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Original Article

Healthy dietary patterns in relation to cognitive performance and Alzheimer's disease mortality☆,☆☆

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ABSTRACT

Background: Dietary factors play a major role in cognitive aging, but few studies have assessed and compared the associations between specific dietary patterns and Alzheimer's disease (AD) mortality.
Methods: We included 27,773 U.S. participants (mean age = 59.8 years, 51.4 % female) from the National Health and Nutrition Examination Survey (NHANES) between 1998 and 2016, with follow-up for AD mortality until December 2019. Five dietary pattern scores were calculated utilizing one (1999–2002) or two repeated (2003–2016) 24hr dietary recalls, including the Healthy Eating Index (HEI-2015), the healthful plant-based diet index (hPDI), the alternate Mediterranean diet (aMED), the Dietary Approach to Stop Hypertension diet (DASH), and the Mediterranean-DASH Intervention for Neurodegeneration Delay diet (MIND) scores. We utilized Cox proportional hazard models to evaluate the associations of these dietary pattern scores with AD mortality.
Results: A total of 260 AD deaths occurred during a median follow-up of 9.8 years. Higher aMED score was associated with a lower risk of AD mortality ($HR_{T3\ vs\ T1}$: 0.72, 95 % CI, 0.52–1.00, p-trend = 0.041). In a sub-sample of 2,713 participants in NHANES 2011-2014, 432 individuals had prevalent psychometric mild cognitive impairment (p-MCI). Higher aMED, MIND, HEI-2015, and hPDI were associated with lower odds of p-MCI. The potential contributors to these associations included higher intake levels of vegetables and nuts, moderate alcohol consumption, and lower intake level of sweets.
Conclusions: The Mediterranean dietary pattern was associated with more favorable cognitive outcomes among middle-aged and older adults, underscoring the importance of a healthy diet for long-term benefits in cognitive and brain health.

1. Introduction

Population aging has led to an increasing prevalence of Alzheimer's disease (AD), which has become the fifth-leading cause of death for Americans aged 65 and older [1]. Among various modifiable factors, diet plays a potential role in the development and progression of AD and related dementia, potentially contributing to mortality from these conditions [2–4].

Foods and nutrients act synergistically on health, forming specific dietary patterns [4]. Existing literature has identified or devised several dietary patterns that potentially benefit health, such as the plant-based, antioxidant-rich alternate Mediterranean diet (aMED) inspired by the

Abbreviations: AD, Alzheimer's disease; aMED, alternate Mediterranean diet; DASH, the Dietary Approach to Stop Hypertension diet; HEI-2015, Healthy Eating Index; hPDI, healthful Plant-based diet index; HPFS, Health Professionals Follow-up Study; ICD-10, International Statistical Classification of Disease, Tenth Revision; mhPDI, modified healthful Plant-based diet index; MIND, Mediterranean-DASH Intervention for Neurodegeneration Delay diet; NHANES, National Health and Nutrition Examination Survey; NHS, Nurses' Health Study; p-MCI, psychometric mild cognitive impairment; SD, standard deviation; 24hr, 24-hour.

☆ The authors have no conflict of interest to declare.

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dietary pattern in the Mediterranean countries [5]; the low-sodium Dietary Approach to Stop Hypertension (DASH) for blood pressure control [6]; the Healthy Eating Index 2015 (HEI-2015), reflecting the Dietary Guidelines for Americans; and the healthful Plant-based Diet Index (hPDI) that emphasize intake of healthful plant-based foods [7–11]. Recent studies also found that the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet, combining features in the Mediterranean and DASH diet, may benefit brain health [3,12,13]. Considering the diverse emphases of various dietary patterns, those that prioritize specific food components closely linked to brain health (such as polyphenols, omega-3 fatty acids) may be more relevant to cognitive outcomes [14–16]. Additionally, previous studies suggested that healthy dietary patterns play beneficial roles in preventing premature all-cause and cardiovascular mortality [17], yet few studies have examined their associations with AD mortality [4]. To date, a cohort study of 119,315 U.S. adults found that the aMED score was inversely associated with the risk of mortality from neurodegenerative disease, while HEI-2015 and hPDI did not show similar associations [4]. Overall, population-based evidence on the associations of healthy dietary patterns with AD mortality remains scarce. Furthermore, while previous studies have suggested that multiple healthy dietary patterns are associated with more favorable cognitive outcomes [12,13,18–20], few studies have evaluated these associations within the same study population, which is challenging but crucial in identifying and optimizing dietary patterns for cognitive health.

In this study, we evaluated the associations of five *a priori*-defined dietary patterns with AD mortality and psychometric mild cognitive impairment (p-MCI) using data from the U.S. National Health and Nutrition Examination Survey (NHANES) from 1998 to 2016.

