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Effect of dietary protein intake on cognitive function in the elderly with chronic kidney disease: analysis of the National Health and Nutrition Examination Survey 2011–2014

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ABSTRACT

Background: Cognitive dysfunction is prevalent among the elderly diagnosed with chronic kidney disease (CKD). Low protein diets are used for retarding the progression of CKD in clinical practice. Nonetheless, the impact of dietary protein consumption on cognitive function in this population remains uncertain.

Methods: We recruited 2306 participants (≥60 years) from 2011 to 2014 National Health and Nutrition Examination Survey (NHANES). 24-h dietary recall questionnaire was utilized to evaluate protein intake. Cognitive function was measured using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), Animal Fluency Test (AFT), and Digit Symbol Substitution Test (DSST). Participants' characteristics were analyzed, and the interaction between protein consumption and CKD on cognitive impairment were analyzed using a logistic regression model.

Results: We divided participants into three groups based on CKD stages: no CKD, CKD stage G1 to G2 (19%), and CKD stage G3 to G5 (18%). The average protein intake was 0.97 g/(kg·d). In the higher protein intake group, CKD stages G1 to G2 elevated the risk of immediate memory impairment (OR: 2.441, 95% CI: 1.161–5.132 for protein consumption in 1.0-1.2g/(kg·d); OR: 2.225, 95% CI: 1.015–4.876 for protein consumption in >1.2 g/(kg·d)). However, no similar resuts were observed in the lower protein intake group. In addition, the interaction between CKD status and protein intake on immediate memory was statistically significant ($p = .041$).

Conclusion: A higher probability of cognitive impairment in the elderly with early-stage CKD may be linked to higher protein intake. Low protein diets may be a potential strategy to release cognitive impairment in the elderly with early-stage CKD.

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1. Introduction

Cognition involves psychological and social behaviors, including learning, memory, language, reasoning, mood, and emotions. Abnormalities in these processes can cause severe learning and memory disorders, accompanied by aphasia, apraxia, agnosia, and other pathological processes, leading to cognitive impairment [1]. By the year 2050, it is projected that approximately 130 million individuals will be impacted by dementia, with a global rise in the prevalence of cognitive decline [2]. Older adults are particularly susceptible to the onset of cognitive impairment and dementia [3,4]. In addition, early screening for cognitive disorders allows measuring the incidence of these disorders in different populations and implementing preventive interventions [5,6]. Chronic kidney disease (CKD) is a progressive disease correlated with a higher incidence of cognitive impairment [7,8]. However, the mechanisms underlying cognitive decline in CKD are incompletely understood and may be due to CKD-associated diseases, including hyperhomocysteinemia [9], neurodegeneration [7,8,10], and cardiovascular and cerebrovascular diseases [11].

Most CKD patients develop end-stage renal disease within a span of several years to decades, necessitating costly therapeutic interventions such as dialysis and kidney transplantation for survival [12,13]. There are approximately 800 million people with CKD worldwide, accounting for 11-13% of the global population, posing a significant health burden. In addition, CKD is linked to a heightened susceptibility to cardiovascular diseases and cerebrovascular events [11], tumors

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[14], and psychiatric disorders [7,8,10]. Therefore, in individuals with CKD, the primary objective of therapeutic interventions is to retard the advancement of CKD toward end-stage kidney disease (ESKD). The treatment of CKD involves pharmaceutic drugs, nutritional support, and dialysis, throughout the disease course (stages G1-G5). Dietary therapies involving low protein intake are essential to retard the advancement to ESKD. In addition, low protein diets reduce complications and mortality in the population diagnosed with CKD [15–17].

Although many studies have attempted to reveal the relationship between dietary patterns and cognitive function, the results of a systematic review indicate that the impact of different healthy dietary patterns on cognitive function in the population still remains highly controversial [18]. Furthermore, the effect of protein intake on cognitive function varies depending on the population [19–21]. Currently, there is a lack of research elucidating the relationship between dietary protein intake and cognitive function in elderly individuals with CKD. This research assessed the influence of dietary protein consumption on cognitive function in elderly individuals diagnosed with CKD, utilizing data from the National Health and Nutrition Examination Survey (NHANES) database.

