Journal of Food and Nutrition Research, 2023, Vol. 11, No. 12, 707-714
Available online at http://pubs.sciepub.com/jfnr/11/12/1
Published by Science and Education Publishing
DOI:10.12691/jfnr-11-12-1

Relationship Between Dietary N ε-(carboxymethyl) lysine Intake and Cognitive Function in U.S. Elderly: Data from NHANES 2011-2014

Di Liu[1,#], Ying Zhang[2,#], Ziyan Ren[1], Xuan Wu[1], Wenzhuo Zhang[1], Yu Xia[3,*], Zhongxiao Wan[1,*]

[1]Department of Nutrition and Food Hygiene, School of Public Health, Soochow University, 199 Ren'ai Road, Suzhou, 215123, China
[2]Xiangcheng District Center for Disease Control and Prevention, 55 Middle Road of Yangcheng Hu, Suzhou, Jiangsu, 215131, China
[3]Departments of Laboratory, Suzhou Center for Disease Control and Prevention, 72 Sanxiang Road, Suzhou, Jiangsu, 215004, China
*Corresponding author: zhxwan@suda.edu.cn

Received October 25, 2023; Revised November 26, 2023; Accepted December 03, 2023

[#]Both authors make equal contribution to this study

Abstract To explore the relationship between dietary Nε-(carboxymethyl) lysine (CML) intake and specific cognitive function of the elderly via the National Health and Nutrition Examination Survey (NHANES). A total of 2,321 eligible participants (⩾60 years old) of NHANES 2011-2014 were included. Dietary CML intake was calculated via coupling the 24-hour dietary recall questionnaire with developed dietary AGEs database. Cognitive assessment was based on scores from the word learning and recall modules. Logistic regression analyses were conducted to examine the associations between the daily intake of dietary CML and cognitive performance, and stratified analysis according to gender, hypertension and diabetes status was also performed. After adjusting for potential confounders, the dietary CML contents were negatively correlated with the overall cognitive function (OR: 1.43; 95% CI: 1.11,1.85). Compared to those with low dietary CML content, the OR with 95% confidence intervals (CIs) of the risk of overall cognitive impairment in participants in the high dietary CML content group was 2.12 (1.19, 3.77) in those aged 60 to 69 years. The ORs for participants with high dietary CML content at the risk of overall cognitive impairment as well as immediate learning ability were 1.95 (1.19, 3.19) and 1.86 (1.08, 3.22) for those without hypertension, and 1.53 (1.15, 2.03), 1.44 (1.01, 2.05) for those without diabetes, respectively. There was a negative correlation between the dietary CML content and cognitive function in the elderly participants aged 60 years and above in the United States. This effect might be more pronounced in those aged 60 to 69 years, non-hypertensive and non-diabetic participants.

Keywords: *dietary advanced glycation end products, Nε-(carboxymethyl) lysine, cognitive impairment, elderly, NHANES*

Cite This Article: Di Liu, Ying Zhang, Ziyan Ren, Xuan Wu, Wenzhuo Zhang, Yu Xia, and Zhongxiao Wan, "Relationship Between Dietary N ε-(carboxymethyl) lysine Intake and Cognitive Function in U.S. Elderly: Data from NHANES 2011-2014." *Journal of Food and Nutrition Research*, vol. 11, no. 12 (2023): 707-714. doi: 10.12691/jfnr-11-12-1.

1. Introduction

Dementia is a type of brain disease that clearly affects the ability of daily life. According to Global Burden of Disease study 2016, it is estimated that 74.7 million cases of dementia will occur in 2030 and 131.5 million in 2050 [1]. From the perspective of public health, interventions to reduce the risk of dementia should focus on high-risk groups. Therefore, management and intervention in people with early cognitive decline is of great significance in order to delay the progression of dementia [2].

Increasing evidence have suggested that dietary advanced glycation end products (AGEs) may be one of the key factors affecting cognitive function [3-5]. Advanced glycation end products (AGEs) are heterogeneous molecules produced by non-enzymatic modification of macromolecules such as proteins, lipids and nucleic acids by glucose or other sugars (fructose and pentose) [6]. At human population level, higher intake of dietary AGEs has been prospectively associated with a faster cognitive decline in old adults with normal cognitive function [4]. Through ecological studies, Perrone et al. [5] found that high dietary AGEs intake was associated with an increased incidence of AD, and low dietary AGEs via the Mediterranean diet could significantly reduce the incidence of AD. At animal level, findings from our laboratory demonstrated that both short-term [7] and long-term [8] dietary AGEs led to cognitive impairment in aged ICR mice. Moreover, Lubitz et al. [9] demonstrated that AD (Tg2576) mice fed with high levels of AGEs had spatial learning disabilities and accelerated deposition of insoluble $A\beta_{42}$ in their brain.

N^{ε}-(carboxymethyl) lysine (CML) is a major and well-studied form of AGEs [10]. It is often used as a substitute for the representative AGE molecules [11]. It has been reported that CML increases with age in four brain regions, i.e. cerebral cortex, midbrain, striatum and hippocampus [12]. In the human brain of AD patients, CML is located in the cytoplasm of neurons and is expressed higher in the hippocampus than in the frontal and temporal cortices [13,14]. In addition, Haddad et al. [15] found that serum CML levels were negatively associated with cognitive scores measured via the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) in patients with AD. However, the impact of CML content in the diet on specific cognitive function in elderly people is still unclear.