2. Methods

2.1. Study population

This study leveraged data from the NHANES, a nationally representative sample of the U.S. population. Since 1999–2000, NHANES has enrolled non-overlapping participants every two years, collecting information on medical history, dietary assessment, and lifestyle. Objective cognitive tests were administered during the 2011–2012 and 2013–2014 waves. Detailed information about NHANES has been described elsewhere [21]. The NHANES protocols were approved by the National Center for Health Statistics Ethics Review Board, and participants provided written informed consent. This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

We conducted two steps of analyses using NHANES data: 1) we performed a prospective analysis to examine the associations between dietary patterns and AD mortality in NHANES participants enrolled from 1999 to 2016 (nine waves), with mortality linkage available until December 2019. Participants aged 40 years and older were included, while those with ineligible mortality information, invalid dietary assessment, or who died within two years after the survey were excluded (Fig. 1). 2) we conducted a cross-sectional analysis to investigate the associations between dietary patterns and p-MCI status in participants aged 60 and above, enrolled in the 2011–2012 and 2013-2014 waves. Similarly, participants with ineligible dietary or cognitive data were excluded (Fig. 1). Finally, 27,773 participants were included in the prospective analysis of AD mortality, and 2,713 participants were included in the cross-sectional analysis of p-MCI.

2.2. Construction of dietary pattern scores

In NHANES, dietary intake was assessed using one (1999–2002) or the mean value of the two repeated (2003–2016) 24hr dietary recalls, employing the United States Department of Agriculture's (USDA's) Automated Multiple-Pass Method [22]. We calculated five *a priori*-defined dietary pattern scores: HEI-2015, aMED, DASH, MIND, and hPDI. The components and scoring criteria for these scores are detailed in **Supplementary Table 1**. The HEI-2015 consisted of 13 components (range: 0–100) [7], the aMED consisted of 9 components (range: 0–9) [8], the DASH score consisted of 8 food and nutrient components (range: 8–40) [9], the MIND score consisted of 15 food groups (range: 0–15) [10], and the hPDI consisted of 15 food groups (range: 15–75) [11]. Each dietary pattern score assigned higher scores to higher intake of recommended food groups and reversed scores for restricted food groups. For example, the hPDI assigned higher scores to healthy plant-based food groups and lower scores to unhealthy plant-based and animal-based food groups. Higher dietary pattern scores indicated greater adherence to the corresponding dietary patterns.

2.3. Assessment of AD mortality

The primary outcome of interest was AD mortality. In NHANES, mortality status was ascertained with death certificate records by linkage to the National Death Index through December 31, 2019, covering 99.8 % of the participating individuals. The cause of death was coded according to the *International Statistical Classification of Disease, Tenth Revision (ICD-10)*. Death cases with a primary cause coded as G30 were identified as AD mortality [23]. We calculated person-time from the study baseline (date of dietary assessment) to the date of death, loss to follow-up, or the end of the follow-up period (December 31, 2019), whichever occurred first.

2.4. Assessment of cognitive function

The secondary outcome was psychometric mild cognitive impairment (p-MCI), defined with a composite score reflecting overall cognitive function. In NHANES, trained interviewers administered cognitive assessments through face-to-face private interviews during two waves (2011–2012 and 2013–2014). The neuropsychological test battery included three cognitive tests: the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word Learning test (to assess memory), the Animal Fluency test (AFT, to assess verbal fluency), and the Digit Symbol Substitution test (DSST, to assess executive function). Details on the administration of these tests are available elsewhere [24]. We summed the normalized individual test scores and re-standardized them to form a total composite score, and p-MCI was defined as total composite scores that are more than 1 standard deviation (SD) below the age-, sex-, and education-adjusted mean, according to a previous study [25].

2.5. Assessment of other covariates

We included multiple covariates, either objectively measured or self-reported at baseline, for confounding adjustments. Sociodemographic variables included age, sex, survey waves, highest level of education (college graduate or above, college, high school graduate, high school, below high school), race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, other races), and income-poverty ratio. Lifestyle factors included smoking status (never smoker, past smoker, current smoker), physical activity (measured by metabolic equivalent score), and total energy intake (kcal/day). Health-related variables included objectively measured body mass index (BMI) categories (underweight and normal weight, < 25.0 kg/m^2; overweight, 25.0–29.9 kg/m^2; or obese, ≥ 30.0 kg/m^2) based on CDC guideline [26], as well as self-reported hypertension, diabetes, and cardiovascular diseases. Multiple imputation with chained equations was used for missing data of covariates [27] (using mice package in R in our analyses).