2. Methods

2.1. Study population and data source

This present cross-sectional investigation comprised a total of 2306 individuals aged ≥60 years, who were selected from the 2011–2012 and 2013–2014 NHANES cycles. NHANES is a comprehensive survey that evaluates the health and nutritional condition of both children and adults residing in the United States. NHANES selects different sample populations for each cycle and completes data collection for each study individual within a specified time frame. NHANES does not conduct follow-up on the study individuals. Data on demographic characteristics, socioeconomic and nutritional status, and laboratory tests were analyzed. The exclusion criteria were age <60 years and participants with missing data on cognitive function, laboratory tests (serum creatinine, urine albumin and creatinine), nutrient intake, and other covariates. This research received ethical approval from the Ethics Committee of the National Center for Health Statistics. Written informed consent was obtained from all participants.

2.2. Cognitive function

Cognitive function was measured using word learning and recall modules from the Consortium to Establish a Registry for Alzheimer's disease (CERAD), Animal Fluency Test (AFT), and Digit Symbol Substitution Test (DSST). CREAD was an organization funded by Alzheimer's Disease Research Centers in 1986 to develop a brief neuropsychological assessment battery which had been widely adopted on cognitive status, especially in the elderly [22]. Immediate and delayed learning of new verbal information (memory subdomain) was assessed using the CERAD Word Learning subtest. The assessment comprised of three successive learning trials to evaluate immediate memory, followed by a delayed recall test to assess delayed memory. Participants were given instructions to orally recite a set of 10 unrelated words and subsequently recall as many words as they could. The AFT measures categorical verbal fluency, which is a crucial aspect of executive function. Participants were instructed to generate the names of as many animals as they could within a time limit of 1 min. The DSST was employed to assess processing speed, sustained attention, and working memory. The test comprises pairs of digits and symbols, followed by a series of digits. Participants were directed to transcribe the corresponding symbols into the 133 adjacent boxes within a two-minute timeframe. Given the absence of a universally accepted criterion for defining cognitive impairment in these assessments, the cutoff point for identifying impairment was determined as the lowest quartile of the scores, as described previously [23,24]. These cutoff points were adjusted for age because age significantly impacts cognitive function [25] (Supplementary Table 3).

2.3. CKD stage

The staging of chronic kidney disease (CKD) is determined by the estimated glomerular filtration rate (eGFR) and the ratio of urinary albumin to urinary creatinine (UACR). The eGFR is calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which is based on the blood creatinine concentration, gender, race, and age (Supplementary Table 2) [26]. Blood creatinine is measured using the JAFFE rate method by the DxC800 modular chemistry system. Detailed detection methods refer to https://wwwn.cdc.gov/Nchs/Nhanes/2011-2012/BIOPRO_G.htm. Urinary albumin and urinary creatinine are measured using a solid-phase fluorescent immunoassay and the Roche/Hitachi Modular P Chemistry Analyzer, respectively. Detailed detection methods refer to https://wwwn.cdc.gov/Nchs/Nhanes/2011-2012/ALB_CR_G.htm. The CKD stages were defined based on eGFR and the urinary albumin-to-creatinine ratio (UACR) as follows: non-CKD (eGFR ≥60 mL/min/1.73 m^2 and UACR <30 mg/g), CKD stages G1 or G2 (eGFR ≥60 mL/min/1.73 m^2 and UACR ≥30 mg/g), and CKD stages G3-G5 (eGFR <60 mL/min/1.73 m^2) [27].

2.4. Dietary protein intake

A report from the Food and Nutrition Board of the Institute of Medicine has shown that 0.8 g/(kg·d) of protein meets the daily requirement for 97.5% of the healthy adult population [28]. High protein intake (1.0–1.2 g/(kg·d)) is recommended for older adults to maintain muscle mass [29]. Based on their protein intake levels (in g/(kg·d)), the participants were categorized into four groups: <0.8, 0.8–1.0, 1.0–1.2, and >1.2. Data on protein intake were collected by 24-h recalls using the US Department of Agriculture Automated Multiple-Pass Method.

