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Original Article

Association of Mediterranean, high-quality, and anti-inflammatory diet with dementia in UK Biobank cohort

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ABSTRACT

Background: This study examined the relationship between adherence to the Mediterranean diet, MIND diet, Recommended Food Score (RFS), Alternative Healthy Eating Index (AHEI), and Energy-adjusted Dietary Inflammatory Index (EDII) and dementia risk in a large UK population cohort.
Methods: We analyzed data from 131,209 participants in the UK Biobank, aged 40–69 years, with no prior diagnosis of dementia at baseline. Dietary intake was assessed using the validated Oxford WebQ tool, and adherence to each dietary pattern was calculated. Dementia incidence was identified using algorithmically defined outcomes based on ICD codes. Fine–Gray subdistribution hazard models adjusted for sociodemographic, genetic, and lifestyle factors were applied to examine the association between dietary indices and dementia risk. Subgroup analyses were conducted based on age, sex, obesity status, and ApoEε4 status.
Results: Over a median follow-up of 13.5 years, 1453 dementia cases were identified. Higher adherence to the MEDAS, MIND diet, RFS, and AHEI was significantly associated with reduced dementia risk (HRs: 0.79, 0.73, 0.72, and 0.77, respectively). Conversely, higher EDII scores, indicating pro-inflammatory diets, were linked to an increased dementia risk (HR: 1.3). These associations were more pronounced in older adults (≥60 years), women, non-obese individuals, and ApoEε4 non-carriers. Subgroup analyses revealed differential impacts of dietary patterns based on demographic and health-related factors.
Conclusion: Greater adherence to Mediterranean, MIND, and high-quality diets is associated with a lower risk of dementia, while pro-inflammatory diets increase the risk. High-quality anti-inflammatory diets play a significant role in reducing the risk of dementia, with stronger effects observed in specific subgroups.

1. Introduction

Dementia, characterized by progressive cognitive decline, is a prevalent neurodegenerative disorder, particularly among older individuals, affecting approximately 57 million people worldwide in 2019 [1]. Dementia is associated with various neuropathological features, including accumulation of abnormal proteins, damage to cerebral blood vessels, and neuroinflammatory processes [2]. Despite its substantial impact, effective treatments to slow or halt its progression remain limited, emphasizing the critical need for early preventive interventions targeting modifiable risk factors [3]. Among the modifiable factors, lifestyle behaviors such as nutrition, physical activity, sleep quality, and social engagement are increasingly recognized as important determinants of dementia risk [4]. Extensive research has established a significant link between dietary patterns and brain health, emphasizing the potential of dietary interventions for preventing dementia [5,6].

Abbreviation: AHEI, Alternative Healthy Eating Index; BMI, Body mass index; DASH, Dietary Approaches to Stop Hypertension; DII, Dietary Inflammatory Index; EDII, Energy-adjusted Dietary Inflammatory Index; ICD, International Classification of Disease; MIND, Mediterranean Dietary Approaches to Stop Hypertension Intervention for Neurodegenerative Delay; RFS, Recommended Food Score.

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The Mediterranean diet, widely researched for its neuroprotective properties, has been linked to a reduced risk of Alzheimer's disease—the most prevalent form of dementia—along with several health benefits associated with a reduced risk of chronic diseases and mortality [7,8]. Based on the principles of the Mediterranean and Dietary Approaches to Stop Hypertension (DASH) diets, the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet was developed specifically to prevent neurodegenerative diseases [9]. Previous research has reported the neuroprotective effects of the MIND diet, demonstrating an association between lower rates of cognitive impairment and dementia incidence [10–12]. However, further exploration of its effects on cognitive function is warranted because of the inconsistencies across studies [13].

The overall quality and inflammatory potential of dietary patterns are implicated in the risk of neurodegenerative diseases and structural changes [14–16]. Although some studies have reported the adverse effects of pro-inflammatory diets on cognitive performance and dementia risk, some have failed to establish a significant link between diet quality and cognitive outcomes [17–19], leading to inconclusive results. Therefore, further research is needed to clarify the role of specific dietary factors in dementia.

Considering the lack of a definitive cure for dementia, dietary interventions targeting specific food components, overall diet quality, and inflammatory potential offer promising approaches for early prevention [20–22]. While previous meta-analyses and systematic reviews regarding dietary intervention for dementia have provided valuable insights into the general association between diet and dementia risk, they have largely overlooked demographic-specific variations in dietary effects [15,18]. For example, previous meta-analyses, such as those by Nucci et al. [8] and McBean et al. [18], have assessed the impact of the Mediterranean diets and diet quality on cognitive decline but has not determined whether these effects differ by age, sex, metabolic status or ApoEε4 status. This raises the need for study focused on effective dietary interventions targeting specific populations.

Accordingly, this study aimed to investigate the association between various dietary indices recognized for their beneficial or adverse effects on chronic diseases and dementia incidence. Specifically, we examined dietary habits according to five distinct dietary indices: the Mediterranean Diet Adherence Screener (MEDAS), MIND diet score, Recommended Food Score (RFS), Alternative Healthy Eating Index (AHEI), and Energy-Adjusted Dietary Inflammatory Index (EDII). Also, we aim to explore variations in dietary effects across demographic factors such as age, sex, obesity status, and ApoEε4 status to fill the gaps in previous studies. This study provides insights into effective dietary strategies for targeted high-risk populations to prevent dementia, contributing to a deeper understanding of the role of diet in neurodegenerative diseases.

2. Methods

2.1. Study population

Data from the UK Biobank, a large population-based prospective study of approximately 500,000 participants aged 40–69 years when recruited between 2006 and 2010, was used. Participants completed a touchscreen questionnaire, computer-assisted interviews, and physical measures in 22 assessment centers across the UK. The information regarding socio-demographic, environmental, physical, genetic, and lifestyle characteristics of the participants was obtained [23]. Data from the UK Biobank are openly accessible. All participants provided informed consent, and ethical approval was obtained from the Northwest Multicenter Research Ethics Committee as Research Tissue Bank approval. This study was performed in accordance with Declaration of Helsinki.