Therefore, this study aimed to clarify the relationship between dietary CML intake and cognitive function in specific areas among elderly people aged 60 and above using 24-hour dietary review data and cognitive testing questionnaires from the National Health and Nutrition Examination Survey (NHANES) database.

2. Methods

2.1. Data Sources and Study Population

NHANES is a cross-sectional nationwide health survey of the non-institutionalized U.S. population. The survey is unique in that it combines interviews and physical examinations. Participants firstly took part in a household interview and then completed a further survey in a mobile examination center (MEC). We merged two cycles, 2011-2012 and 2013-2014, for this analysis. Weights were created in NHANES to account for the complex survey design (including oversampling), survey non-response, and post-stratification adjustment to match total population counts from the Census Bureau. In this study, a total of 19,931 individuals participated in the NHANES during 2011–2014 were included, and our analyses were limited to the adult participants aged 60 years or older who participated in the MEC cognitive tests (n=3,632). Those who did not complete the cognitive function surveys or with missing or unreliable values for the four cognitive function measures (n=698) were then excluded. Furthermore, those with incomplete dietary CML data were further excluded (n=232). Meanwhile, participants who reported themselves with stroke were also excluded from the study (n=169). Moreover, 34 participants with implausible daily energy intake levels (<800kcal or 4200kcal for men and <500kcal or >3500kcal for women.) were further excluded. Finally, 2,321 participants aged 60 years or older (1112 men and 1209 women) were included in the analyses (Figure 1).

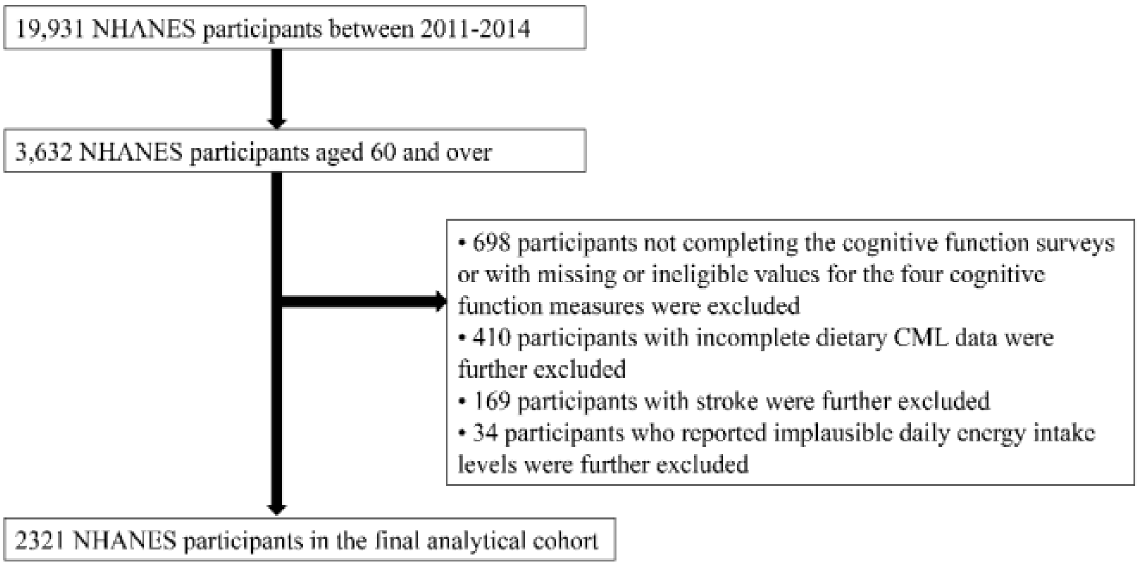

Figure 1. Flow chart of the screening process for the selection of eligible participants