2.5. Covariates

Information regarding demographic characteristics, lifestyle factors, and health status was gathered. Demographic information included age, sex, race (non-Hispanic white, non-Hispanic black, Mexican American, non-Hispanic Asians, other Hispanics, other races), education (secondary and high school, university degree), and the poverty impact ratio. Lifestyle information included smoking status (never smoker, former smoker, current smoker), and alcohol consumption (none, 1–5, 5–10, or >10 drinks/month). Health information included body mass index (BMI), history of hypertension (systolic blood pressure >130 mmHg or diastolic blood pressure >80 mmHg), diabetes (hemoglobin A1C concentration ≥6.5%, fasting plasma glucose ≥126 mg/dL, or self-reported diabetes), stroke and depression (none, mild to moderate, moderate to severe). The depression status of participants was evaluated using the Patient Health Questionnaire-9 (PHQ-9) [30].

2.6. Statistical analysis

The patients were divided into three subgroups: non-CKD, CKD stages G1-G2, and CKD stages G3-G5. Continuous variables that followed a normal distribution were represented using mean values and standard deviations, while categorical variables were expressed as percentages. To assess the significance of variations in means for continuous variables and categorical variables, analysis of variance and Pearson's χ^2 test were employed, respectively. The mobile examination center sample weights were used, and the results represented the US civilian population [31]. Unweighted characteristics are shown in Supplementary Table 1. We evaluated the cognitive function of participants with different CKD stages. To evaluate the influence of CKD status on cognitive function, a weighted logistic regression model was employed, controlling for potential confounding factors, including gender, age, BMI, education, smoking, alcohol consumption, medical history of hypertension, stroke, and depression. The interaction between CKD status and protein intake was analyzed. The unadjusted logistic regression model is shown in Supplementary Table 5. We developed weighted linear regression models (Supplementary Table 6), excluded participants with depression (Supplementary Table 7) and included participants who were initially excluded from the logistic regression model because of incomplete data on covariates for sensitive analysis (Supplementary Table 8). The robustness of the observed significant relationship between protein intake, CKD status, and cognitive function was confirmed in the sensitivity analysis. The statistical analysis was performed using R software version 4.2.2. All statistical tests were two-tailed, and statistical significance was defined as p-values less than .05.

3. Results

3.1. Baseline characteristics of the participants

Among 19931 subjects, 2306 were included in the study after applying the exclusion criteria (Figure 1). The demographic and clinical characteristics of the study participants are presented in Table 1 and Supplementary Table 1 (unweighted). In our participants, 21.8% were aged ≥80 years, 51% were non-Hispanic white, and 50.7% were female. In addition, the participants with CKD were more likely to be smokers and have lower levels of protein intake, alcohol intake, and education, and a higher risk of hypertension, diabetes, stroke, and depression.

3.2. CKD status and cognitive function

Performance on the cognitive function of participants with and without CKD are shown in Figure 2. People with CKD performed worse than the non-CKD population in the four cognitive tests, and people with CKD stage G1 or G2 performed worse than those with stages G3, G4, or G5, and the difference was significant in the four cognitive function tests (Supplementary Table 4). In the weighted logistic regression model unadjusted for covariates, CKD increased the risk of cognitive impairment, and the risk was higher in CKD stages G1 and G2 than in stages G3-G5 (Supplementary Table 5). In the adjusted multivariate logistic regression model, CKD stages G1 and G2 increased the risk of immediate memory impairment by 47.4% (OR: 1.474, 95% CI: 1.027–2.117, $p = .037$) and the risk of cognitive impairment (according to the DSST) 122.4% (OR: 2.224, 95% CI: 1.648–3.057, $p < .01$) but did not significantly affect delayed memory and verbal fluency. CKD stages G3-G5 were not associated with cognitive impairment in the four domains (Table 2).