2.6. Statistical analysis

We described the baseline characteristics of participants, using mean (SD) for continuous variables and number (percentage) for categorical

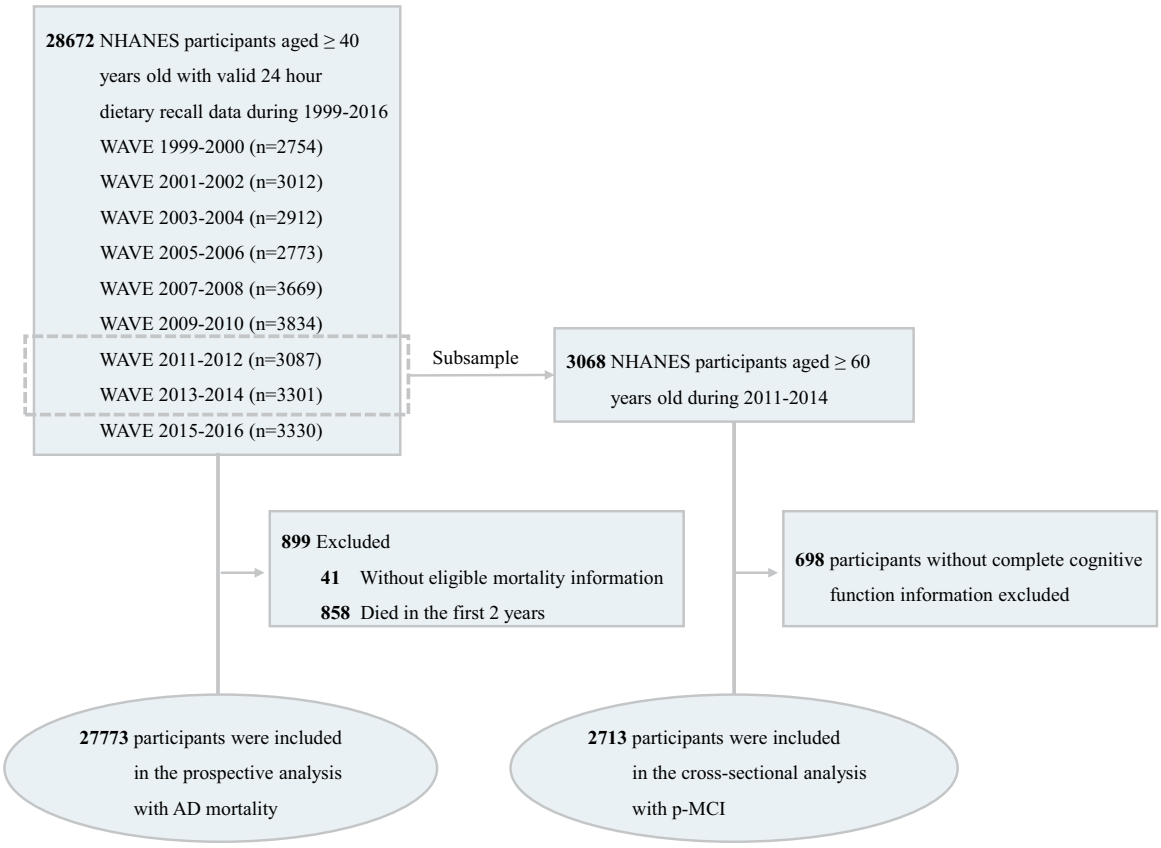

Fig. 1. Flow chart of participant inclusion.

variables. In the primary analysis, we assessed the association of five healthy dietary patterns with AD mortality using Cox proportional hazard models, with sequential adjustments for the fore-mentioned baseline sociodemographic factors, lifestyle, and health-related factors. In the secondary analysis, we evaluated the association of these dietary patterns with prevalent p-MCI using logistic regression models, adjusted for the same set of covariates. Proportional hazard assumption was tested and verified by including a cross-product term with time in the model using Schoenfeld's residual methods. We assessed the associations of the five healthy dietary patterns as continuous variables (per SD increase) and categorical variables (tertiles) with the risk of AD mortality and p-MCI in separate models. Additionally, we analyzed dietary patterns in relation to all-cause mortality and mortality due to heart disease, malignant neoplasms, chronic lower respiratory diseases, and cerebrovascular diseases using Cox proportional hazard models. Furthermore, we evaluated dietary patterns in relation to specific cognitive test z-scores using linear regression models.

We performed prespecified stratified analyses by sex (male, female), age (< 65 years, ≥ 65 years), education level (high school and below, above high school), race (non-Hispanic White, non-Hispanic Black, other races), smoking status (never smoker, past smoker, current smoker), hypertension, diabetes, and cardiovascular diseases. We tested for interactions using likelihood ratio tests.

We conducted several sensitivity analyses to test the robustness of our primary findings. First, we modified the hPDI by scoring fish intake positively, thus forming a modified hPDI (mhPDI) [28] to reflect adherence to a pesco-vegetarian diet. Second, we excluded participants with baseline p-MCI to account for reverse causality in the analysis of AD mortality. Third, we restricted the analysis to participants aged 60 years and above. Fourth, we excluded participants who died within the first 5 years of follow-up to further reduce the potential impact of reverse causation in the analysis of AD mortality. Fifth, we additionally adjusted the models for the number of people living in the household, as living alone may be linked to an elevated risk of dementia [4,29]. Furthermore, we restricted our analyses to participants without baseline self-reported diabetes and cardiovascular diseases to further minimize their potential confounding effects.

