Initiative; CN, cognitively normal; MCI, mild cognitive impairment; AD, Alzheimer's Disease.

Results

Baseline characteristics of ADNI participants were compared (CN vs. MCI) (Table 1). Baseline race, ethnicity, years of education, plasma levels of C8:0, and comorbidity of cardiometabolic diseases did not differ significantly between CN and MCI participants, whereas participants with MCI at baseline were likely to be younger, male, APOE $\epsilon 4$ carriers, amyloid-positive, and have higher ADAS-Cog 13 scores.

Associations between circulating levels of C8:0 and risk of incident MCI among CN participants are presented in Table 2. The association between log-transformed circulating levels of C8:0 and risk of incident MCI was statistically significant in the crude model ($P = 0.04$) with an OR (95% CI) of 0.80 (0.64–0.99). The association became of borderline significance after adjusting for all covariates in model 3 ($P = 0.08$) with an OR (95% CI) of 0.81 (0.64–

Table 1. Baseline characteristics of ADNI participants

Variables	Cognitively Normal n=226	Mild Cognitive Impairment n=392	P-values
Age, years	76.02 (4.98)	74.96 (7.49)	0.03*
Sex: male (%)	52.21	64.80	<0.01**
Race, %			0.12
white	91.59	93.62	
black	7.08	3.83	
other	1.33	2.55	
Ethnicity, %			0.16
Hispanic or Latino	0.88	3.32	
Not Hispanic or Latino	98.67	96.17	
Unknown	0.44	0.51	
Education, years	16.08 (2.86)	15.63 (3.03)	0.06
APOE ε4 alleles, %			<0.001***
0	73.45	46.68	
1	24.34	41.58	
2	2.21	11.73	
Circulating Caprylic acid (C8:0)	1073.72 (1771.96)	973.15 (1299.51)	0.46
Comorbidity of one or more cardiometabolic diseases			
Yes, %	81.86	84.95	0.36
ADAS-Cog 13	9.50 (4.19)	18.66 (6.28)	<.0001***
Amyloid-positive, % †	29.91	70.27	<.0001***

Data are presented as mean (SD) unless otherwise indicated. P values are calculated using Chi-square test for categorical variables and independent t test for continuous variables. † The classification of amyloid-positive cases was based on 292 participants with available Elecsys p-tau/Aβ42 ratio data, not including 327 missing values. Abbreviations: ADNI, the Alzheimer's Disease Neuroimaging Initiative; ADAS-Cog 13 (range: 0–85; higher scores indicate greater dysfunction), the 13-item Alzheimer's Disease Assessment Scale - Cognitive Subscale. *P<0.05, **P<0.01, ***P<0.001.

1.03). The OR (95%CI) associated with a one standard deviation change in log-transformed levels of circulating C8:0 was 0.85 (0.71-1.02) in model 3. In secondary analyses, no associations were observed between circulating levels of C10:0 and C12:0 and risk of incident MCI among CN participants (Supplemental Tables S2-S3).

In subgroup analyses stratified by comorbidity of cardiometabolic diseases, the inverse association between levels of C8:0 and risk of incident MCI was statistically significant among participants with one or more cardiometabolic diseases after adjusting for all covariates with an OR (95% CI) of 0.75 (0.58-0.98) (P=0.03) (Table 2). However, the association was not present among those without comorbidity of cardiometabolic diseases. In subgroup analyses stratified by APOE ε4 alleles, the inverse association between levels of C8:0 and risk of incident MCI was statistically significant only among participants with one copy of APOE ε4 alleles after adjusting for all covariates with an OR (95% CI) of 0.43 (0.21-0.89) (P=0.02). The association attenuated when we collapsed those with two copies of APOE ε4 alleles to those with one copy, with an OR (95%CI) of 0.56 (0.31-1.02) (P=0.06). The sample size was too small to