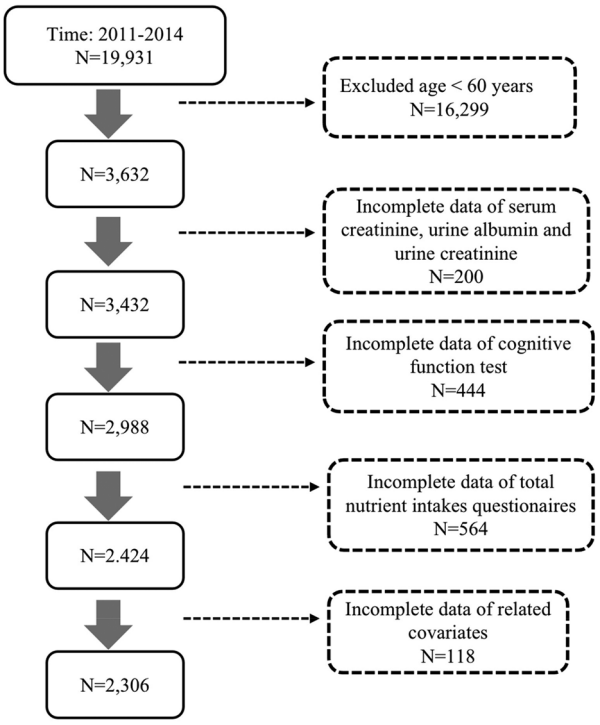

Figure 1. Flow chart of the screening process for the selection of eligible participants.

Table 1. Characteristics of participants aged 60 years and older from the NHANES (2011–2014).

Characteristics	Overall (*N* = 2306)	Non-CKD (*N* = 1458)	CKD stage G1-G2 (*N* = 433)	CKD stage G3-G5 (*N* = 415)	*p*-value
Age group, *n* (%)					<.0001
60–69 years	1177(51.04)	867(61.64)	179(40.50)	131(32.38)	
70–79 years	634(27.49)	370(24.23)	122(28.49)	142(36.92)	
80+ years	495(21.47)	221(14.13)	132(31.00)	142(30.69)	
Sex, *n* (%)					.47
male	1137(49.31)	713(47.45)	226(46.63)	198(43.69)	
female	1169(50.69)	745(52.55)	207(53.37)	217(56.31)	
Race, *n* (%)					<.001
Non-Hispanic White	1175(50.95)	728(81.06)	207(74.14)	240(81.91)	
Non-Hispanic Black	516(22.38)	288(6.48)	109(10.87)	119(10.95)	
Mexican American	200(8.67)	148(3.68)	38(4.51)	14(1.49)	
Non-Hispanic Asian	157(6.81)	117(3.68)	28(3.72)	12(1.58)	
Other Hispanic	225(9.76)	158(3.73)	44(4.18)	23(2.00)	
Other/multiracial	33(1.43)	19(1.35)	7(2.58)	7(2.06)	
Education, *n* (%)					<.001
≤High school graduate	1077(46.7)	634(33.79)	241(48.68)	202(37.20)	
≥Collage	1229(53.3)	824(66.21)	192(51.32)	213(62.80)	
PIR, mean (SD)	3.17(0.08)	3.30(0.09)	2.71(0.11)	3.06(0.12)	<.001
Body mass index (BMI), mean (SD)	29.06(0.23)	28.75(0.29)	29.72(0.41)	29.68(0.36)	.06
Smoking status, *n* (%)					.01
Never Smoker	1130(49)	745(51.01)	188(44.50)	197(49.68)	
Former Smoker	887(38.46)	543(37.82)	169(40.52)	175(43.44)	
Current Smoker	289(12.53)	170(11.17)	76(14.98)	43(6.88)	
Alcohol consumption, *n* (%)					.04
Non-drinker	699(30.31)	422(24.71)	144(34.36)	133(28.01)	
1–5 drinks/month	1125(48.79)	712(48.28)	210(46.49)	203(50.25)	
5–10 drinks/month	108(4.68)	74(6.04)	18(3.23)	16(4.24)	
10+ drinks/month	374(16.22)	250(20.96)	61(15.92)	63(17.50)	
Hypertension, *n* (%)					<.0001
No	496(21.51)	379(29.79)	52(13.27)	65(15.99)	
Yes	1810(78.49)	1079(70.21)	381(86.73)	350(84.01)	
Diabetes, *n* (%)					<.0001
No	1638(71.03)	1125(82.23)	219(57.22)	294(73.65)	
Yes	668(28.97)	333(17.77)	214(42.78)	121(26.35)	
Stroke, *n* (%)					.001
No	2154(93.41)	1388(95.56)	388(90.02)	378(91.86)	
Yes	152(6.59)	70(4.44)	45(9.98)	37(8.14)	
Depression, *n* (%)					.002
Non-depression	1748(75.8)	1140(81.00)	291(71.32)	317(78.12)	
Mild to Moderate	483(20.95)	279(17.00)	118(23.05)	86(20.35)	
Moderately Sever to Sever	75(3.25)	39(2.01)	24(5.63)	12(1.53)	
Protein intake at different level, *n* (%)					.003
<0.8	965(41.85)	555(35.49)	207(48.09)	203(46.03)	
0.8–1.0	466(20.21)	306(21.96)	90(23.48)	70(17.09)	
1.0–1.2	362(15.7)	235(17.36)	60(11.37)	67(18.60)	
>1.2	513(22.25)	362(25.20)	76(17.06)	75(18.28)	
Dietary protein intake, mean (SD)	0.97(0.01)	1.00(0.01)	0.87(0.02)	0.91(0.03)	<.0001