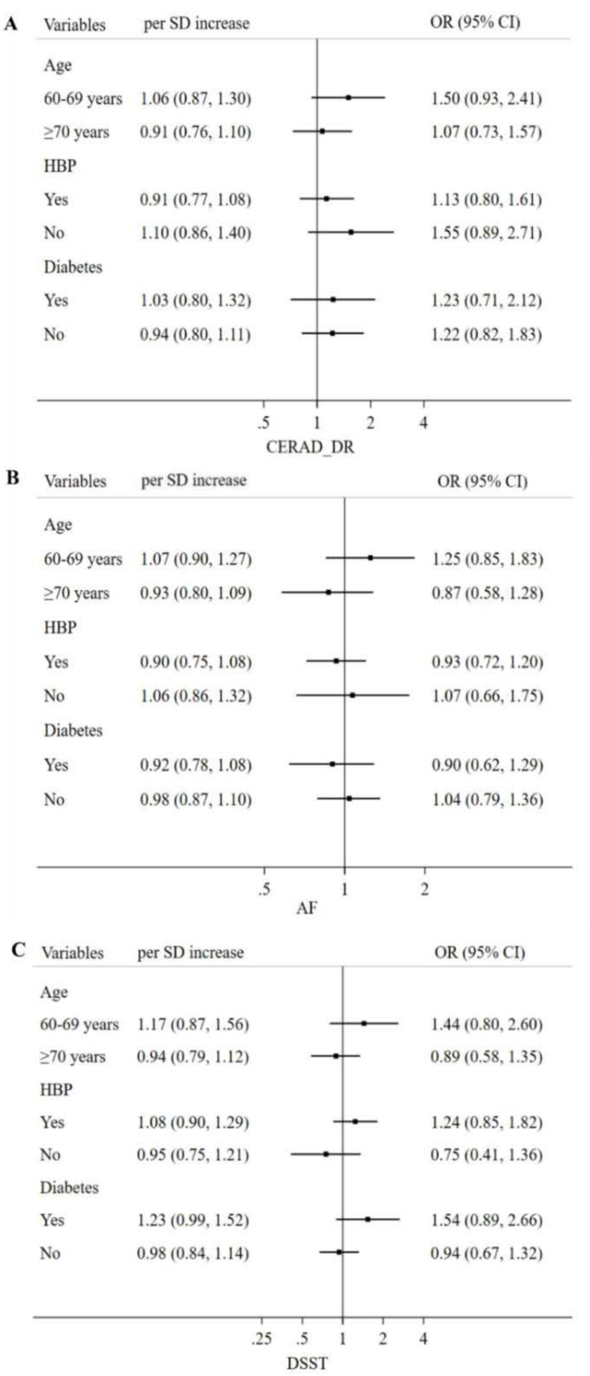

Figure 2. Stratified analysis of the relationship between dietary CML content and specific cognitive function. HBP, hypertension

2.2. Assessment of Dietary CML Contents

Dietary intake data in NHANES was measured using two 24-hour dietary recall interviews among all participants. The first dietary recall interview was collected in-person in the MEC and the second interview was collected by telephone 3 to 10 days later. The dietary interview component, called What We Eat in America (WWEIA), was conducted as a partnership between the U.S. Department of Agriculture (USDA) and the U.S. Department of Health and Human Services (DHHS)[16]. There are approximately 150 unique categories and each category has a 4-digit number and description, which are designed flexibly and can be combined as needed to solve specific research problems. According to the dietary AGEs database developed by Scheijen et al. [17], and combined with the complete description of food (including food names and cooking methods) in the dietary interview data, we evaluated the dietary CML of each participant. The dietary AGEs database used a highly sensitive, specific, and fast ultra high performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS) method for analyzing CML in protein components of 190 food [17].

Firstly, we directly matched the dietary CML content of foods in the AGEs database with the foods in NHANES. Secondly, some foods in NHANES did not appear in the dietary AGEs database, the CML content of these specific products were estimated by matching them with other products that were comparable in macronutrient profiles and preparation methods. For example, lentils used the same value of CML as peas. The CML value was not applicable to all fruits or vegetables, so we used the average value of available fruits or vegetables to replace other foods [18]. We averaged the CML content of two days. Since there was an obvious correlation between dietary CML and energy (Spearman partial correlation coefficient = 0.634, adjusted for age), dietary CML was divided by energy and then multiplied by 2000kcal, which was used as the energy adjusted dietary CML level for subsequent statistical analysis [18].

2.3. Measurement of Cognitive Function

The cognitive tests in NHANES 2011 to 2014 include 3 components: the word learning and recall modules from the Consortium to Establish a Registry for Alzheimer's disease (CERAD) including The CERAD Word Learning subtest (CERAD W-L) and the word learning test from CERAD (CERAD_IR), the Animal Fluency test (AF), and the Digit Symbol Substitution test (DSST). The detailed information for cognitive function assessment was shown in supplementary methods. Cognitive test scores were first converted to ***z*** scores using the baseline mean and standard deviation for the entire study. Then the 4 ***z*** scores were averaged to obtain the global cognitive scores. Because so far there was no gold standard on the cutoff scores for the CERAD, AF and DSST to indicate low cognitive performance, we selected the lowest quartile in the study group as the cut-off values to indicate different types of low cognitive performance, which had been widely used in published literatures [19,20]. For each measurement, participants were divided into two groups: those with scores below the cut-off values were assigned to the cognitive impairment group, while the others were assigned to the normal cognitive performance group.

2.4. Other Covariates

Demographic covariates were age, gender (male, female), educational level (less than high school, high school, above high school), race (Non-Hispanic White, Non-Hispanic Black, Hispanic, and Other race/ethnicity) and marital status (married/living with partner, others). We also covaried for body mass index (BMI), a commonly used measure of nutritional status in older adults [21]. For health-related lifestyle factors, recreational physical activity was classified into four levels: sedentary (no regular physical activity), insufficient (regular activity, <500 metabolic equivalent MET minutes/week), moderate (500 to 1000 MET minutes/week), and high (>1000 MET minutes/week) [21]. Smokers were the subjects who reported at least 100 lifetime cigarettes, and smoking status was categorized into three groups of never, current, and past. We also included vascular risk factors (hypertension, type 2 diabetes and self-reported heart disease). Hypertension was defined as systolic blood pressure≥140mmHg or diastolic blood pressure≥90mmHg or use of antihypertensive medication based on the WHO guidelines for the management of hypertension [22]. Diabetes was defined based on current treatment within insulin or oral hypoglycaemic medication or 8-h fasting plasma glucose≥126mg/dL as recommended by the American Diabetes Association [23]. What's more, depression was measured by the brief Patient Health Questionnaire (PHQ-9), and a cut-off score of 10 was applied to identify clinically relevant depression [24].