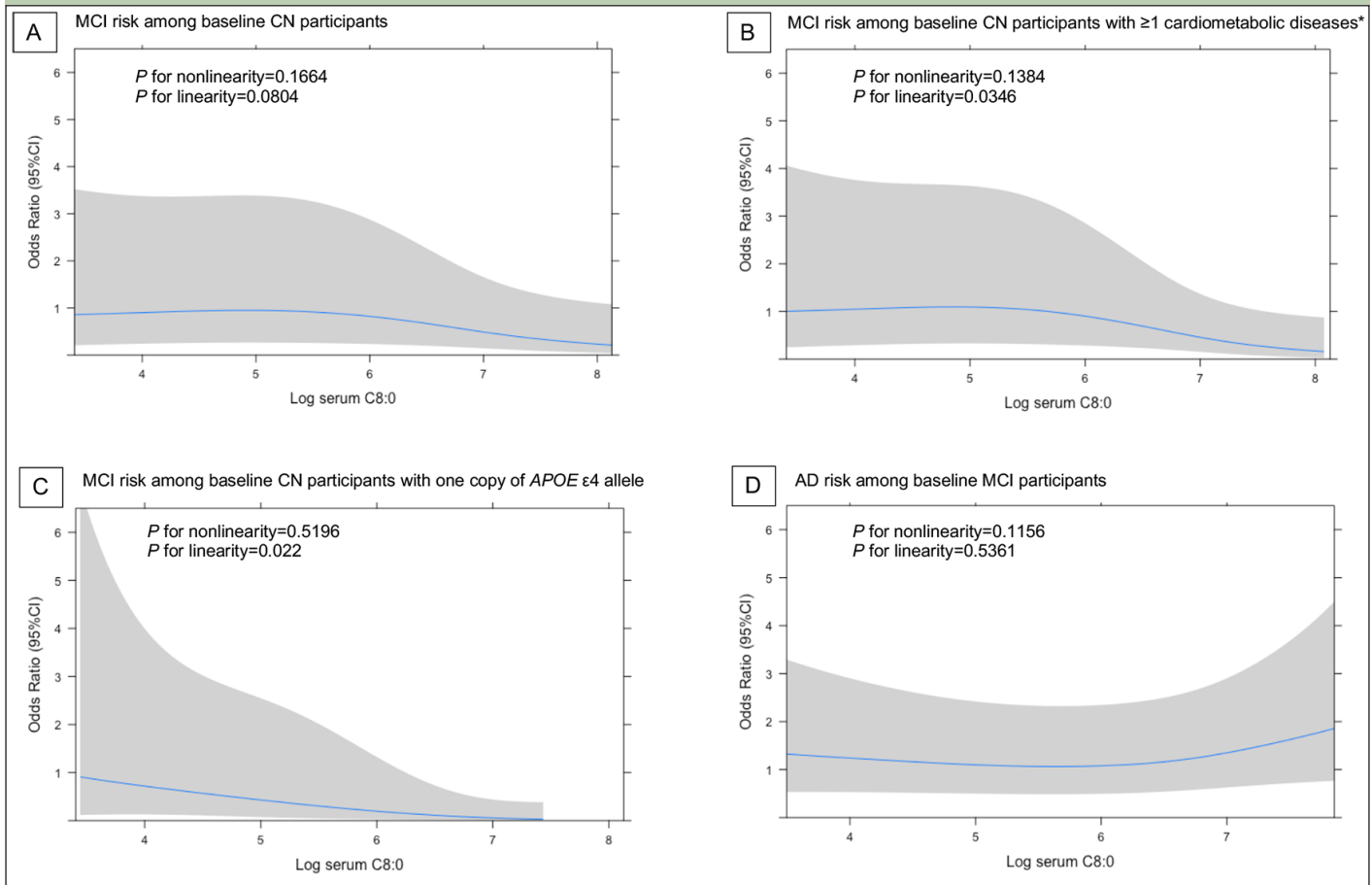
run the analyses among those with two copies of APOE ε4 alleles alone. In subgroup analyses stratified by sex, the inverse association between levels of C8:0 and risk of incident MCI was statistically significant only among female participants after adjusting for all covariates with an OR (95% CI) of 0.60 (0.38-0.94) (P=0.0248) (P for interaction=0.1458). We conducted additional analyses among participants with normal cognition at baseline stratified by cognition (ADAS-Cog13) below or above the median, separately. Although the P for interaction was not significant, C8:0 was associated with reduced risk of incident MCI among participants with normal cognition and ADAS-Cog 13 above the median at baseline with OR (95%CI) of 0.69 (0.50-0.97) in the multivariable-adjusted model (Table 2).