Normally distributed continuous variables were displayed as means and standard deviations (SDs), categorical variables were displayed as proportions. Analysis of Variance (ANOVA) were used for comparison of Continuous variables and Pearson's χ^2 test were used for comparison of categorical variables. The mobile examination center sample weights were accounted and the results represented the US civilian resident population.

3.3. The association between CKD status and cognitive function differed depending on dietary protein intake

The association between CKD status and immediate memory impairment differed depending on protein intake in participants with and without CKD (p for interaction = 0.041). In the population on a high protein diet, compared with the absence of CKD, CKD stages G1 and G2 increased the risk of immediate memory impairment (OR: 2.441, 95% CI: 1.161–5.132 for a protein intake of 1.0–1.2 g/(kg·d); OR: 2.225, 95% CI: 1.015–4.876 for an intake of >1.2 g/(kg·d)) (Table 2). The increase in the risk of short-term memory impairment was not significant in the group on a low protein diet. The effect of the interaction between CKD and protein intake was not significant for the other cognitive domains.

4. Discussion

This study utilized data from the NHANES 2011–2014 to investigate the correlation between cognitive function and dietary protein intake among elderly individuals diagnosed with CKD. The results showed that CKD stages G1 and G2 were strongly associated with worse cognitive performance in immediate memory and executive and processing function. In turn, there was no significant correlation between CKD stages G3–G5 and the level of cognitive impairment