Two-sided *P* values less than 0.05 were considered statistically significant. All statistical analyses were performed using R version 4.2.1.

3. Results

3.1. Participant characteristics

In this study, we included a total of 27,773 participants from NHANES, with a mean age of 59.8 (SD: 12.6) years, of whom 51.4 % were female (Table 1). Participants with higher dietary pattern scores were older, more likely to be female, better educated, non-smokers, had higher household income. (Table 1, **Supplementary Table 2–3**) Moderate pairwise correlations (r = 0.41–0.67) were observed between the five dietary pattern scores (**Supplementary Table 4**).

3.2. Associations of dietary patterns with AD mortality

During the follow-up period (mean = 9.8 years), we documented 260 cases of AD mortality. A higher aMED score was associated with a lower risk of AD mortality, with adjusted hazard ratios (HRs) of 0.72 (95 %CI, 0.52–1.00) when comparing extreme aMED tertiles. Although not statistically significant, MIND and HEI-2015 also showed suggestive inverse associations with AD mortality. The HRs for the highest versus lowest tertiles were 0.80 (95 %CI, 0.59–1.08) for the MIND score and 0.80 (0.58–1.11) for HEI-2015. For the DASH score, the HR was 0.98 (95 %CI, 0.71–1.36). In contrast, the HR for hPDI was 1.14 (95 %CI, 0.82, 1.57) (Fig. 2, **Supplementary Table 5**).

Regarding all-cause and other cause-specific mortality, the five dietary pattern scores were each significantly associated with a lower

Table 1
Baseline characteristics of participants according to tertiles of the aMED dietary scores.

Characteristic	Overall	aMED			
		Tertile 1	Tertile 2	Tertile 3	p value
n	27,773	11,790	10,266	5,717	
Age (mean (SD))	59.8 (12.6)	59.0 (12.7)	60.0 (12.6)	60.9 (12.5)	< 0.001
Female (No. (%))	14,274 (51.4)	5768 (48.9)	5376 (52.4)	3130 (52.7)	< 0.001
Total energy intake, kcal/day (mean (SD))	1934.8 (813.6)	1848.0 (831.2)	1975.7 (811.4)	2040.1 (761.4)	< 0.001
Race (No. (%))					< 0.001
Mexican American	4643 (16.7)	1875 (15.9)	1807 (17.6)	961 (16.8)	
Other Hispanic	2204 (7.9)	898 (7.6)	877 (8.5)	429 (7.5)	
Non-Hispanic White	13,394 (48.2)	5719 (48.5)	4866 (47.4)	2809 (49.1)	
Non-Hispanic Black	5729 (20.6)	2746 (23.3)	2041 (19.9)	942 (16.5)	
Other Race	1803 (6.5)	552 (4.7)	675 (6.6)	576 (10.1)	
Education level (No. (%))					< 0.001
Less Than 9th Grade	4200 (15.1)	2025 (17.2)	1538 (15.0)	637 (11.1)	
9–11th Grade	4176 (15.0)	2225 (18.9)	1379 (13.4)	572 (10.0)	
High School Grade/GED or Equivalent	6371 (22.9)	3070 (26.0)	2291 (22.3)	1010 (17.7)	
Some College or AA degree	7140 (25.7)	2900 (24.6)	2771 (27.0)	1469 (25.7)	
College Graduate or above	5852 (21.1)	1554 (13.2)	2279 (22.2)	2019 (35.3)	
Income-Poverty Ratio (mean (SD))	2.7 (1.6)	2.4 (1.6)	2.7 (1.6)	3.1 (1.6)	< 0.001
Smoking status (No. (%))					< 0.001
Never smoker	13,946 (50.2)	5187 (44.0)	5420 (52.8)	3339 (58.4)	
Past smoker	8627 (31.1)	3416 (29.0)	3278 (31.9)	1933 (33.8)	
Current smoker	5200 (18.7)	3187 (27.0)	1568 (15.3)	445 (7.8)	
MET score (mean (SD))	37.1 (74.8)	39.0 (81.6)	36.7 (74.1)	34.1 (59.7)	< 0.001
BMI category (No. (%))					< 0.001
< 25.0 kg/m^2	7141 (25.7)	2861 (24.3)	2505 (24.4)	1775 (31.0)	
25.0–29.9 kg/m2	10,100 (36.4)	4142 (35.1)	3808 (37.1)	2150 (37.6)	
≥ 30.0 kg/m^2	10,532 (37.9)	4787 (40.6)	3953 (38.5)	1792 (31.3)	
Hypertension [a] (No. (%))	18,826 (67.8)	8231 (69.8)	6852 (66.7)	3743 (65.5)	< 0.001
Diabetes (No. (%))	5327 (19.2)	2369 (20.1)	2033 (19.8)	925 (16.2)	< 0.001
Cardiovascular diseases (No. (%))	4283 (15.4)	1975 (16.8)	1541 (15.0)	767 (13.4)	< 0.001
Cancer (No. (%))	3529 (12.7)	1386 (11.8)	1301 (12.7)	842 (14.7)	< 0.001

[a] Hypertension is defined by a self-reported diagnosis, a medication use, or a measured blood pressure of above 130/85 mmHg.Abbreviations: HEI-2015, Healthy Eating Index 2015; aMED, Alternate Mediterranean Diet; DASH, Dietary Approaches to Stop Hypertension; MET, metabolic equivalent.

risk of mortality from heart disease, malignant neoplasms, and all-cause mortality (**Supplementary Table 6**).