Of 502,506 participants recruited at baseline in the UK biobank, 210,950 participants who completed at least one Oxford WebQ—a web based 24-h food recall assessment conducted in 2009–2012, were included. Notably, 79,741 participants who had dementia at baseline (n = 61), did not follow a typical diet the previous day when they answered the 24-h dietary recall assessment (n = 18,040), and those with missing covariate data (n = 61,640) were excluded. Finally, 131,209 participants, including 81,680 participants for the MEDAS, 85,564 for the MIND diet, 78,140 for the RFS, 95,128 for the AHEI, and 83,748 for the EDII, were selected. The matched data was exactly matched for age and sex for each dietary index, as shown in Fig. 1.

2.2. Dietary assessment

Dietary intake was assessed using data from the Oxford WebQ that has been validated in large-scale cohort studies, such as the UK Biobank. Participants in the UK Biobank completed the Oxford WebQ dietary recall assessment on five occasions from 2009 to 2012 and information on the intake of 206 foods and 32 drinks was collected. The daily quantity of food and drink was calculated by multiplying the assigned portion sizes, and the nutrient intake was derived using a nutrient composition table [24]. When participants answered the Oxford WebQ questionnaire $\geq$ 2 times, the average intake was used in the study.

2.3. Dietary indices

The MEDAS, comprising 14 items, is a tool to assess adherence to the Mediterranean diet [25], which has been validated in the UK population [26]. To calculate the MEDAS score, 1 point is assigned for each item that meets the specific criteria. The items include the consumption of olive oil, vegetables, fruits, wine, pulses, fish/shellfish, and nuts while avoiding red meat, butter/margarine, sugar, and sweet foods. Our study included 13 items with a score ranging between 0 and 13 because data regarding daily olive oil consumption was lacking, as in a previous study [27].

MIND diet score, a tool to measure adherence to the MIND diet, comprises 15 components (green leafy vegetables, other vegetables, berries, nuts, olive oil, butter/margarine, cheese, whole grains, fish, beans, poultry, red meat, fast foods, pastries and sweets, and wine). A score of 0, 0.5, or 1 point was assigned to each component according to the set criteria. For example, for olive oil, 1 point was assigned if "the type of fat/oil used in cooking yesterday" was olive oil, and 0 points was assigned if it was not. "Boiled/mashed white potatoes" was excluded from the other vegetables category, and "added sugars and preserves" were converted into servings (15 g = 1 serving) and included in the pastries and sweets category as in the previous study [13].

The RFS is a tool used to measure the overall quality of a diet based on the consumption of recommended foods according to current dietary guidelines [28]. The RFS comprises five food groups, each containing 21 sub-food items. "Fruits," "vegetables," "whole grains," "lean meat and alternatives," and "low-fat dairy" groups comprise 7, 7, 2, 3, and 2 items, respectively. One point was assigned when the consumption of each item is above 15 g/day for non-beverages and 30 g/day for beverages, as in previous studies [28,29]. A score of 0 was assigned if the criteria were unmet, and the total score ranged from 0 to 21.

The AHEI-2010 is a renewed version of the Healthy Eating Index 2005, which measures adherence to American dietary guidelines [30]. AHEI-2010 comprises 11 components (vegetables, fruits, whole grains, sugar-sweetened beverages, nuts and legumes, red/processed meat, trans fatty acids, omega-3 fatty acids, polyunsaturated fatty acids, sodium, and alcohol), with each component having a maximum and minimum score of 10 and 0, respectively. Points are assigned proportionally for values between the maximum and minimum score criteria, with the total score ranging from 0 to 110. We used "oily fish" intake as a proxy for omega-3 fatty acid intake, as in the previous study, because the specific amount of omega-3 fatty acid intake is not available in the UK Biobank [13].

The inflammatory potential of a diet was measured using EDII, which is an adjusted Dietary Inflammatory Index (DII) for energy intake [31]. We used 18 of the 45 components of the original DII because of a lack of