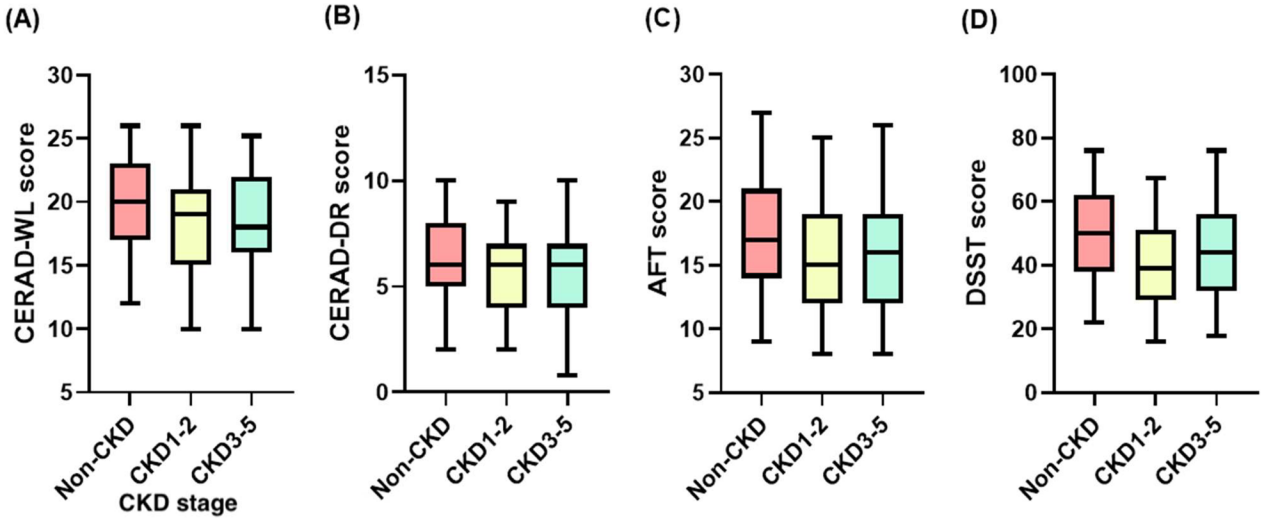

Figure 2. Cognitive function test scores by CKD stage among participants ≥60 years old from the NHANES (2011–2014) (overall (*N* = 2306); non-CKD (*N* = 1458); CKD stage G1-G2 (*N* = 433); CKD stage G3-G5 (*N* = 415)).

Table 2. CKD status and cognitive function impairment by levels of dietary protein intake among participants aged 60 years and older from the NHANES (2011–2014).

		CKD stage G1-G2 (*N* = 433)		CKD stage G3-G5 (*N* = 415)			
Character	non-CKD (*N* = 1458)	OR (95%CI)	*p* value	OR (95%CI)	*p* value	*p* for trend *p* for interaction	*p* for interaction
CERAD immediate recall							**.041**
Total	ref	1.474(1.027, 2.117)	**0.037**	1.042(0.672, 1.617)	0.844	0.486 **0.041**	
<0.8	ref	1.259(0.736, 2.155)	0.377	1.002(0.581, 1.727)	0.994	0.83	
0.8–1.0	ref	1.009(0.475, 2.144)	0.981	0.885(0.397, 1.973)	0.749	0.97	
1.0–1.2	ref	2.441(1.161, 5.132)	**0.022**	2.174(0.770, 6.137)	0.132	0.101	
>1.2	ref	2.225(1.015, 4.876)	**0.046**	0.505(0.168, 1.516)	0.206	**0.01**	
CERAD delayed recall							.228
Total	ref	1.333(0.932, 1.907)	0.108	1.219(0.800, 1.857)	0.333	0.252 0.228	
<0.8	ref	1.172(0.741, 1.854)	0.473	1.486(0.948, 2.332)	0.080	0.08	
0.8–1.0	ref	1.198(0.518, 2.771)	0.652	0.474(0.239, 0.942)	0.035	0.86	
1.0–1.2	ref	1.031(0.418, 2.540)	0.944	1.449(0.582, 3.610)	0.401	0.421	
>1.2	ref	2.062(0.862, 4.935)	0.098	1.040(0.451, 2.398)	0.921	0.254	
The Animal Fluency test (AFT)							.187
Total	ref	1.275(0.920, 1.767)	0.135	1.362(0.966, 1.918)	0.074	**0.043** 0.187	
<0.8	ref	1.396(0.911, 2.139)	0.117	1.654(0.995, 2.751)	0.052	**0.036**	
0.8–1.0	ref	0.579(0.266, 1.263)	0.156	0.864(0.369, 2.025)	0.720	0.153	
1.0–1.2	ref	2.070(1.003, 4.268)	**0.049**	1.198(0.400, 3.584)	0.731	0.512	
>1.2	ref	1.381(0.562, 3.393)	0.457	1.381(0.594, 3.213)	0.429	1	
The Digit Symbol Substitution test (DSST)							.097
Total	Ref	2.244(1.648, 3.057)	**<0.0001**	1.295(0.789, 2.125)	0.284	0.056 0.097	
<0.8	Ref	1.598(1.131, 2.259)	**0.011**	1.204(0.637, 2.276)	0.545	0.353	
0.8–1.0	Ref	2.532(1.106, 5.797)	**0.030**	1.388(0.409, 4.713)	0.576	**0.033**	
1.0–1.2	Ref	7.882(2.482, 25.024)	**0.002**	1.026(0.235, 4.484)	0.971	0.315	
>1.2	Ref	2.250(0.953, 5.312)	0.063	1.206(0.539, 2.696)	0.628	0.223	

The logistic regression model was adjusted by age, gender, BMI, education, smoking, alcohol intake, hypertension, diabetes, stroke, depression. Sampling weights were considered in logistic regression analyses to obtain nationally representative estimates.

and no significant association between CKD status and delayed memory.