3.3. Associations of dietary patterns with p-MCI

In a sub-sample of 2,713 participants who completed objective cognitive tests in 2011–2014, 432 had prevalent p-MCI. Higher aMED, MIND, HEI-2015, and hPDI scores were associated with lower odds of p-MCI, with the aMED score demonstrating the strongest association (Table 2). The adjusted odds ratios (ORs) were 0.69 (95 %CI, 0.50–0.96) comparing extreme tertiles of aMED, followed by MIND (0.70, 95 %CI, 0.53–0.92), HEI-2015 (0.73, 95 %CI, 0.56–0.97) and hPDI (0.73, 95 %CI, 0.54, 0.98), respectively. A better diet quality was generally associated with higher global cognitive function score, CREAD, AFT, and DSST scores **(Supplementary Table 7)**.

Regarding specific components in these dietary patterns, higher consumptions of vegetables, nuts, and moderate alcohol intake were associated with lower odds of p-MCI (**Supplementary Figure 1–2)**. Green-leafy vegetables and non-fried poultry, which are unique components of the MIND diet, exhibited a significant inverse association (adjusted OR comparing extreme tertiles, 0.70, 95 %CI, 0.55–0.89 for green-leafy vegetables and 0.77, 95 %CI, 0.59–0.99 for poultry); total protein foods (OR comparing extreme tertiles, 0.73, 95 %CI:, 0.58-0.92) and seafood and plant protein (adjusted OR, 0.72, 95 %CI, 0.58-0.90) in the HEI-2015 also showed significant inverse associations. Higher intake levels of added sugar, sweets, dairy, refined grains, fruit juice, and white potato were associated with higher odds of prevalent p-MCI, despite lacking statistical significance.

3.4. Subgroup and sensitivity analysis

In the subgroup analyses by age, sex, education, race, smoking status, and health-related diseases, the associations of dietary pattern scores with AD mortality were generally consistent **(Supplementary Figure 3–4)**. However, the associations of aMED score with AD mortality was only significant in participants without diabetes (adjusted HR comparing extreme tertiles = 0.58, 95 %CI, 0.40–0.84), but not in those with diabetes (adjusted HR, 1.86, 95 %CI, 0.85–4.09, p-interaction = 0.020). The association of the MIND score differed by education (p-interaction = 0.045): among individuals with education above high school, the HR was 0.42 (95 %CI, 0.26–0.70), while in participants without tertiary education, the association was not significant (adjusted HR, 1.09, 95 %CI, 0.75–1.61).

In the sensitivity analysis, the observed associations between dietary pattern scores with AD mortality were not substantially changed (**Supplementary Table 8–9**). The associations were slightly attenuated when we excluded participants who died in the first 5 years and adjusted the models for living status. In addition, excluding participants with p-MCI, excluding participants with cardiovascular diseases or diabetes at baseline, and including only participants aged 60 and above yielded stronger inverse associations. Additionally, the HR for mhPDI positively scoring fish intake was 0.94 (95 %CI, 0.68, 1.31).

4. Discussion

In this cohort study among U.S. middle-aged and older adults, a higher aMED score was significantly associated with 28 % (95 % CI, 0–48 %) lower risk of AD mortality and 31 % (95 % CI, 4 %–50 %) lower odds of p-MCI when comparing extreme tertiles. Other dietary patterns such as MIND, HEI-2015, and hPDI were also associated with lower odds of p-MCI, with OR ranging from 0.81 to 0.89 when comparing extreme tertiles. Collectively, our findings supported the importance of a healthy diet for maintaining cognitive health and highlighted the Mediterranean diet as a potential diet for future dietary recommendations targeting cognitive health.