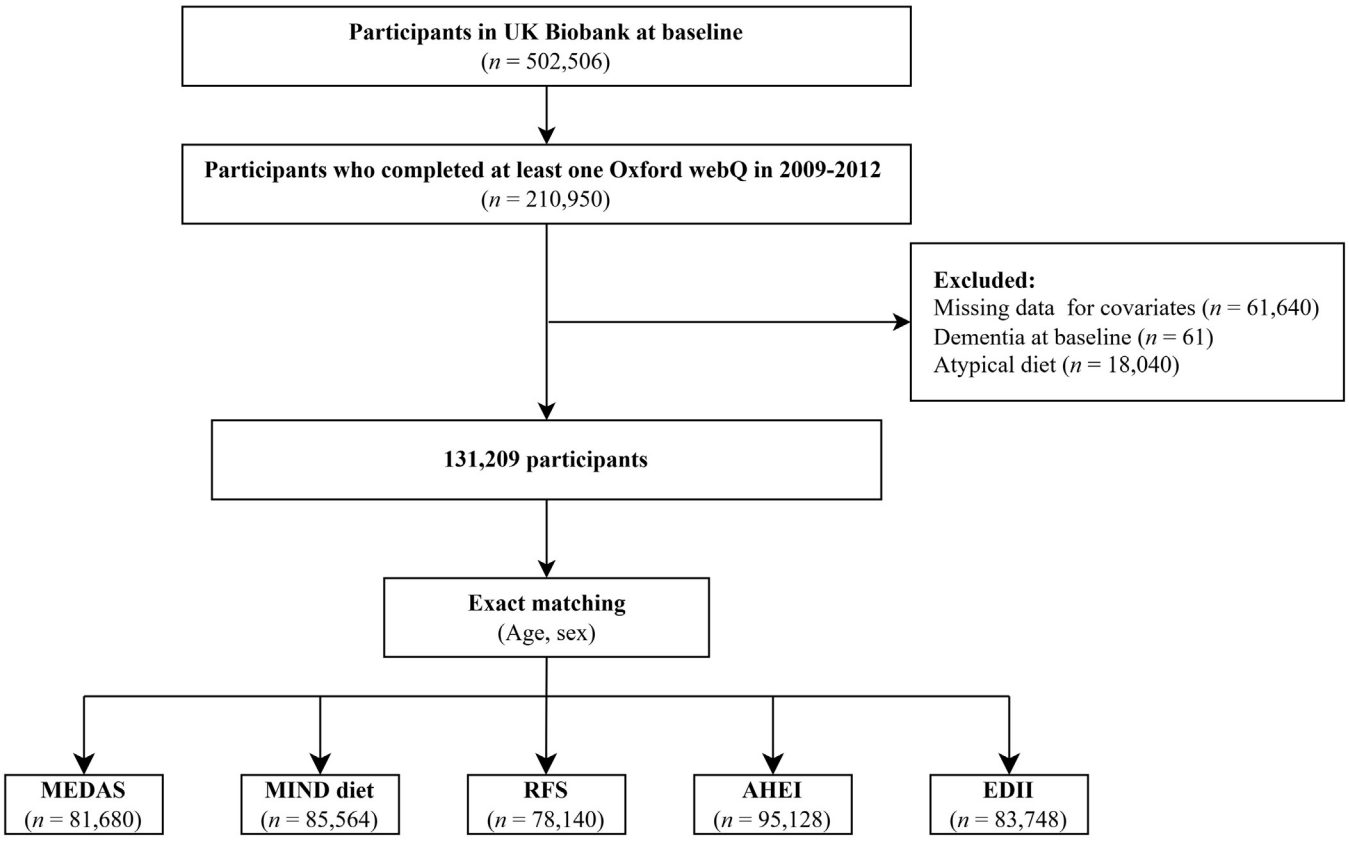

Fig. 1. Flowchart of the participant selection.
Participants who completed a food recall survey were included and excluded if data were missing, if they had dementia at baseline, or if they had an atypical diet. The final selected participants were exact matched for age and sex for each dietary index.

data, as in a previous study [32]. The components used in this study included alcohol, carbohydrates, fiber, folate, saturated fat, polyunsaturated fat, total fat, protein, vitamins B6, B12, C, and E, iron, magnesium, tea, garlic, onions, and total energy. Food intake of the cohort and the global database was expressed as per 1000 kcal, and the EDII was derived using the method proposed by Shivappa et al. [31].

2.4. Dementia outcomes

Diagnosis of all-cause and specific types of dementia was determined based on algorithmically defined dementia outcomes: first occurrence data reported Alzheimer's dementia onset within nervous system disorder, mental and behavioral disorder, death register, hospital inpatient data, and primary care data field as in a previous study [33]. The International Classification of Disease 9th revision (ICD-9) codes, ICD-10 codes, and read codes version 2 (read V2) and 3 were used to identify participants with incident dementia. We included cases wherein the date of dementia diagnosis was preceded by the date of the first visit to the assessment center to exclude prevalent dementia. Additionally, mild cognitive impairment (MCI) was included in the analysis, identified using ICD-10 codes, to capture early-stage cognitive decline and provide a more comprehensive assessment of neurocognitive outcomes. The ICD-10 codes used for the definitions of dementia and MCI are provided in Supplementary Table S1.

2.5. Covariates

Sociodemographic covariates, such as age, sex, ethnicity, mental status, and family history, and lifestyle covariates, such as smoking, alcohol status, and physical activity, were examined through self-reporting. Physical activity was expressed as the metabolic equivalent of tasks (min/week), which was calculated based on self-reported responses from the International Physical Activity Questionnaire (IPAQ) guidelines. These variables were included as a continuous covariate in the statistical models to account for its potential confounding effect on dementia risk. Alcohol consumption and smoking status were categorized as never, previous, and current, based on self-reported responses and adjusted to control potential confounding effects on dementia risk as categorical variables. Body mass index (BMI) was calculated by dividing the weight (kg) by the square of height (m). ApoEε4 carriers were identified as rs7412 or rs429358 in single nucleotide polymorphism data, assayed by the UK Biobank Axiom genotype array.

2.6. Statistical analysis

Each dietary index score was divided into quartiles. We performed exact matching for age and sex to minimize heterogeneity in the distribution of age and sex across the quartile groups of dietary index scores. Continuous variables are presented as the mean ± standard deviation, and categorical variables as numbers (percentages). A *t*-test or analysis of variance was performed to assess differences in continuous variables between groups, and the Chi-squared test was used for categorical variables. As individuals who died did not develop dementia, we performed a competing risk analysis for new-onset dementia. We estimated the cumulative incidence of dementia throughout the follow-up period using the Kaplan–Meier analysis. The Gray's test was used to assess differences in cumulative incidence among the quartile groups of dietary index scores. Fine–Gray subdistribution hazard models were used to evaluate hazard ratios (HRs) and 95% confidence intervals (CIs) for incident dementia according to quartiles in each dietary index with

adjustment for ethnicity, BMI, alcohol, smoking, physical activity, ApoEε4 genotype, and family history of dementia. We analyzed the Supplementary Table S3 and Fig. S1 results for unmatched data (crude sample). To examine the impact of follow-up duration on the association between dietary patterns and dementia, a landmark analysis was conducted by stratifying the follow-up period into three groups: ∼5 years, 5–10 years, and 10 + years. Subgroup analyses were conducted for age, sex, and obesity status to examine the differences in the associations between the dietary index score and the incidence of dementia in each demographic subgroup. An additional subgroup analysis was conducted based on ApoEε4 status to investigate whether genetic predisposition modifies this association. All statistical analyses were performed using the R software (version 4.4.1; R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $p < 0.05$.

3. Results

3.1. Baseline characteristics

The baseline characteristics of the 131,209 participants stratified by the incidence of dementia are presented in Table 1. The mean age of the study population at the baseline was 56 ± 8 years, and 48% were male. Within a follow-up period, 1453 cases of all-cause dementia were reported. Participants with incident dementia tended to be older, male, obese, have higher blood pressure, and have more comorbidities such as diabetes, hypertension, dyslipidemia, and cardiovascular disease than those without dementia. The incidental dementia group had a higher proportion of participants with a family history of dementia, ApoEε4 genotype, and no college degree than the non-incident dementia group. The mean MEDAS, MIND diet score, RFS, AHEI, and EDII in the study population were 4.9 ± 1.9, 6.4 ± 1.9, 9.1 ± 3.5, 50 ± 13, and −0.1 ± 1.4, respectively. Baseline characteristics according to each dietary score before and after exact matching are presented in Supplementary Table S2.