2.5. Statistical Analyses

Characteristics of the study population were described as mean ± SEs for continuous variables and number (percentages) for categorical variables. Dietary CML were divided into high and low CML group with the 75th percentile as the cut-off value. We tested differences in characteristics between groups with Student's t-test for continuous variables and Chi-square test for categorical variables. Then, the relationship between dietary CML level (as binary variables or continuous variable per standard deviation increment) and four specific cognitive functions was explored through multivariable adjusted logistic regression analysis, with the odds ratio (OR) and 95% confidence interval (CI) reported. The variables adjusted by the model include age, gender, educational level, race, marital status, BMI, recreational physical activity, smoking status, hypertension, diabetes, heart disease, and depression. Subsequently, a stratified analysis was conducted based on the adjusted model to examine the impact of dietary CML on cognitive function according to different age, hypertension and diabetes status. Data were analyzed using SAS version 9.4 and STATA version 16.0 software. A two-tailed P value < 0.05 was considered statistically significant.

3. Results

3.1. Descriptive Statistics

The characteristics of the study population according to dietary CML level were shown in Table 1. The mean age was 68.93 years old, and 45.28% of the participants were male. Participants with higher level of dietary CML were more likely to be older, Hispanic or other race, lower educational levels, and with diabetes (P<0.05 for all). Among other covariates, no significant differences were observed between low and high CML level group.

3.2. The Correlation Between Dietary CML Level and Specific Cognitive Functions

As shown in Table 2, after adjusting for potential confounders, the dietary CML content was associated with increased risk of low cognitive impairment (OR:1.43; 95% CI:1.11, 1.85). Otherwise, no significant association of dietary CML with other specific cognitive functions was found.

The contents of dietary CML were divided into two segments with the 75th percentile as the cut-off value. Models were adjusted for age, gender, educational level, race, marital status, BMI, recreational physical activity, smoke, hypertension, diabetes, heart disease, and depression.

CERAD_IR, the word learning test from CERAD; CERAD_DR, the learning recall test from CERAD; AF, the Animal Fluency test; DSST, the Digit Symbol Substitution test. CML, energy adjusted carboxymethyl lysine. B1, below the 75th percentile; B2, 75th percentile and above.

Bold letters indicate p value<0.05.

3.3. Stratified Analysis of the Relationship Between Dietary CML and Specific Cognitive Functions

The results of the stratified analysis were shown in Figure 2. After adjusting for potential confounding factors, the OR with 95% confidence intervals (CIs) of the risk of overall cognitive impairment for participants in the high dietary CML content group was 2.12 (1.19, 3.77) for those aged 60 to 69 years compared to those in the group of low dietary CML content. In participants without hypertension, the OR for participants with high dietary CML content was 1.95 (1.19, 3.19) compared to those with low dietary CML content. In addition, each SD increase in dietary CML content was associated with a 36% increase in the risk of overall cognitive impairment (OR: 1.36; 95% CI: 1.06, 1.73). Moreover, in participants without diabetes, compared with the group of low dietary CML content, the OR corresponding to the overall cognitive impairment of participants in the high dietary CML content group was 1.53 (1.15, 2.03). For the word learning test of CERAD (CERAD_IR), the OR for participants with high dietary CML content at the risk of immediate learning disabilities was 1.86 (1.08, 3.22) compared to those with low dietary CML content in participants without hypertension. Furthermore, dietary CML content was negatively correlated with immediate learning ability (OR: 1.44; 95% CI: 1.01, 2.05) among people without diabetes. However, for the learning recall test from CERAD (CERAD_DR), the Animal Fluency Test (AF) and the Digital Symbol Substitution Test (DSST), the significant relationship between dietary CML content and specific cognitive functions was not found in different subgroups (Supplementary Figure 1).

Table 1. Characteristics from NHANES 2011–2014 participants aged over 60 years old by binary of dietary CML level (N=2321)