Multivariable-adjusted restricted cubic spline analyses indicated no evidence of nonlinear associations between circulating levels of C8:0 and risk of incident MCI among CN participants (P for nonlinearity=0.17); as circulating levels of C8:0 increased, there was a clear dose-response decreasing trend for risk of incident MCI, particularly at higher circulating levels of C8:0 (Figure 2A); and the dose-response trend became slightly steeper among

Table 2. Multivariable-adjusted Odds Ratios (95% CIs) for Circulating Caprylic Acid Level and Risk of Incident MCI among Baseline CN Participants

Caprylic acid (C8:0) ¹	No. of cases/all	Odds Ratio (95% CI)	Odds Ratio (95% CI) Per STD	P	P for interaction
All CN participants at baseline ²					
Model 1	59/223	0.80 (0.64-0.99)	0.84 (0.72-0.99)	0.0454*	
Model 2		0.81 (0.65-1.02)	0.85 (0.72-1.02)	0.0757	
Model 3		0.81 (0.64-1.03)	0.85 (0.71-1.02)	0.0804	
Stratify by comorbidity of cardiometabolic diseases					0.3555
<i>With ≥ 1 cardiometabolic diseases</i>					
Model 1	50/182	0.77 (0.60-0.98)	0.82 (0.68-0.98)	0.0344*	
Model 2		0.76 (0.59-0.98)	0.81 (0.67-0.99)	0.0378*	
Model 3		0.75 (0.58-0.98)	0.81 (0.66-0.98)	0.0346*	
<i>Without cardiometabolic diseases</i>					
Model 1	9/41	0.91 (0.55-1.50)	0.93 (0.64-1.36)	0.7066	
Model 2		1.08 (0.59-1.99)	1.06 (0.67-1.68)	0.8008	
Model 3		1.08 (0.59-1.99)	1.06 (0.67-1.68)	0.8008	
Stratify by APOE ε4 alleles ³					0.7321
<i>APOE ε4 alleles=0</i>					
Model 1	35/164	0.83 (0.63-1.08)	0.86 (0.70-1.06)	0.1691	
Model 2		0.83 (0.62-1.10)	0.86 (0.70-1.07)	0.1891	
Model 3		0.82(0.60-1.10)	0.86 (0.68-1.08)	0.186	
<i>APOE ε4 alleles=1</i>					
Model 1	22/54	0.74 (0.49-1.12)	0.79 (0.58-1.09)	0.1519	
Model 2		0.67 (0.43-1.06)	0.74 (0.53-1.04)	0.0872	
Model 3		0.43 (0.21-0.89)	0.53 (0.31-0.91)	0.022*	
Stratify by sex					0.1458
<i>Men</i>					
Model 1	33/116	0.91 (0.67-1.22)	0.93 (0.74-1.16)	0.517	
Model 2		0.90 (0.67-1.23)	0.93 (0.74-1.17)	0.5229	
Model 3		0.90 (0.66-1.25)	0.93 (0.73-1.18)	0.5381	
<i>Women</i>					
Model 1	26/107	0.69 (0.49-0.96)	0.76 (0.59-0.97)	0.0303*	
Model 2		0.65 (0.44-0.97)	0.72 (0.54-0.98)	0.0343*	
Model 3		0.60 (0.38-0.94)	0.68 (0.49-0.95)	0.0248*	
Stratify by ADAS-Cog 13					0.3708
<i>ADAS-Cog 13 < median</i>					
Model 1	20/106	0.92 (0.65-1.31)	0.94 (0.72-1.23)	0.6563	
Model 2		0.94 (0.63-1.38)	0.95 (0.71-1.28)	0.7385	
Model 3		0.95 (0.64-1.42)	0.96 (0.71-1.30)	0.8109	
<i>ADAS-Cog 13 ≥ median</i>					
Model 1	39/117	0.72 (0.53-0.97)	0.77 (0.61-0.98)	0.0307*	
Model 2		0.71 (0.52-0.98)	0.77 (0.61-0.98)	0.0368*	
Model 3		0.69 (0.50-0.97)	0.76 (0.59-0.97)	0.031*	

1. Circulating C8:0 level was log transformed. 2. All CN participants at baseline excluded three participants with diagnoses converting directly from CN to AD without MCI phase. 3. Participants with two copies of APOE ε4 alleles were not included for stratified analysis due to small sample size (n=5). Model 1 presented crude values; model 2 was adjusted for age, sex, race, ethnicity, education years, and APOE ε4 alleles; model 3 was additionally adjusted for type 2 diabetes, hypertension, stroke, cardiovascular disease, and metabolic diseases. *P<0.05, **P<0.01, ***P<0.001. Abbreviations: CN, cognitively normal; MCI, significant memory concern; AD, Alzheimer's Disease; STD, standard deviation; ADAS-Cog 13 (range: 0-85; higher scores indicate greater dysfunction), the 13-item Alzheimer's Disease Assessment Scale - Cognitive Subscale.