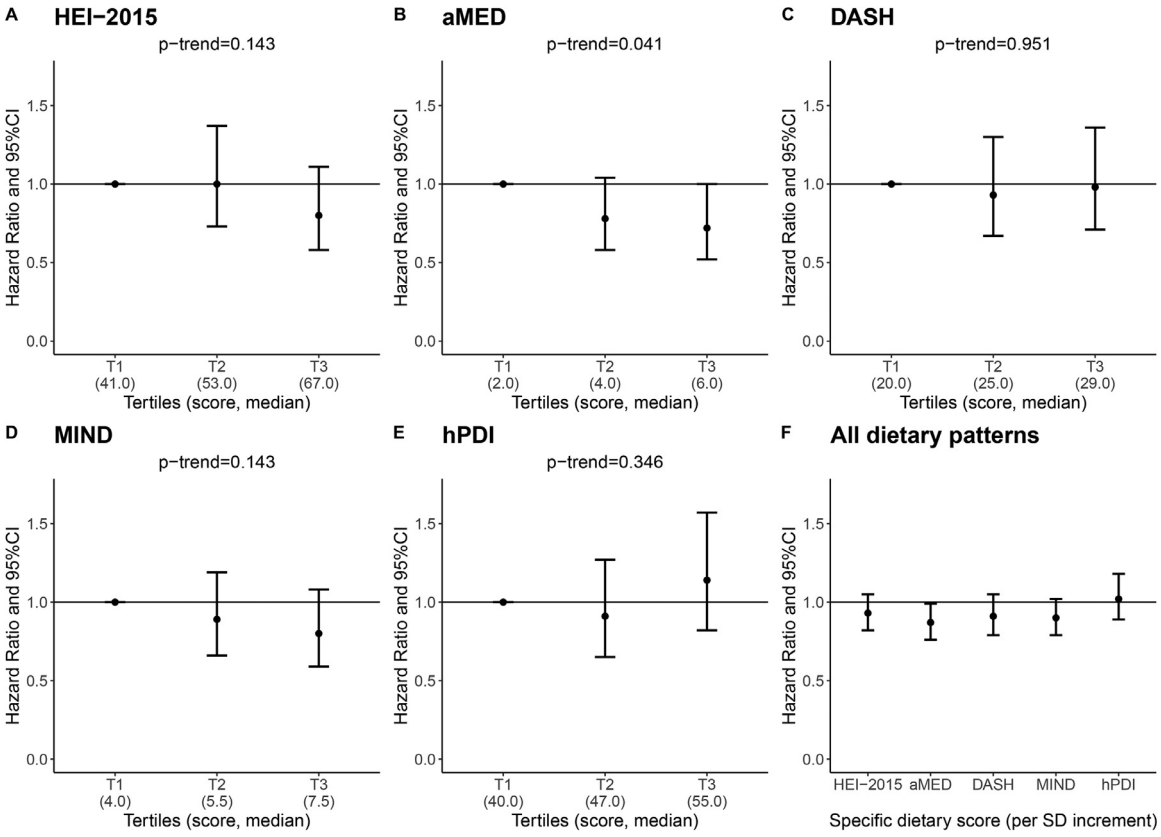

Fig. 2. Hazard ratios of AD mortality with the dietary pattern scores.
Abbreviations: HEI-2015, Healthy Eating Index 2015; aMED, Alternate Mediterranean Diet; DASH, Dietary Approaches to Stop Hypertension; MIND, Mediterranean-DASH Diet Intervention for Neurodegenerative Delay; hPDI, healthful Plant-based Diet Index;
Model was adjusted for age, sex, total energy intake, race, education, poverty-income ratio, smoking status, metabolic equivalent score, body mass index category, and additionally adjusted for baseline hypertension, diabetes, and cardiovascular diseases.

Extensive studies have investigated the associations of healthy dietary patterns with all-cause mortality and mortality from cardiovascular, cancer, and respiratory diseases [17,30–32]. However, evidence for AD mortality remained limited [4]. In the Nurses' Health Study (NHS) (1984–2020) and the Health Professionals Follow-up Study (HPFS) (1986–2020), the aMED was inversely associated with risk of mortality from neurodegenerative disease (HR comparing extreme quintiles, 0.94, 95 % CI, 0.90–0.99), while HEI-2015 and hPDI did not show significant associations [4].Our study found a similar inverse association between aMED and AD mortality. Additionally, our findings suggest that other dietary pattern scores, such as the MIND and HEI-2015, might also be inversely associated with AD mortality, although these associations did not reach statistical significance. Compared to previous studies among U.S. population [4,13,33], the NHANES participants across extreme quantiles had a smaller score difference for MIND [3] and HEI-2015 [34,35], while the difference for aMED remained similar [35]. Besides, the lack of significant associations for certain dietary patterns may be attributed to the limited number of AD mortality cases. The Million Women Study [36] found that only 37 % of individuals diagnosed with dementia prior to their death had this condition recorded on their death certificates. Therefore, using AD mortality as a proxy for AD incidence might bias the study findings, indicating a need for future large-scale cohort studies with more accurate diagnostic approaches of the cognitive outcomes to validate our findings. Furthermore, while numerous studies have suggested that multiple dietary patterns were associated with lower all-cause mortality and mortality from other causes [17,30], their associations with AD mortality were not uniformly significant. These inconsistencies highlight the necessity for more detailed investigations of optimal dietary patterns for cognitive health.