3.2. Dietary patterns and dementia

The cumulative incidence of dementia during the follow-up period in each quartile group of dietary indices was adjusted for age and sex using exact matching as shown in Fig. 2. The trend of the lower score quartile groups developing a higher incidence of dementia was statistically significant for the Mediterranean diet, MIND diet, and RFS ($p = 0.03$, 0.02, and 0.004, respectively). Specifically, the lowest score group for each dietary index had the highest incidence of dementia at the end of the follow-up period of 16 years. For AHEI and EDII, although the highest AHEI score group exhibited the lowest incidence of dementia and the lowest EDII group had the lowest incidence of dementia after the follow-up period, no significant differences were observed among the quartile groups.

Fine–Gray subdistribution hazard models were used to determine the HRs and 95% CIs for incident dementia across each dietary index. These models were exact matched for age and sex and further adjusted for ethnicity, BMI, alcohol use, smoking, physical activity, ApoEε4 genotype, and family history of dementia, as shown in Table 2. Higher scores for the MEDAS, MIND diet, RFS, and AHEI were significantly associated with a reduced risk of dementia, with HRs (95% CIs) of 0.79 (0.67–0.93), 0.73 (0.62–0.86), 0.72 (0.61–0.84), and 0.77 (0.66–0.90), respectively. Conversely, a higher EDII score was associated with an increased risk of dementia with an HR (95% CI) of 1.3 (1.1–1.5). The adjusted cubic spline model of the HRs for each dietary index after exact matching is described in Fig. 3.

The association between dietary indices and dementia incidence remained significant in adjusted Fine–Gray subdistribution hazard models without exact matching (Supplementary Table S3 and Fig. S1). Furthermore, the association persisted even after additional adjustments for comorbidities such as diabetes, dyslipidemia, hypertension, cardiovascular disease, and socioeconomic factors, including educational attainment (college or university degree) (Supplementary Table S4). Additionally, higher adherence to the MIND diet, RFS, and AHEI were significantly associated with a lower risk of MCI, further supporting the protective effects of these dietary patterns on cognitive health (Supplementary Table S5).

3.3. Dietary patterns and dementia risk by follow-up period

To disentangle the effects of age and follow-up duration, we additionally performed a landmark analysis by stratifying the follow-up period into three intervals: <5 years, 5–10 years, and ≥10 years (Supplementary Table S6). In the <5-year interval, where the cohort was relatively younger, the associations between dietary indices and dementia risk were generally less pronounced, with only the MIND diet showing a significant protective effect with HR (95% CI) of 0.37 (0.19–0.72). In the 5–10-year interval, stronger associations were observed; Higher adherence to the MIND diet, RFS, and AHEI were associated with a significantly reduced risk of dementia with HRs (95% CIs) of 0.62 (0.47−0.80), 0.58 (0.45−0.75), and 0.61 (0.47−0.79), respectively. Higher EDII scores were also linked to an increased risk in quartile 2 with an HR (95% CI) of 1.4 (1.1–1.8). In the ≥10-year interval, the protective associations persisted for some indices; notably, the highest quartile of MEDAS was associated with a 24% lower dementia risk with an HR (95% CI) of 0.76 (0.60–0.95), and the highest quartile of EDII remained significantly associated with increased risk with HR (95% CI) of 1.4 (1.1–1.7).

3.4. Subgroup analysis of dietary patterns and dementia risk

The effect of lowering the risk of dementia through adherence to specific dietary patterns varied in subgroups stratified by age, sex, and obesity status, as shown in Fig. 4, after the same exact matching and adjustment as the Fine–Gray subdistribution hazard models. For the MEDAS and AHEI, greater adherence was associated with a lower incidence of dementia only in the older age group (≥60 years) (p for interaction < 0.001). The association between the MIND diet, RFS, and EDII was significant in both age groups (p for interaction < 0.001).

Sex-stratified analysis revealed that higher adherence to MEDAS, MIND diet, AHEI, and lower EDII scores were significantly associated with a reduced dementia risk only in females (p for interaction < 0.001). While RFS was significantly associated with lower dementia risk in both sexes, the risk reduction was more pronounced in females (p for interaction < 0.001). According to obesity status, a higher EDII score was significantly associated with a higher dementia risk only in the obese group, whereas a higher MIND diet score, RFS, and AHEI were associated with a lower risk of dementia only in the non-obese group. The MEDAS exhibited a significant association in both groups.

To examine the variation in associations based on genetic predisposition which can impact dementia risks, we further conducted a subgroup analysis according to ApoEε4 carrier status (Supplementary Table S7). Higher adherence to the MEDAS, MIND diet score, and AHEI was significantly associated with a reduced risk of dementia only in ApoEε4 non-carriers. For EDII, a higher score was significantly associated with an increased dementia risk in the ApoEε4 non-carrier group, while no significant association was observed in carriers. In contrast, adherence to RFS was significantly associated with a reduced dementia risk regardless of ApoEε4 status.

4. Discussion

In this large population-based cohort study, greater adherence to the Mediterranean diet, MIND diet, and overall diet quality (as measured using RFS and AHEI) were significantly associated with a reduced incidence of dementia over a median 13.5-year follow-up period.

Table 1
Baseline characteristics of participants according to dementia incidence.