Figure 2. Multivariable-adjusted Odds Ratios and 95% Confidence Intervals of Incident MCI or AD Associated with Circulating Levels of C8:0

Restricted cubic spline analyses used 3 knots and the 5% highest and lowest log serum C8:0 were trimmed to minimize the impact of potential outliers. All models were adjusted for age, sex, race, ethnicity, education years, APOE ϵ 4 alleles, type 2 diabetes, hypertension, stroke, cardiovascular disease, and metabolic diseases. *Model was adjusted for age, sex, race, ethnicity, education years, and APOE ϵ 4 alleles.

Table 3. Multivariable-adjusted Odds Ratios (95% CIs) for Circulating Caprylic Acid Level and Risk of Incident AD among Participants with MCI at Baseline

Caprylic acid (C8:0) ¹	No. of cases/all	Odds Ratio (95% CI)	Odds Ratio (95% CI) Per STD	P Value
All MCI participants at baseline				
Model 1	210/392	1.04 (0.89-1.22)	1.03 (0.91-1.18)	0.6258
Model 2		1.06 (0.89-1.25)	1.04 (0.91-1.19)	0.5216
Model 3		1.05 (0.89-1.24)	1.04 (0.91-1.19)	0.5361

1. Circulating C8:0 level was log transformed. Model 1 presented crude values; model 2 was adjusted for age, sex, race, ethnicity, education years, and APOE ϵ 4 alleles; model 3 was additionally adjusted for type 2 diabetes, hypertension, stroke, cardiovascular disease, and metabolic diseases. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. Abbreviations: MCI, significant memory concern; AD, Alzheimer's Disease; STD, standard deviation.

participants with one or more cardiometabolic diseases (Figure 2B) while the trend not only became much steeper but also started to decline at lower levels of C8:0 among those with one copy of APOE ϵ 4 alleles (Figure 2C). On the other hand, there was no dose-response trend for the association between circulating levels of C8:0 and risk incident AD among baseline MCI participants (P for nonlinearity=0.11) (Figure 2D).

In exploratory analyses among baseline CN participants using a multinomial logistic regression model, we found that the inverse association between

levels of C8:0 and risk of incident MCI only was statistically significant in the crude model ($P=0.04$) with an OR (95% CI) of 0.78 (0.61-0.99) and was of borderline significance after adjusting for all covariates with an OR (95% CI) of 0.78 (0.60-1.01) ($P=0.06$) (Supplemental Table S1). The associations between levels of C8:0 and risk of incident AD among baseline CN participants were not statistically significant in all 3 models.

Associations between circulating levels of C8:0 and risk of incident AD among baseline MCI participants and stratified analyses are presented in Table 3 and

Supplemental Table S4, respectively. There were null associations between log-transformed circulating levels of C8:0 and risk of incident AD among MCI participants in main models as well as stratified analyses. After excluding amyloid-negative MCI patients classified by CSF p-tau/A β 42 ratio, the sensitivity analysis did not show evidence of a significant association between circulating C8:0 level and AD incidence among baseline MCI patients. No associations were observed between circulating levels of C10:0 and C12:0 and risk of incident AD among MCI participants (Supplemental Tables S5-S6). We also repeated the analyses using Cox regression models and found similar results (Supplemental Tables S7-S8).

Discussion

This study examined the relationship between circulating MCFAs levels and risk of incident MCI or AD in the ADNI cohort. We found that increasing circulating level of C8:0 was significantly and prospectively associated with a reduced risk of incident MCI among cognitively normal participants in a dose-response manner, particularly among female individuals, those with one or more cardiometabolic diseases, or one APOE ϵ 4 allele, or higher ADAS-Cog 13 scores at baseline. However, no associations were observed between circulating C8:0 and risk of incident AD among those with MCI at baseline overall and regardless of strata.

To the best of our knowledge, the present study is the first to longitudinally examine the association of C8:0 and risk of developing MCI or AD. Our findings are supported by previous short-term clinical trials conducted in patients with MCI or AD. The modified MCT ketogenic diet, which mainly consists of MCFAs, has been shown to be beneficial in patients with neurologic and metabolic disorders, including drug-resistant epilepsy (47, 48), obesity and type-2 diabetes (49, 50), and AD (51, 52). Although more flexible, the MCT ketogenic diet still necessitates carbohydrate restriction (8). However, in a 6-month randomized placebo-controlled trial, a 30 g/day ketogenic MCT drink (60% C8:0 and 40% C10:0) resulted in significantly improved cognitive function in MCI patients (25). A human study of case records from eight patients with mild-to-moderate AD who were treated with tricaprylin (20 gram/day) for \geq 6 months showed delayed cognitive impairment and progression of AD compared to historical conventional pharmacotherapy (28). A randomized, double-blind, placebo controlled, multicenter trial of oral administration of AC-1202, an MCT composed almost entirely of C8:0, showed positive effects in improving cognitive function among patients with mild to moderate AD (26). Furthermore, C8:0 has also been suggested to be beneficial in ameliorating neurodegenerative disorders other than AD due to its role in promoting brain hypometabolism. For example, *in vivo* studies