Characteristics[a]	N	CML		
		B1	B2	P value
Age (years), mean (SE)[c]	68.93 (0.21)	68.50 (0.25)	70.21 (0.35)	0.0003
Gender, n (%)[b]				0.0532
Male	1112 (45.28)	815 (46.65)	297 (41.14)	
Female	1209 (54.72)	858 (53.35)	351 (58.86)	
Race/ethnicity, n (%)[b]				0.0016
Non-Hispanic White	1156 (81.29)	856 (82.90)	300 (76.40)	
Non-Hispanic Black	539 (7.81)	404 (7.82)	135 (7.79)	
Hispanic	433 (6.64)	300 (5.99)	133 (8.59)	
Other race/ethnicity	193 (4.26)	113 (3.29)	80 (7.22)	
Education, n (%)[b]				0.0011
Less than High School	544 (14.72)	374 (13.84)	170 (17.35)	
High School	542 (21.46)	394 (20.16)	148 (25.39)	
Above High School	1233 (63.82)	904 (65.99)	329 (57.26)	
Marital status, n (%)[b]				0.1306
Married/ Living with partner	1371 (66.63)	1005 (67.72)	366 (63.33)	
Widowed/ Divorced/ Separated	817 (29.27)	580 (28.72)	237 (30.94)	
Never married	130 (4.10)	86 (3.56)	44 (5.73)	
BMI, kg/m^{2b}				0.5029
0~25	600 (26.31)	412 (25.48)	188 (28.81)	
25~30	812 (36.00)	586 (36.08)	226 (35.78)	
≥30	886 (37.69)	661 (38.44)	225 (35.41)	
Recreational PA, MET minutes/week[b]				0.9254
0	1320 (52.96)	963 (52.61)	357 (54.03)	
0~500	339 (14.60)	237 (14.44)	102 (15.11)	
500~1000	262 (12.29)	183 (12.30)	79 (1 2.27)	
>1000	399 (20.15)	290 (20.66)	109 (18.59)	
Smoke, n (%)[b]				0.4332
never	1169 (50.31)	813 (49.40)	356 (53.03)	
ever	890 (40.01)	648 (40.41)	242 (38.80)	
current	261 (9.68)	211 (10.18)	50 (8.17)	
Hypertension, n (%)[b]				0.6592
yes	1514 (62.26)	1087 (62.66)	427 (61.05)	
no	762 (37.74)	557 (37.34)	205 (38.95)	
Diabetes, n (%)[b]				0.0093
yes	570 (19.65)	378 (17.98)	192 (24.70)	
no	1751 (80.35)	1295 (82.02)	456 (75.30)	
Depression, n (%)[b]				0.6611
0~9	2113 (93.41)	1527 (93.59)	586 (92.87)	
≥10	185 (6.59)	132 (6.41)	53 (7.13)	
Heart disease[b]				0.5087
yes	183 (8.06)	126 (7.69)	57 (9.18)	
no	2137 (91.94)	1546 (92.31)	591 (90.82)	

[a] All means and SEs for continuous variables and percentages for categorical variables were weighted, except for the number of participants.
[b] Chi-square test was used to compare the percentage between the low dietary CML group and the high dietary CML group.
[c] Student's t-test was used to compare the mean levels between the low dietary CML group and the high dietary CML group.
SE, standard error; **CML,** energy adjusted carboxymethyl lysine. **B1,** below the 75th percentile; **B2,** 75th percentile and above.
Bold letters indicate p value<0.05.

Table 2. The associations between dietary CML content and cognitive function

	CML			
	B1	B2	P trend	per SD increase
Global cognitive scores	1 (*ref.*)	**1.43 (1.11, 1.85)**	**0.0069**	1.07 (0.95, 1.21)
CERAD_IR	1 (*ref.*)	1.27 (0.91, 1.78)	0.1586	1.03 (0.87, 1.21)
CERAD_DR	1 (*ref.*)	1.26 (0.90, 1.75)	0.1676	0.98 (0.85, 1.12)
AF	1 (*ref.*)	0.99 (0.80, 1.21)	0.8905	0.96 (0.87, 1.06)
DSST	1 (*ref.*)	1.07 (0.79, 1.45)	0.6717	1.03 (0.91, 1.18)

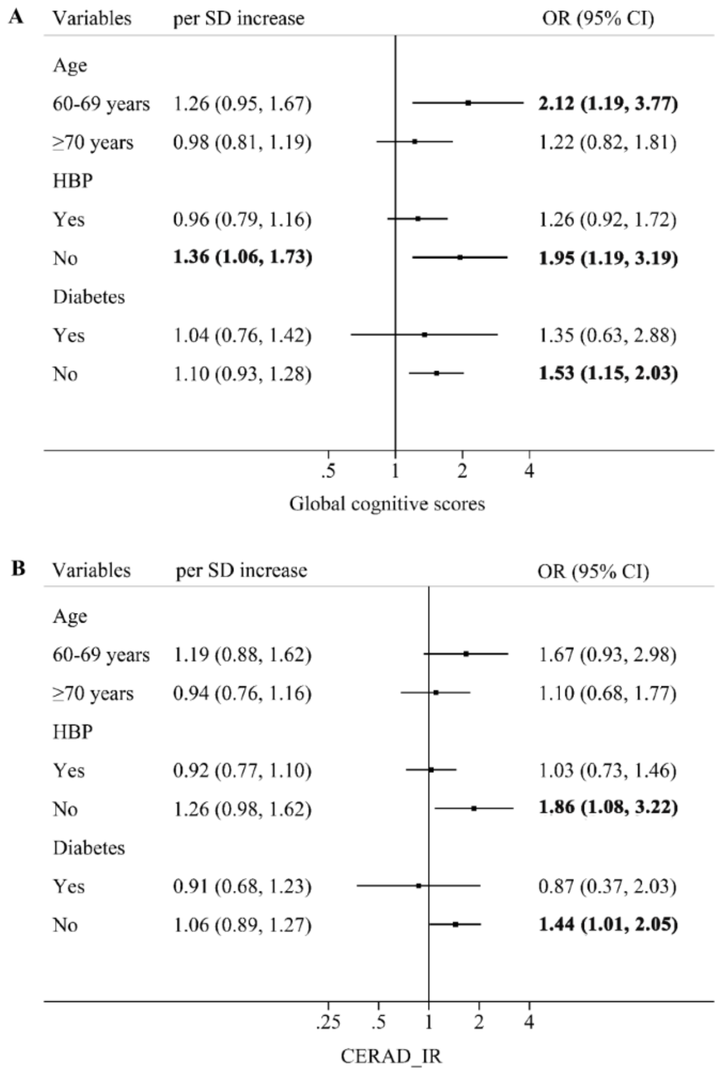

Figure 3. Stratified analysis of the relationship between dietary CML content and cognitive function. HBP, hypertension

4. Discussion

This study found that higher levels of dietary CML were associated with a greater risk of overall cognitive impairment among participants aged 60 years and older in the United States. Further subgroup analysis demonstrated that the positive association between dietary CML level and risk of overall cognitive impairment mainly existed in those aged 60-69 years old, without hypertension, and without type 2 diabetes. Moreover, our study also showed that dietary CML content was negatively correlated with immediate learning ability especially in those without hypertension, and without type 2 diabetes.