Characteristics	Overall (n = 131,208)	Non-incident dementia (n = 129,755)	Incident dementia (n = 1453)	p-value
Age (years)	56 ± 8.0	56 ± 7.9	64 ± 4.8	<0.001
Sex, n (%)				<0.001
Male	62,320 (48%)	61,460 (47%)	860 (59%)	
Female	68,890 (53%)	68,290 (53%)	590 (41%)	
Ethnicity, n (%)				0.04
White	5310 (4.0%)	5260 (4.1%)	43 (3.0%)	
Non-white	125,900 (96.0%)	124,490 (95.9%)	1,410 (97.0%)	
BMI, kg/m^2	27 ± 4.6	27 ± 4.6	27 ± 4.7	0.005
Waist, cm	89 ± 13	89 ± 13	92 ± 14	<0.001
SBP, mmHg	140 ± 18	140 ± 18	140 ± 19	<0.001
DBP, mmHg	82 ± 10	82 ± 10	81 ± 9.8	0.2
APOEε4 carriers	0.3 ± 0.4	0.3 ± 0.4	0.5 ± 0.5	<0.001
Glucose, mmol/L	5.1 ± 1.1	5.1 ± 1.1	5.4 ± 1.5	<0.001
HbA1c, mmol/mol	36 ± 6.0	36 ± 6.0	38 ± 7.5	<0.001
Creatinine, umol/L	72 ± 18	72 ± 18	76 ± 21	<0.001
Total cholesterol, mmol/L	5.7 ± 1.1	5.7 ± 1.1	5.6 ± 1.2	<0.001
Triglyceride, mmol/L	1.7 ± 1.0	1.7 ± 1.0	1.7 ± 1.0	0.5
HDL cholesterol, mmol/L	1.5 ± 0.4	1.5 ± 0.4	1.4 ± 0.4	0.006
LDL cholesterol, mmol/L	3.6 ± 0.9	3.6 ± 0.9	3.4 ± 0.9	<0.001
College or university degree, n (%)	58,080 (44%)	57,560 (44%)	520 (36%)	<0.001
Alcohol consumption (g/day)	17 ± 21	17 ± 21	15 ± 21	0.006
Alcohol status, n (%)				<0.001
Never	4050 (3.1%)	3980 (3.1%)	60 (4.3%)	
Previous	3960 (3.0%)	3880 (3.0%)	80 (5.4%)	
Current	123,200 (93.9%)	121,890 (93.9%)	1310 (90.2%)	
Smoking status, n (%)				<0.001
Never	73,980 (56%)	73,300 (57%)	680 (47%)	
Previous	47,070 (36%)	46,400 (36%)	670 (46%)	
Current	10,160 (7.7%)	10,050 (7.7%)	100 (7.0%)	
METS-min/week	2510 ± 2470	2510 ± 2470	2680 ± 2680	0.008
Family history of dementia, n (%)	17,240 (13%)	16,860 (13%)	370 (26%)	<0.001
Co-morbidities, n (%)				
Diabetes	5380 (4.1%)	5240 (4.0%)	140 (9.8%)	<0.001
Dyslipidemia	17,810 (14%)	17,420 (13%)	390 (27%)	<0.001
Hypertension	31,630 (24%)	31,050 (24%)	580 (40%)	<0.001
Cardiovascular disease	9670 (7.4%)	9420 (7.3%)	280 (19%)	<0.001
Recent depressive symptom (RDS-4 score)	5.3 ± 1.9	5.3 ± 1.9	5.3 ± 2.0	0.5
Total energy, kcal/day	2070 ± 590	2070 ± 590	2100 ± 640	0.1
Carbohydrate (g/day)	260 ± 80	260 ± 80	270 ± 87	<0.001
Fat (g/day)	73 ± 29	73 ± 29	73 ± 31	0.6
Protein (g/day)	81 ± 24	81 ± 24	82 ± 26	0.2
SFA (g/1000 kcal)	13 ± 3.6	13 ± 3.6	13 ± 3.9	0.4
Omega-3 PUFA (g/1,000 kcal)	1.0 ± 0.4	1.0 ± 0.4	1.0 ± 0.5	0.6
Omega-6 PUFA (g/1,000 kcal)	5.3 ± 1.8	5.3 ± 1.8	5.0 ± 1.7	<0.001
Fiber (g/1,000 kcal)	8.9 ± 2.8	8.9 ± 2.8	9.2 ± 3.1	<0.001
Cholesterol (mg/1,000 kcal)	120 ± 73	120 ± 73	120 ± 76	0.5
Vitamin A (μg RAE)	980 ± 1010	980 ± 1010	1060 ± 1120	0.002
Retinol (μg)	470 ± 880	470 ± 880	500 ± 980	0.2
β-Carotene (μg)	2700 ± 2440	2690 ± 2430	2970 ± 2760	<0.001
Vitamin D (μg)	3.7 ± 2.9	3.7 ± 2.9	4.0 ± 3.4	<0.001
Vitamin E (mg)	11 ± 4.6	11 ± 4.6	11 ± 5.0	0.7
Vitamin C (mg)	130 ± 78	130 ± 78	140 ± 88	<0.001
Thiamine (mg)	1.9 ± 0.7	1.9 ± 0.7	2.0 ± 0.8	<0.001
Riboflavin (mg)	1.9 ± 0.6	1.9 ± 0.6	2.0 ± 0.7	<0.001
Niacin equivalent (mg)	38 ± 12	38 ± 12	39 ± 12	0.5
Vitamin B6 (mg)	2.1 ± 0.7	2.1 ± 0.7	2.2 ± 0.7	<0.001
Folate (μg)	320 ± 110	320 ± 110	330 ± 120	<0.001
Vitamin B12 (μg)	6.2 ± 3.3	6.2 ± 3.3	6.6 ± 3.7	<0.001
Ca (mg)	990 ± 340	990 ± 340	1030 ± 370	<0.001
P (mg)	1440 ± 400	1440 ± 400	1470 ± 440	0.003
Na (mg)	1960 ± 770	1960 ± 770	1970 ± 860	0.6
K (mg)	3700 ± 1070	3700 ± 1070	3830 ± 1170	<0.001
MEDAS	4.9 ± 1.9	4.9 ± 1.9	4.8 ± 1.8	0.02
MIND diet score	6.4 ± 1.9	6.4 ± 1.9	6.2 ± 1.8	<0.001
RFS	9.1 ± 3.5	9.1 ± 3.5	9.1 ± 3.5	0.9
AHEI	50 ± 13	50 ± 13	50 ± 13	0.1
EDII	−0.1 ± 1.4	−0.1 ± 1.4	0.0 ± 1.4	0.2

Abbreviations: BMI, Body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; METS, metabolic equivalents; SFA, saturated fatty acid; PUFA, polyunsaturated fatty acid; RAE, retinol activity equivalent; MEDAS, Mediterranean Diet Adherence Screener; MIND, Mediterranean Dietary Approach to Systolic Hypertension Intervention for Neurodegenerative Delay; RFS, Recommended Food Score; AHEI, Alternative Healthy Eating Index; EDII, Energy-adjusted Dietary Inflammatory Index.
Notes: Continuous variables are expressed as the mean ± standard deviation, and categorical variables are expressed as numbers (percentages).