A recent review of observational studies pointed out that higher adherence to the Mediterranean diet was associated with slower cognitive decline and a lower risk of MCI and dementia, while the evidence for the MIND, DASH, and hPDI was less consistent [37]. A meta-analysis of 26 cohort studies and 2 intervention studies reported that higher adherence to the Mediterranean diet was related to a lower risk of AD and MCI, with relative risks of 0.71 (95 %CI, 0.56–0.89) and 0.75 (95 %CI, 0.66–0.86), respectively [38]. Another review of population-based studies, on the other hand, showed that MIND exhibited the strongest association among the dietary patterns investigated [18]. Our results showed that aMED, MIND, HEI-2015, and hPDI scores were inversely associated with p-MCI. When comparing their associations within the same population, the strongest association was observed for aMED, followed by MIND, HEI-2015, and then hPDI. Overall, while current evidence is still limited, our study together with previous studies, suggested that Mediterranean-style diets may confer long-term cognitive benefits [37]. A detailed investigation into the food groups revealed that the potential contributors included vegetables, nuts, and moderate alcohol consumption, as recommended by multiple patterns. Certain diets also emphasized specific components, including green leafy vegetables and poultry recommended by the MIND diet, as well as protein-rich foods highlighed by the HEI-2015.Although not statistically significant, higher consumption of added sugar, sweets, dairy, refined grains, fruit juice, and white potatoes indicated trends toward poorer cognitive performance. Furthermore, the inclusion of components that have minimal cognitive effects may dilute the associations between dietary patterns and p-MCI. For instance, specific recommendations like dairy in the DASH diet may not be particularly relevant to brain health [16]. Future studies are warranted to refine the dietary patterns for brain health

Table 2
Odds ratios of psychometric mild cognitive impairment according to tertiles of the dietary scores (N = 2,713).

	Tertile 1	Tertile 2	Tertile 3	Per SD	P for trend
HEI-2015					
Score, median (IQR)	44 (38–47)	57 (54–60)	71 (67–76)		
Cases/N	160/905	146/904	126/904		
Model 1 OR (95 % CI) [a]	1.00 (ref)	0.89 (0.69, 1.14)	0.74 (0.57, 0.96)	0.90 (0.81, 1.01)	0.023
Model 2 OR (95 % CI) [b]	1.00 (ref)	0.87 (0.67, 1.13)	**0.72 (0.55, 0.95)**	**0.89 (0.79, 0.99)**	**0.020**
Model 3 OR (95 % CI) [c]	1.00 (ref)	0.87 (0.67, 1.13)	**0.73 (0.56, 0.97)**	**0.89 (0.80, 1.00)**	**0.029**
aMED					
Score, median (IQR)	3 (2–3)	4 (4–5)	6 (6–7)		
Cases/N	190/1019	171/1096	71/598		
Model 1 OR (95 % CI) [a]	1.00 (ref)	0.90 (0.71, 1.14)	**0.71 (0.53, 0.97)**	**0.86 (0.77, 0.96)**	**0.034**
Model 2 OR (95 % CI) [b]	1.00 (ref)	0.87 (0.68, 1.11)	**0.69 (0.50, 0.95)**	**0.84 (0.75, 0.94)**	**0.024**
Model 3 OR (95 % CI) [c]	1.00 (ref)	0.88 (0.69, 1.12)	**0.69 (0.50, 0.96)**	**0.84 (0.75, 0.95)**	**0.030**
DASH					
Score, median (IQR)	21 (19–22)	26 (25–27)	30 (29–31)		
Cases/N	183/1055	135/863	114/795		
Model 1 OR (95 % CI) [a]	1.00 (ref)	0.85 (0.66, 1.09)	**0.75 (0.58, 0.98)**	**0.89 (0.80, 0.99)**	**0.031**
Model 2 OR (95 % CI) [b]	1.00 (ref)	0.85 (0.65, 1.11)	0.81 (0.61, 1.07)	0.90 (0.80, 1.02)	0.129
Model 3 OR (95 % CI) [c]	1.00 (ref)	0.85 (0.65, 1.11)	0.82 (0.62, 1.09)	0.91 (0.81, 1.03)	0.159
MIND					
Score, median (IQR)	4.0 (3.5–5.0)	6.0 (5.5–6.5)	8.0 (7.0–8.5)		
Cases/N	207/1074	109/774	116/865		
Model 1 OR (95 % CI) [a]	1.00 (ref)	**0.68 (0.52, 0.88)**	**0.66 (0.51, 0.84)**	**0.79 (0.71, 0.88)**	**0.001**
Model 2 OR (95 % CI) [b]	1.00 (ref)	**0.73 (0.56, 0.95)**	**0.69 (0.52, 0.90)**	**0.81 (0.72, 0.91)**	**0.005**
Model 3 OR (95 % CI) [c]	1.00 (ref)	**0.73 (0.55, 0.95)**	**0.70 (0.53, 0.92)**	**0.81 (0.72, 0.92)**	**0.008**
hPDI					
Score, median (IQR)	41 (38–43)	48 (46–49)	55 (53–57)		
Cases/N	137/922	174/949	121/842		
Model 1 OR (95 % CI) [a]	1.00 (ref)	1.01 (0.78, 1.30)	**0.69 (0.52, 0.92)**	**0.86 (0.77, 0.97)**	**0.010**
Model 2 OR (95 % CI) [b]	1.00 (ref)	1.07 (0.82, 1.39)	**0.73 (0.54, 0.98)**	**0.89 (0.78, 1.00)**	**0.032**
Model 3 OR (95 % CI) [c]	1.00 (ref)	1.05 (0.81, 1.38)	**0.73 (0.54, 0.98)**	**0.89 (0.78, 1.00)**	**0.033**