Previous studies have suggested dietary AGEs intake might be a risk factor for cognitive decline [4] [25-27]. For example, Beeri et al. [4] reported that total dietary AGEs could accelerate the rate of decline in episodic memory and perceptual speed, but had no effects on semantic memory, working memory and visuospatial cognitive domains. In a study of immunostaining of brain slices from 25 patients in the Oxford Project to Investigate Memory and Ageing (OPTIMA) cohort, it was found that patients with poor cognitive ability had a higher probability of positive CML staining of cortical neurons, and the accumulation of CML in the brain was related to the severity of cognitive impairment [25]. Consistent with previous findings, our study demonstrated that dietary CML intake is negatively associated global cognitive function in U.S. adults aged 60 years old and above. We further found that this negative association mainly existed in participants aged 60~69 years. Likewise, a cross-sectional survey of community-dwelling elderly aged≥60 years old in Japan found that the accumulation of AGEs was associated with lower cognitive performance [26]. In contrast, West et al. [27] reported that high levels of dietary AGEs were associated with a faster rate of memory decline over time in elderly averaged 71.0 (±8.1 SD) years of old. Nevertheless, it was suggested that for the elderly, attention should be paid to dietary CML intake, in order to reduce the risk of cognitive decline.

Our results also found that the positive association between dietary CML intake and risk of decline in overall cognitive function and immediate learning ability were more pronounced in non-hypertensive participants, and in those without type 2 diabetes. This is in contradictory to the findings by Zhang et al. [28], who reported that there was a negative correlation between plasma CML levels and cognitive function scores in patients with type 2 diabetes. It is likely that participants with hypertension or type 2 diabetes might take medications, thereby counteracting the deleterious effects of dietary CML on cognitive function. For instance, Stirban et al. [29] demonstrated that patients with type 2 diabetes who consumed a high AGEs diet showed a reduction in circulating AGEs levels after treatment with benfotiamine, as well as a reduction in oxidative stress levels [29]. In addition, hypertensive patients or diabetics might improve their dietary quality, which might also affect the associations between dietary CML level and cognitive performance. For example, also based on NHANES2011-2014, Zhang et al. [30] found that the adverse effects of uncontrolled hypertension on cognitive impairment in the elderly might be affected by dietary fiber intake [30].

From a mechanistic perspective, AGEs including CML mainly increase oxidative stress and inflammation by binding to specific cell surface related receptors, namely AGEs receptors (RAGE), and exert their cytotoxic effects. CML is also a ligand for RAGE receptors. The interaction between CML and RAGE promotes the production of free radicals and nuclear factors κB(NF-κB). The activation and expression of pro-inflammatory cytokines can lead to cellular dysfunction. The activation of RAGE also leads to the activation of glial cells, as well as the production of cytokines and reactive oxygen species (ROS) in the brain [31]. In addition, based on the results of Akhter et al. [3], CML increased significantly with age in the cerebral cortex and hippocampus of mice, which might reduce the activity of mitochondrial respiratory chain complex I and IV and ATP levels and increase oxidative stress, thus causing cognitive decline [3].

To our knowledge, this is the first study to evaluate dietary CML intake in the elderly in the United States based on 24 hr dietary recall and the developed UPLC-MS/MS based dietary AGEs database, and further explore the relationship between dietary CML content and overall as well as specific cognitive function in different populations. However, there are some limitations in the study. Firstly, this was a cross-sectional survey, and we were unable to determine the causal relationship of dietary CML and cognitive function. Secondly, the dietary data in the NHANES database was self-reported and not directly measured, with some information bias. Furthermore, the reported levels of CML may include other dietary components associated with cognitive function, thus requiring further validation of its relationship with serum CML levels.

5. Conclusions

Higher dietary CML intake in adults aged higher than 60 years old was associated with a greater risk of cognitive impairment. Further randomized controlled trials are needed to confirm the possible protective effect of dietary AGEs restriction on cognitive impairment.

ACKNOWLEDGEMENTS

This work was supported by the National Natural Science Foundation of China (grant NO. 82073535). We thank all team members and participants in the NHANES study.

Conflict of Interest

The authors declare no conflict of interest.