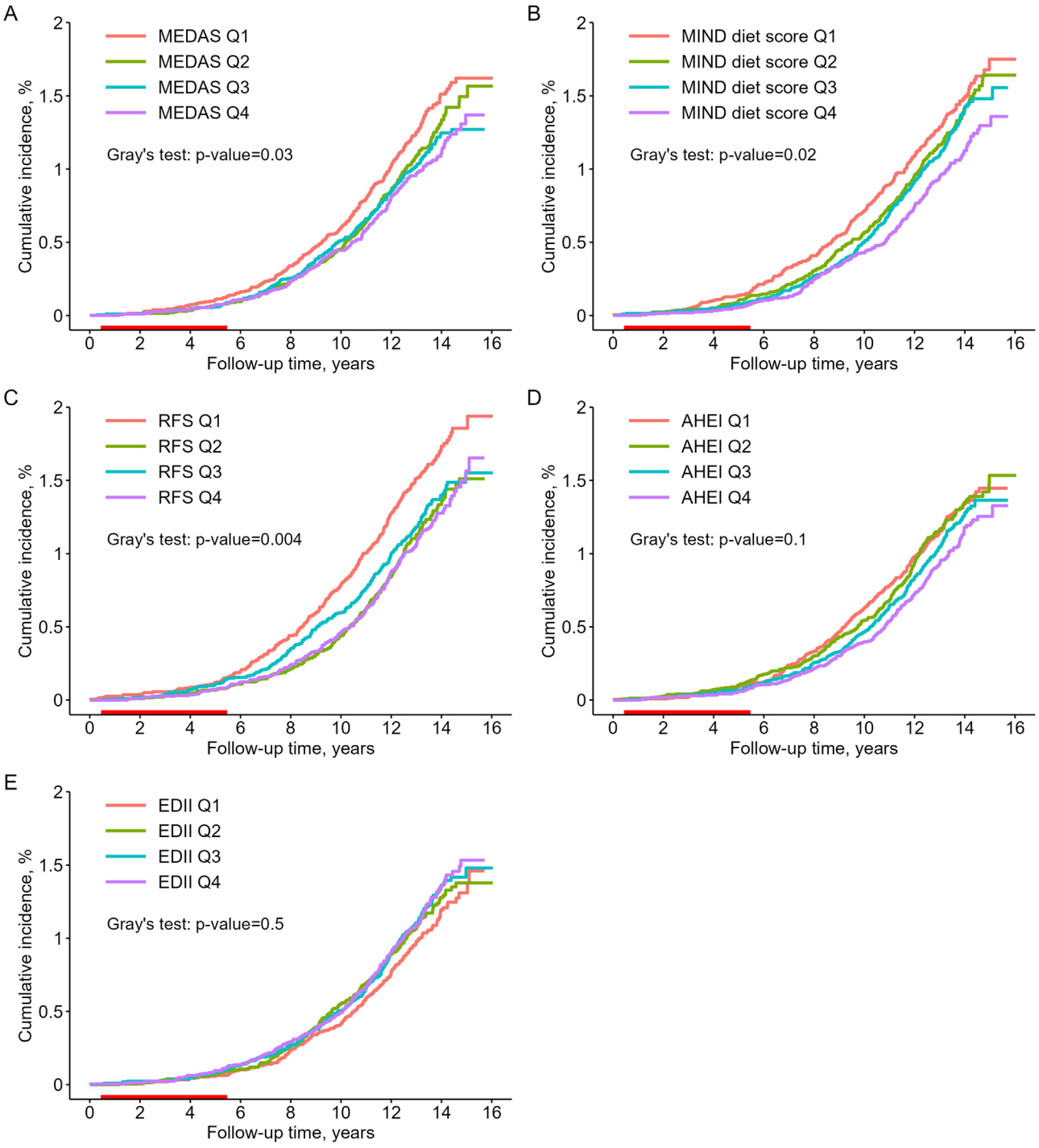

Fig. 2. Cumulative incidence of dementia according to baseline dietary index score following exact matching.
A: Mediterranean diet adherence screener (MEDAS), B: Mediterranean Dietary Approaches to Stop Hypertension Intervention for Neurodegenerative Delay (MIND) diet, C: Recommended Food Score (RFS), D: Alternative Healthy Eating Index (AHEI), E: Energy-adjusted Dietary Inflammatory Index (EDII). The Kaplan–Meier curve was exact matched for age and sex. Gray's test was performed, and $p < 0.05$ was considered statistically significant. The red line on the x-axis represents the duration between the first and last instances of the 24-h dietary recall assessment. The first assessment took place 0.43 years after the start of follow-up, while the last assessment was conducted 5.47 years after the follow-up began.

Conversely, higher EDII scores, which indicate a diet with greater inflammatory potential, were associated with an increased risk of dementia. Even in MCI, which has a high rate of progression to dementia in a short period, higher adherence to the MIND diet, RFS, and AHEI was associated with a lower incidence of progression. This suggests that these dietary interventions may help reduce the transition into the pre-dementia stage. The associations between dietary patterns and dementia were stronger in older adults and women and varied between the obese and non-obese groups, highlighting the differential impact of dietary patterns across subgroups. Our findings underscore the potential of dietary interventions as modifiable factors to reduce the risk of dementia, particularly in vulnerable populations.