Abbreviations: HEI-2015, Healthy Eating Index 2015; aMED, Alternate Mediterranean Diet; DASH, Dietary Approaches to Stop Hypertension; MIND, Mediterranean-DASH Diet Intervention for Neurodegenerative Delay; hPDI, healthful Plant-based Diet Index; OR, odds ratio.

[a] Model 1 was adjusted for age, sex, and total energy intake.

[b] Model 2 was based on Model 1 and further adjusted for race, education, poverty-income ratio, smoking status, metabolic equivalent score, and body mass index category.

[c] Model 3 was based on Model 2 and additionally adjusted for baseline hypertension, diabetes, and cardiovascular diseases.

by incorporating evidence from food groups that are beneficial for brain health.

Although we did not provide direct evidence for the underlying mechanisms, several pathways may explain the observed associations. Healthy dietary patterns like aMED emphasize several food groups associated with brain health such as vegetables, and nuts [39], which was confirmed in this study. These food groups are rich in antioxidants, polyphenols, omega-3 fatty acids, and B vitamins that may mitigate neuroinflammation and protect against oxidative stress in the brain [40,41]. Additionally, healthy dietary patterns could also lower the risk of cardiovascular diseases (CVD), a crucial risk factor for AD [42].

Overall, our study adds the existing evidence to this field and provided important insights for public health practice. The Dietary Guidelines for Americans (DGA) recommend healthy dietary patterns, emphasizing the importance of overall eating patterns rather than focusing on individual nutrients or foods. Our findings provide population-based evidence that could support more targeted recommendations for the aging population. Specifically, we identified that the aMED, as a potentially advantageous dietary pattern for enhancing cognitive performance and reducing AD mortality risk in late-life, which could be incorporated in future dietary recommendations to promote healthy brain aging. Furthermore, our findings also called for investigations into the biological pathways that underlie these associations.

The current study had several merits including a relatively long-term follow-up within a population-based cohort, comparative evaluations of multiple dietary patterns, and the careful control of confounding variables. Nevertheless, some potential limitations should be noted. First, dietary patterns were assessed using repeated 24hr dietary recalls, which may be limited in representing long-term dietary intake [43] and are subject to measurement error and reporting bias. Second, using AD mortality cases as the study outcome may underestimate the incidence of AD and limit the statistical power to detect significant associations. Third, despite adjusting for many covariates, residual confounding may still exist. Considering the long-term preclinical and prodromal phases of AD, reverse causation could be a concern, although we have tried to address this issue by excluding earlier cases. Finally, the cohort study was based on the US population, whether our findings can be generalized to other populations warrants further investigations.

5. Conclusion

Our study findings suggest that the Mediterranean diet may play a role in maintaining long-term cognitive health in middle-aged and older adults in the U.S. population. Several other healthy dietary patterns showed promise for cognitive health, but further investigations is necessary. Overall, this study underscores the importance of a healthy diet for cognitive and brain health. Future studies are needed to confirm these findings and to explore the underlying mechanisms.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Yiying Gong: Writing – original draft, Formal analysis. **Hui Chen:** Writing – review & editing, Formal analysis. **Yuxuan Gu:** Writing – review & editing. **Jie Shen:** Writing – review & editing. **Ting Shen:**

Writing – review & editing. **Yihong Ding:** Writing – review & editing. **Mengxi Lu:** Writing – review & editing. **Liyan Huang:** Writing – review & editing. **Minqing Yan:** Writing – review & editing. **Peige Song:** Writing – review & editing. **Yajie Zhu:** Writing – review & editing. **Shuang Rong:** Writing – review & editing. **Changzheng Yuan:** Writing – review & editing, Supervision, Project administration.

Ethical approval

The project protocols of the NHANES were all approved by the National Center for Health Statistics Ethics Review Board. All the participants signed the informed consent before data collection.

Data sharing plan

Data described in the manuscript and codebook are publicly and freely available without restriction at https://www.cdc.gov/nchs/nhane.

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Disclosure

All authors report no disclosures relevant to the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100100.

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