List of Abbreviations

Aβ42	Amyloidβ-42
AD	Alzheimer′s Disease
AF	Animal Fluency test
AGEs	advanced glycation end products
ATP	Association of Tennis Professionals
BMI	body mass index
CERAD	Consortium to Establish a Registry for Alzheimer's disease
CERAD W-L	CERAD Word Learning subtest
CERAD_IR	learning test from CERAD
CI	confidence interval
CML	N^{ε}-(carboxymethyl) lysine
DHHS	Department of Health and Human Services
DSST	Digit Symbol Substitution test
HBP	Hypertension
ICR	Institute of Cancer Research
MEC	mobile examination center
MET	metabolic equivalent
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
NCHS	National Center for Health Statistics
NF-κB	nuclear factors κB
NHANES	National Health and Nutrition Examination Survey
OR	odds ratio
OPTIMA	Oxford Project to Investigate Memory and Ageing
PHQ-9	Patient Health Questionnaire
RAGE	AGEs receptors
ROS	reactive oxygen species
SEs	standard error
U.S.	United States
USDA	U.S. Department of Agriculture
UPLC-MS/MS	ultra high performance liquid chromatography tandem mass spectrometry
WHO	World Health Organization
WWEIA	We Eat in America

References

[1] Collaborators, G.B.D.N., "Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016", *Lancet Neurol*, 18 (5), 459-480, May, 2019.

[2] Eshkoor, S.A., Hamid, T.A., Mun, C.Y.,Ng, C.K., "Mild cognitive impairment and its management in older people", *Clin Interv Aging,* 10, 687-693, 2015.

[3] Akhter, F., Chen, D., Akhter, A., Sosunov, A.A., Chen, A., McKhann, G.M., Yan, S.F.,Yan, S.S., "High Dietary Advanced Glycation End Products Impair Mitochondrial and Cognitive Function", *J Alzheimers Dis*, 76 (1), 165-178, 2020.

[4] Schnaider Beeri, M., Lotan, R., Uribarri, J., Leurgans, S., Bennett, D.A.,Buchman, A.S., "Higher Dietary Intake of Advanced Glycation End Products Is Associated with Faster Cognitive Decline in Community-Dwelling Older Adults", *Nutrients*, 14 (7), Mar 31, 2022.

[5] Perrone, L.,Grant, W.B., "Observational and ecological studies of dietary advanced glycation end products in national diets and Alzheimer's disease incidence and prevalence", *J Alzheimers Dis,* 45 (3), 965-979, 2015.

[6] Shen, C.Y., Lu, C.H., Wu, C.H., Li, K.J., Kuo, Y.M., Hsieh, S.C.,Yu, C.L., "The Development of Maillard Reaction, and Advanced Glycation End Product (AGE)-Receptor for AGE (RAGE) Signaling Inhibitors as Novel Therapeutic Strategies for Patients with AGE-Related Diseases", *Molecules,* 25 (23), Nov 27, 2020.

[7] Yang, S., Zhou, H., Wang, G., Zhong, X.H., Shen, Q.L., Zhang, X.J., Li, R.Y., Chen, L.H., Zhang, Y.H.,Wan, Z., "Quercetin is protective against short-term dietary advanced glycation end products intake induced cognitive dysfunction in aged ICR mice", *J Food Biochem,* 44 (4), e13164, Apr, 2020.

[8] Yang, S., Wang, G., Ma, Z.F., Qin, L.Q., Zhai, Y.J., Yu, Z.L., Xue, M., Zhang, Y.H.,Wan, Z., "DietaryAdvancedGlycationEnd Products-InducedCognitive Impairment in Aged ICR Mice: Protective Role of Quercetin", *Mol Nutr Food Res,* 64 (3), e1901019, Feb, 2020.

[9] Lubitz, I., Ricny, J., Atrakchi-Baranes, D., Shemesh, C., Kravitz, E., Liraz-Zaltsman, S., Maksin-Matveev, A., Cooper, I., Leibowitz, A., Uribarri, J., Schmeidler, J., Cai, W., Kristofikova, Z., Ripova, D., LeRoith, D.,Schnaider-Beeri, M., "High dietary advanced glycation end products are associated with poorer spatial learning and accelerated Abeta deposition in an Alzheimer mouse model", *Aging Cell,* 15 (2), 309-316, Apr, 2016.

[10] Ikeda, K., Higashi, T., Sano, H., Jinnouchi, Y., Yoshida, M., Araki, T., Ueda, S.,Horiuchi, S., "N (epsilon)-(carboxymethyl)lysine protein adduct is a major immunological epitope in proteins modified with advanced glycation end products of the Maillard reaction", *Biochemistry,* 35 (24), 8075-8083, Jun 18, 1996.

[11] Twarda-Clapa, A., Olczak, A., Bialkowska, A.M.,Koziolkiewicz, M., "Advanced Glycation End-Products (AGEs): Formation, Chemistry, Classification, Receptors, and Diseases Related to AGEs", *Cells,* 11 (8), Apr 12, 2022.

[12] Thangthaeng, N., Sumien, N.,Forster, M.J., "Dissociation of functional status from accrual of CML and RAGE in the aged mouse brain", *Exp Gerontol,* 43 (12), 1077-1085, Dec, 2008.

[13] Castellani, R.J., Harris, P.L., Sayre, L.M., Fujii, J., Taniguchi, N., Vitek, M.P., Founds, H., Atwood, C.S., Perry, G.,Smith, M.A., "Active glycation in neurofibrillary pathology of Alzheimer disease: N(epsilon)-(carboxymethyl) lysine and hexitol-lysine", *Free Radic Biol Med,* 31 (2), 175-180, Jul 15, 2001.