Our results are consistent with those of previous studies, demonstrating the cognitive benefits of the Mediterranean and MIND diets in

Table 2
Fine–Gray subdistribution hazard model for dementia incidence according to quartile groups of dietary indices.

Dietary index	MEDAS		MIND diet		RFS	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Q1	Reference		reference		reference	
Q2	0.85 (0.72–0.99)	0.045	0.87 (0.74–1.0)	0.08	0.76 (0.65–0.9)	<0.001
Q3	0.80 (0.68–0.94)	0.007	0.83 (0.71–0.97)	0.02	0.74 (0.63–0.86)	<0.001
Q4	0.79 (0.67–0.93)	0.005	0.73 (0.62–0.86)	<0.001	0.72 (0.61–0.84)	<0.001

Dietary index	AHEI		EDII	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Q1	Reference		reference	
Q2	0.95 (0.82–1.1)	0.5	1.1 (0.97–1.4)	0.1
Q3	0.85 (0.73–0.99)	0.04	1.3 (1.1–1.5)	0.009
Q4	0.77 (0.66–0.90)	0.001	1.3 (1.1–1.5)	0.008

Abbreviations: HR, hazard ratio; CI, confidence interval; MEDAS, Mediterranean Diet Adherence Screener; MIND, Mediterranean-Dietary Approach to Systolic Hypertension Intervention for Neurodegenerative Delay; RFS, Recommended Food Score; AHEI, Alternative Healthy Eating Index; EDII, Energy-adjusted Dietary Inflammatory Index.
Notes: The Fine–Gray subdistribution hazard model was performed for exact matched data for age and sex, and further adjusted for ethnicity, BMI, alcohol, smoking, physical activity, ApoEε4, and family history of dementia.

lowering the risk of Alzheimer's disease and dementia [8,10–12,34,35]. Diets rich in vegetables, fruit, whole grains, olive oil, legumes, and fish can delay cognitive decline [9]. A systematic review of 32 studies of 5 randomized controlled trials and 27 observational studies reported an association of greater adherence to the Mediterranean diet with improved cognitive performance and reduced risk of Alzheimer's disease and dementia [36]. Similarly, a meta-analysis of cohort studies reported that greater adherence to the MIND diet significantly lowered the risk of incident dementia [34,35].

Although prior studies on overall diet quality, assessed using RFS and AHEI, have demonstrated inconsistent results, our findings are consistent with those of large cohort studies, such as the ARIC study, which reported a weak but significant association between higher AHEI adherence and reduced dementia risk [37]. Furthermore, our study demonstrated the negative impact of pro-inflammatory diets, as measured using EDII, indicating that diets rich in pro-inflammatory foods such as saturated fats and refined carbohydrates are associated with an increased risk of dementia [38]. This finding aligns with that of the previous study from the UK Biobank cohort, which also reported a strong association between higher DII scores and increased dementia risk, particularly in individuals with metabolic challenges such as obesity [16]. Similarly, a previous study found that the association between inflammatory diet and chronic disease was more pronounced in individuals with a higher BMI, underscoring inflammatory dietary components amid increasing obesity trends [39].

Our study effectively addresses several limitations of previous studies on diet and dementia. Many earlier studies relied on a single dietary scoring system without comparing multiple dietary patterns [8,11] or had relatively short follow-up periods, limiting their ability to assess long-term effects [17]. In contrast, our study adopted a more comprehensive approach by evaluating multiple dietary patterns (Mediterranean, MIND, RFS, AHEI, and EDII) in a large cohort of >130,000 participants with up to 13.5 years of follow-up, offering robust and nuanced insights into the association between diet and dementia. We also identified effect variation according to demographic and genetic factors, providing insights into tailored dietary intervention. Furthermore, by using exact matching to account for age and gender differences, we enhanced the accuracy and reliability of our study, offering a clearer understanding of the independent effects of diet on dementia risk.

The protective effects of Mediterranean and MIND diets against dementia can be explained by several fundamental biological mechanisms. Both diets are rich in bioactive compounds with anti-inflammatory, antioxidant, and neuroprotective properties [6], including long-chain omega-3 fatty acids (such as docosahexaenoic acid), polyphenols, vitamin D, and phenolic acids found in vegetables, fruits, and fish, which form the core of dietary patterns [40]. These nutrients reduce inflammation, combat oxidative stress, and inhibit the development of beta-amyloid plaques, which are associated with the progression of Alzheimer's disease [6]. Additionally, greater adherence to dietary patterns, such as AHEI, can increase the intake of lipid-soluble micronutrients, such as tocopherols, which exhibit anti-inflammatory properties [41]. Similarly, a higher RFS score has been correlated with greater consumption of antioxidants such as ascorbic acid, tocopherols, and beta-carotene, which help reduce oxidative damage in the brain and protect nerve cell degeneration [42]. The microbiota–gut–brain axis plays a significant role in the relationship between diet and cognitive health [43]. Inflammation triggered by poor dietary choices can affect the brain through this pathway, leading to neuroinflammation and reactive oxygen species generation, disrupting synaptic function and contributing to cognitive decline, particularly memory impairment [44,45]. Although we did not directly investigate these mechanisms, our findings strongly support the importance of anti-inflammatory and nutrient-dense foods in preserving brain health.

In our study, the effects of dietary patterns on dementia risk varied across subgroups. The MEDAS and AHEI showed more potent protective effects in older adults (≥60 years), likely due to the cumulative benefits of long-term adherence to healthy eating, increased vulnerability to neurodegeneration, and greater reliance on external protective factors. This finding is consistent with previous studies that oxidative stress contributes to neurodegeneration and antioxidant-rich diets help mitigate brain [46,47]. Additionally, dementia incidence in the UK declines in individuals under 60 but rises sharply after 80, reflecting an overall increase with age [48,49]. Considering these findings, our results underscore the importance of maintaining healthy dietary habits to reduce dementia risk, particularly in aging populations. Sex-specific differences were also observed, with the MEDAS, MIND diets, and AHEI offering greater protection in females, whereas the RFS benefited both sexes. These findings reflect differences in nutritional needs, metabolism, and susceptibility to neurodegenerative diseases between males and females [50,51], as Alzheimer's disease is more common in older women [52,53]. Estrogen plays a neuroprotective role and postmenopausal estrogen decline is linked to neuroinflammation and mitochondrial dysfunction [54,55]. Nutrients such as omega-3 fatty acids and lycopene in diet may help counteract these effects, potentially enhancing cognitive benefits in women [56]. Additionally, sex-based differences in the gut-brain axis may further influence dietary impacts on cognitive health [57].