The association between CKD status and cognitive performance differed depending on protein intake in patients with CKD stage G1 to G2 compared with those without CKD. In the group on a high protein diet, the participants with CKD stage G1 to G2 had poorer immediate memory than those without CKD; however, this association was not found among subjects on a low protein diet. These results indicate that high protein intake is a risk factor for impaired immediate memory in elderly individuals with CKD stages G1 to G2, while low protein intake may improve this adverse impact.

Cognitive health is a public health concern [32]. With the aging of society, the morbidity and mortality of CKD and the risk of cognitive impairment are increasing in countries with long life expectancy [33]. This study found that CKD increased the risk of impairment of memory, executive function, information processing speed, and sustained attention, in line with the previous literature [34–36]. A prospective cohort study demonstrated that kidney dysfunction was associated with higher cognitive impairment, even in subjects with early-stage

CKD [37]. A community-based cross-sectional study with 923 individuals showed that early-stage CKD reduced cognitive performance and cognitive function [38]. The results of prospective studies from Germany and the United States found that CKD severity was positively associated with the degree of cognitive impairment [36,37]. Nonetheless, this relationship was not significant in our study, and cognitive function was marginally worse in subjects with CKD stages G1 or G2 than in those with stage G3 - G5. Some previous studies have also reported no significant correlation between eGFR and cognitive impairment [39], and the reasons for this phenomenon seem difficult to explain. For this study, one possible explanation is that the non-dialysis population with CKD stage G4 and G5 was relatively small (Supplementary Table 9), which may have underestimated the relationship between protein intake, advanced CKD, and cognitive function. In the future, researchers can further investigate the relationship between CKD and cognitive impairment in the elderly by expanding the sample size of CKD stage G4–G5, or validating through multiple databases.

Low protein diets are widely used for treating CKD before dialysis in stages G3–G5 to delay disease progression. The evidence from the PROT-AGE Study Group suggests that a low-protein diet (0.6 g/(kg·d)) can delay the progression of CKD in elderly patients with advanced CKD (eGFR < 30 mL/min/1.73 m^2), and adequate energy supplementation can effectively prevent the occurrence of malnutrition [40]. Protein intake is associated with cardiovascular health, metabolism, cognition, and other functions in older adults [41–43]. Nonetheless, in the elderly population, there remains a lack of consensus regarding the connection between protein consumption and cognitive performance. For instance, a study found that protein intake in the elderly with dementia living in nursing homes in France was significantly higher than those without dementia [19]. A cross-sectional study based on NHANES showed that higher protein intake from milk and dairy products was related to poorer cognitive performance [43]. In addition, the Mediterranean diet, characterized by low protein intake, is linked with a lower likelihood of incident cognitive impairment, better cognitive performance, and lower learning and memory decline in middle-aged and elderly people [44–46].

Animal studies provide indirect evidence of the detrimental effects of high protein intake on cognitive function. High protein diets worsen spatial memory deficits in rats with cirrhosis [47]. Furthermore, brain weight in mice with Alzheimer-like pathology consuming a high protein diet was smaller than that of controls, and neuronal density and size in hippocampal subregions tended to be lower in the former [48]. We found that older people with CKD stage G1 or G2 on a high protein diet had poorer memory function than those without CKD. In addition, the relationship between CKD and memory function could be reversed by low protein intake. In contrast, other studies showed that high protein intake in patients with psychiatric disorders was associated with less cognitive decline [20,21]. Thus, further subgroup studies are necessary to address inconsistencies in the results.