[14] Jono, T., Kimura, T., Takamatsu, J., Nagai, R., Miyazaki, K., Yuzuriha, T., Kitamura, T.,Horiuchi, S., "Accumulation of imidazolone, pentosidine and N(epsilon)-(carboxymethyl)lysine in hippocampal CA4 pyramidal neurons of aged human brain", *Pathol Int,* 52 (9), 563-571, Sep, 2002.

[15] Haddad, M., Perrotte, M., Landri, S., Lepage, A., Fulop, T.,Ramassamy, C., "Circulating and Extracellular Vesicles Levels of N-(1-Carboxymethyl)-L-Lysine (CML) Differentiate Early to Moderate Alzheimer's Disease", *J Alzheimers Dis,* 69 (3), 751-762, 2019.

[16] "Food Surveys Research Group: Beltsville, MD".

[17] Scheijen, J., Clevers, E., Engelen, L., Dagnelie, P.C., Brouns, F., Stehouwer, C.D.A.,Schalkwijk, C.G., "Analysis of advanced glycation endproducts in selected food items by ultra-performance liquid chromatography tandem mass spectrometry: Presentation of a dietary AGE database", *Food Chem,* 190, 1145-1150, Jan 1, 2016.

[18] Mirmiran, P., Yousefi, R., Mottaghi, A.,Azizi, F., "Advanced glycation end products and risk of hypertension in Iranian adults: Tehran lipid and glucose study", *J Res Med Sci,* 23, 43, 2018.

[19] Li, S., Sun, W.,Zhang, D., "Association of Zinc, Iron, Copper, and Selenium Intakes with Low Cognitive Performance in Older Adults: A Cross-Sectional Study from National Health and Nutrition Examination Survey (NHANES)", *J Alzheimers Dis,* 72 (4), 1145-1157, 2019.

[20] Liu, D., Xie, F., Zeng, N., Han, R., Cao, D., Yu, Z., Wang, Y.,Wan, Z., "Urine caffeine metabolites are positively associated with cognitive performance in older adults: An analysis of US National Health and Nutrition Examination Survey (NHANES) 2011 to 2014", *Nutr Res,* 109, 12-25, Jan, 2023.

[21] Fayemendy, P., Mabiama, G., Vernier, T., Massoulard-Gainant, A., Villemonteix, C., Desport, J.C.,Jésus, P., "Nutritional status, dementia, and mobility among nursing home's residents: First exhaustive cross-sectional study in Limousin territory (France)", *PLoS One,* 16 (4), e0250595, 2021.

[22] "1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. Guidelines Subcommittee", *J Hypertens,* 17 (2), 151-183, Feb, 1999.

[23] "2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2022", *Diabetes Care,* 45 (Suppl 1), S17-s38, Jan 1, 2022.

[24] Gu, Y., Guo, J.,Moshfegh, A.J., "Race/ethnicity and gender modify the association between diet and cognition in U.S. older adults: National Health and Nutrition Examination Survey 2011-2014", *Alzheimers Dement (N Y),* 7 (1), e12128, 2021.

[25] Southern, L., Williams, J.,Esiri, M.M., "Immunohistochemical study of N-epsilon-carboxymethyl lysine (CML) in human brain: relation to vascular dementia", *BMC Neurol,* 7, 35, Oct 16, 2007.

[26] Tabara, Y., Yamanaka, M., Setoh, K., Segawa, H., Kawaguchi, T., Kosugi, S., Nakayama, T., Matsuda, F.,Nagahama Study, G., "Advanced Glycation End Product Accumulation is Associated with Lower Cognitive Performance in an Older General Population: The Nagahama Study", *J Alzheimers Dis,* 74 (3), 741-746, 2020.

[27] West, R.K., Moshier, E., Lubitz, I., Schmeidler, J., Godbold, J., Cai, W., Uribarri, J., Vlassara, H., Silverman, J.M.,Beeri, M.S., "Dietary advanced glycation end products are associated with decline in memory in young elderly", *Mech Ageing Dev,* 140, 10-12, Sep, 2014.

[28] Zhang, J.H., Xu, H.Z., Shen, Q.F., Lin, Y.Z., Sun, C.K., Sha, L., Ge, Y.S., Liu, Y.,Wang, C., "Nepsilon-(carboxymethyl)-lysine, White Matter, and Cognitive Function in Diabetes Patients", *Can J Neurol Sci,* 43 (4), 518-522, Jul, 2016.

[29] Stirban, A., Negrean, M., Stratmann, B., Gawlowski, T., Horstmann, T., Götting, C., Kleesiek, K., Mueller-Roesel, M., Koschinsky, T., Uribarri, J., Vlassara, H.,Tschoepe, D., "Benfotiamine prevents macro- and microvascular endothelial dysfunction and oxidative stress following a meal rich in advanced glycation end products in individuals with type 2 diabetes", *Diabetes Care,* 29 (9), 2064-2071, Sep, 2006.

[30] Zhang, H., Tian, W., Qi, G.,Sun, Y., "Hypertension, dietary fiber intake, and cognitive function in older adults [from the National Health and Nutrition Examination Survey Data (2011-2014)]", *Front Nutr,* 9, 1024627, 2022.

[31] Younessi, P.,Yoonessi, A., "Advanced glycation end-products and their receptor-mediated roles: inflammation and oxidative stress", *Iran J Med Sci,* 36 (3), 154-166, Sep, 2011.