demonstrated that C8:0 triglyceride significantly promoted the mitochondrial oxygen consumption rate and alleviated amyotrophic lateral sclerosis (ALS)-type motor impairment through restoration of energy metabolism in transgenic ALS animal models (53). Although interventional studies have consistently reported the beneficial effects of C8:0 among patients with MCI, AD and other neurodegenerative disorders, no studies to date have prospectively examined the role of C8:0 in the etiology of developing MCI or AD among AD-free older adults.

Previous studies relatively consistently reported the beneficial effects of C8:0 supplementation among clinically diagnosed MCI or AD patients. In these randomized trials, large doses of interventional C8:0 supplementation were used to improve cognition. The improvement in cognition could be short-term and did not change the disease etiology course. In contrast, in the current study we used the ADNI cohort, an observational study which included free-living older adults. Dietary intakes of MCFAs in typical western diets are much lower than treatment doses used in previous randomized trials. Thus, one possible explanation for the disparities in results between the current study on AD risk and previous interventional studies may be due to the differences in doses of MCFAs.

Our findings of an inverse association between circulating levels of C8:0 and risk of incident MCI among female participants, those with cardiometabolic risk factors or one APOE ϵ 4 allele, or higher ADAS-Cog 13 scores at baseline, are biologically plausible. The brain primarily utilizes glucose for energy production under normal conditions. AD patients have been commonly characterized with impaired glucose uptake and cerebral hypometabolism in the brain monitored by 18F-FDG PET, which is correlated with clinical cognitive decline and pathological progression of AD (54). Among CN individuals, high C8:0 levels may lead to mild-to-moderate ketosis, which provides brain cells with a more efficient energy source than glucose, resulting in improvement in cognition as well as neuroprotective effects. C8:0, the most ketogenic MCFA, can be rapidly broken down to produce ketone bodies (55). Although the mechanism by which ketones could improve cognitive function is as yet elusive, it has been shown that mild to moderate ketosis may stimulate mitochondrial biogenesis, and improve oxidative phosphorylation and ATP generation in the brain (12–16, 56). Some studies, including a recent review, argue that MCFAs may exert neuroprotective effects through mechanisms independent of ketone bodies (8). The proposed therapeutic mechanism of ketones implicated in human studies cannot be entirely replicated in animal models and several studies observed a poor correlation between plasma ketone levels and clinical phenotype, raising the question of the role of other components involved (57–59). As one of the MCFAs that can cross the brain blood-barrier and permeate the mitochondrial membrane

independently of the carnitine transport system, C8:0 may directly rescue brain energy hypometabolism through promoting mitochondrial biogenesis (21). On the other hand, CN individuals with low levels of C8:0 may be a biomarker of a low capacity of alternative energy supplies or exhausting alternative energy supplies during cerebral hypometabolism. Finally, unlike other MCFAs, C8:0 serves as the precursor for the biosynthesis of α -lipoic acid in mitochondrial (29), one essential antioxidant in energy metabolism (30).

Older adults with insulin resistance show the same pattern of brain glucose hypometabolism as in AD (60), with glucose hypometabolism being most significant in frontal, parietotemporal and cingulate regions, areas affected in AD (60). Furthermore, brain hypometabolism has been longitudinally linked to insulin resistance (6). There is significant evidence demonstrating that individuals with insulin resistance, type 2 diabetes and metabolic syndrome are at increased risk for AD and cognitive decline (60–65). Thus, circulating levels of C8:0 may provide a promising risk stratification biomarker among CN older adults, especially those with cardiometabolic diseases and those carrying one APOE ϵ 4 allele. Increasing levels of C8:0 may be an effective intervention for the prevention of MCI or AD among older adults with lower levels of C8:0 and/or cardiometabolic and genetic risk factors. The main finding of this study is the absence of an association with conversion to AD among those with MCI at baseline and presence of an association with conversion to MCI among CN participants. The etiologic significance of the finding is that it predicts the true onset of the disease versus the progression of the disease, marked by MCI. Further studies are warranted to understand these and other potential mechanisms.