The previous study found that compared with the low protein intake, people who had high protein intake had higher concentrations of inflammatory markers in peripheral blood [49,50]. In addition, CKD patients have systemic inflammation [51]. Past studies have suggested that inflammation may be related to AD and cognitive impairment. Inflammatory models of neurodegeneration showed that higher circulating inflammation levels would cause cognitive decline [52]. Therefore, a high protein diet may affect the cognitive function of patients with early stages of CKD by aggravating the inflammation.

Elevated levels of homocysteine in the bloodstream could be a contributing factor to the detrimental impact of high level of protein consumption on cognitive decline. A cross-sectional study found that the population with a high protein diet had higher blood concentration of homocysteine [53]. In addition, the albumin excretion rate is strongly associated with fasting plasma homocysteine levels [54], and increased homocysteine level is a risk factor for Alzheimer's disease and dementia [55–57]. Homocysteine increases the risk of cognitive impairment by promoting thrombosis and endothelial dysfunction [58,59]. Further, homocysteine has neurotoxic effects by activating the N-methyl-D-aspartate receptor [60]. Nonetheless, the underlying mechanisms are unclear.

This study indicated the potential benefits of low protein diets on cognitive function in elderly patients with early-stage CKD. However, present dietary treatments focus on non-dialysis patients with CKD stages G3–G5. Thus, additional prospective studies are necessary to assess the effects of low protein diets on cognitive function in patients with early-stage CKD.

However, it cannot be ignored that protein intake may be related to overall food intake, and food intake is related to calorie intake. We found that there are only limited studies attempting to reveal the relationship between calorie intake and cognitive function, and the conclusions are inconsistent. A cross-sectional study from Korea showed that participants aged 70–84 years who had calorie intake below the recommended levels were more likely to have cognitive impairment, mainly characterized by memory decline [61]. A 6-month RCT study showed that calorie restriction did not change the cognitive function of the participants [62]. However, animal experiments have found that calorie restriction is associated with reduced beta-amyloid deposition, hippocampal synaptic adaptation, and vascular health, which are the pathophysiological basis for improving cognitive function [63]. Therefore, future research needs to consider controlling calorie intake to reduce bias caused by differences in calorie intake.

This study has limitations. First, causal relationships between CKD, protein intake, and cognitive function were not evaluated, future cohort studies and RCT studies may compensate for this limitation. Second, unknown confounders were not controlled in logistic regression. Third, it is difficult to measure protein intake levels accurately because of recall bias. Future studies can test such as urine nitrogen excretion or quantitation of nitrogen appearance to quantitatively analyze protein intake, in order to obtain more accurate data on protein intake.

The study has strengths. First, the study based on the NHANES database increased sample representativeness through weighted analysis. Second, the chosen indicators allowed analyzing multiple cognitive function domains. Third, the CKD-EPI formula estimates the glomerular filtration rate by race, sex, and age, and the CKD stage was identified using eGFR and ACR, which ensured the accurate identification of people with early CKD stages.

5. Conclusion

Renal impairment has been linked to cognitive deterioration in the geriatric population, while low protein diets can potentially reduce memory impairment in this population. These data may help develop effective nutritional management strategies for cognitive impairment in elderly population diagnosed as CKD. To prevent cognitive dysfunction, clinicians should consider using low protein diets in patients with CKD stage G1 or G2. Furthermore, older adults with CKD on a high protein diet should be screened for cognitive impairment.

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Authors contributions

JD.H and MD.S conceptualized the research topic and framework; JD.H and YH.W identified the methodological details of the research; JD.H, Y.Y and HM.L used statistical software for data analysis; JD.H, Y.Y wrote the main manuscript text; JD.H and MD.S conducted Writing-review and editing. All authors reviewed the manuscript.

Ethical approval

The CDC/NCHS Research Ethics Review Board granted approval for the detailed methods and protocols employed in the NHANES study. These procedures, including informed consent protocols for participants, can be accessed on the CDC.gov website. All methods adhered to the applicable guidelines and regulations. Since the data used in this study are publicly available, it was exempt from ethical review involving human subjects.

Disclosure statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Data availability statement

All data can be downloaded from the NHANES website (https://www.cdc.gov/nchs/nhanes/about_nhanes.htm).

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