This study has a number of strengths. First, ADNI is a longitudinal multicenter cohort, which was designed to incorporate clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of AD progression. Based on this unique resource, we examined the prospective relationship between circulating levels of C8:0 and risk of incident MCI and AD over a long-term follow-up interval, up to 13.4 years. Second, AD patients at baseline were excluded prior to study entry and multiple clinic visits per person were performed to confirm and track the diagnoses during the follow-up which minimized the possibility of outcome misclassification. Third, because the risk of MCI in baseline CN participants and risk of AD in baseline MCI participants were analyzed separately, the imbalance of baseline characteristics such as age and APOE ϵ 4 alleles may not impact the results. Nevertheless, we adjusted all available covariates in the models including age, sex, race, ethnicity, education years, APOE ϵ 4 alleles, and cardiometabolic diseases. Finally, results from the exploratory analysis were consistent with the main analysis, suggesting that the significant inverse

association was present only with risk of incident MCI, but not risk of incident AD among baseline CN participants.

There are also some limitations for the current study. First, the sample size is limited for those with data on circulating levels of MCFAs. Although we separately examined the associations between circulating levels of C8:0 and risks of incident MCI among CN participants and incident AD among MCI participants, the non-significant associations may be attributable to insufficient statistical power. Nevertheless, we found that the inverse associations with C8:0 were present only for the development of MCI, but not AD. This finding is consistent with the fact that other protective factors, such as physical activity (66) and intakes of omega 3 fatty acids (67, 68) are linked to benefits in the prodromal period of AD but not in the conversion from MCI to AD. Likewise, in subgroup analyses, we found that the inverse association between levels of C8:0 and risk of incident MCI was only present in CN female participants, those with one or more cardiometabolic diseases or one APOE ϵ 4 allele. Therefore, cardiometabolic disease may be instrumental in further depleting reserve and edging the patient toward the clinical threshold of cognitive dysfunction. The non-significant association in participants with zero or two APOE ϵ 4 alleles could be due to lack of sufficient power in these subgroups. In addition, unlike our finding, two previous studies found that C8:0 supplementation improved cognitive function in APOE ϵ 4-negative AD patients (26, 27). One possible explanation is that the presence of an APOE ϵ 4 allele overwhelms the protective effect from supplementation of C8:0 among AD patients. A previous study conducted in the ADNI cohort utilized logistic regression models for the risk of conversion from MCI to AD (37). Following this previous report (37), we used logistic regression models to compare converted patients to non-converted controls in the current study. The reason that we used logistic regression models, which were less powerful than Cox regression models in cohort studies, was because there were several limitations to identify the exact diagnosis or censoring dates for a number of participants. Using more conservative logistic regression models rather than Cox regression models (69), it is possible that some significant associations may become non-significant. Nevertheless, the results from Cox regression models were similar to the main results from logistic regression models. We only had baseline data, and circulating levels of C8:0 levels likely varied over time during the 13-year follow up period. This non-differential misclassification of exposure usually biases the results toward the null value, indicating that true associations are stronger than what we have observed. Future longitudinal studies with repeated measures of circulating C8:0 levels are needed to examine whether the inverse associations would be stronger. Finally, the covariates used in the current study were derived from physician-diagnosed medical

history that were collected by self-reported survey questionnaires, thus, it may lead to misclassification that usually biases the association towards the null.

Conclusion

In summary, higher circulating levels of C8:0 were associated with a reduced risk of incident MCI among cognitively normal female participants, and those with one or more cardiometabolic diseases, or one APOE ϵ 4 allele, or higher ADAS-Cog 13 scores at baseline during the 13-year follow up. No associations with incident AD were found among participants with MCI at baseline. Future studies, including randomized trials, are needed to confirm these findings. If confirmed, this finding will facilitate precision prevention of MCI or AD among CN older adults, i.e., circulating levels of C8:0 together with sex, cardiometabolic disease status, APOE ϵ 4 alleles and ADAS-Cog 13 can be used to identify a subgroup of CN older adults at higher risk of developing MCI or AD, in whom dietary or supplemental use of C8:0 that results in elevated circulating C8:0 levels, and in turn, preventing or delaying the onset of MCI or AD.

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Ethical standards: We used the existing data collected from the ADNI. In ADNI, "Written informed consent for the study must be obtained from all subjects and/or authorized representatives and study partners before protocol-specific procedures are carried out.

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