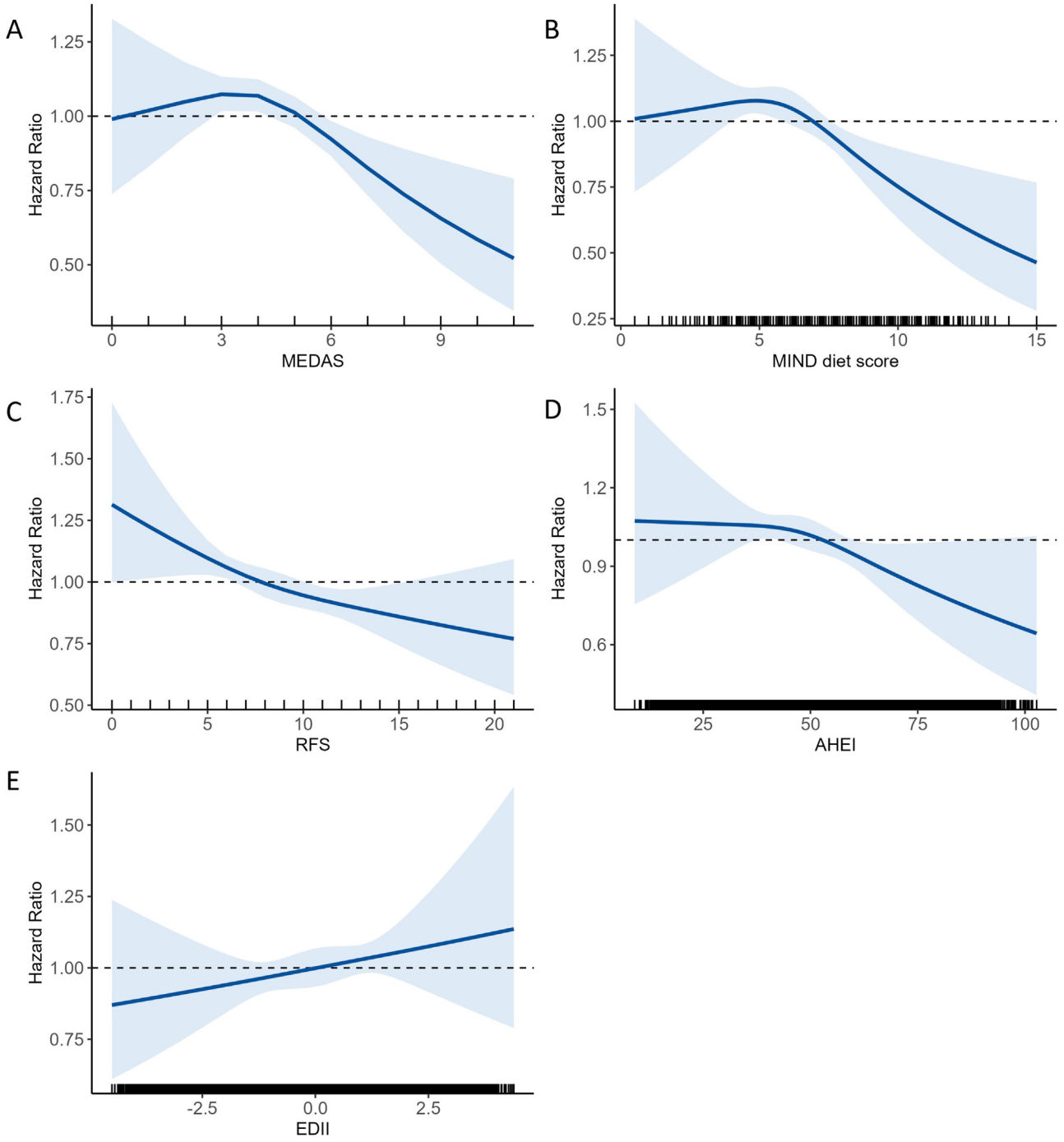

Fig. 3. Adjusted cubic spline model of dietary index score and dementia risk after exact matching.
A: Mediterranean diet adherence screener (MEDAS), B: Mediterranean Dietary Approaches to Stop Hypertension Intervention for Neurodegenerative Delay (MIND) diet, C: Recommended Food Score (RFS), D: Alternative Healthy Eating Index (AHEI), E: Energy-adjusted Dietary Inflammatory Index (EDII). Models were exact matched for age and sex, and further adjusted for ethnicity, BMI, alcohol, smoking, physical activity, ApoEε4 genotype, and family history of dementia. HR, hazard ratio; CI, confidence interval; BMI, body mass index.

Obesity modified the effects of dietary patterns on dementia risk. Pro-inflammatory diets (higher EDII scores) were associated with increased dementia risk in obese individuals, likely due to their synergy with existing inflammation [58]. In contrast, anti-inflammatory diets, such as the MIND diet, RFS, and AHEI, showed more substantial protective effects in non-obese individuals, where baseline inflammation is lower. Given obesity's links to chronic inflammation and insulin resistance—both contributors to cognitive decline—excess adiposity may reduce the neuroprotective benefits of an anti-inflammatory diet. These findings emphasize the necessity of integrating dietary interventions with weight management strategies for effective dementia prevention [59]. Future research should further investigate the underlying biological mechanisms, including hormonal regulation and gut-brain interactions, to refine personalized dietary recommendations.

The association between dietary patterns and dementia was primarily significant in ApoEε4 non-carriers; this highlights the need for additional prevention strategies beyond diet for carriers while reinforcing dietary interventions as a practical approach for non-carriers. Dietary effects also

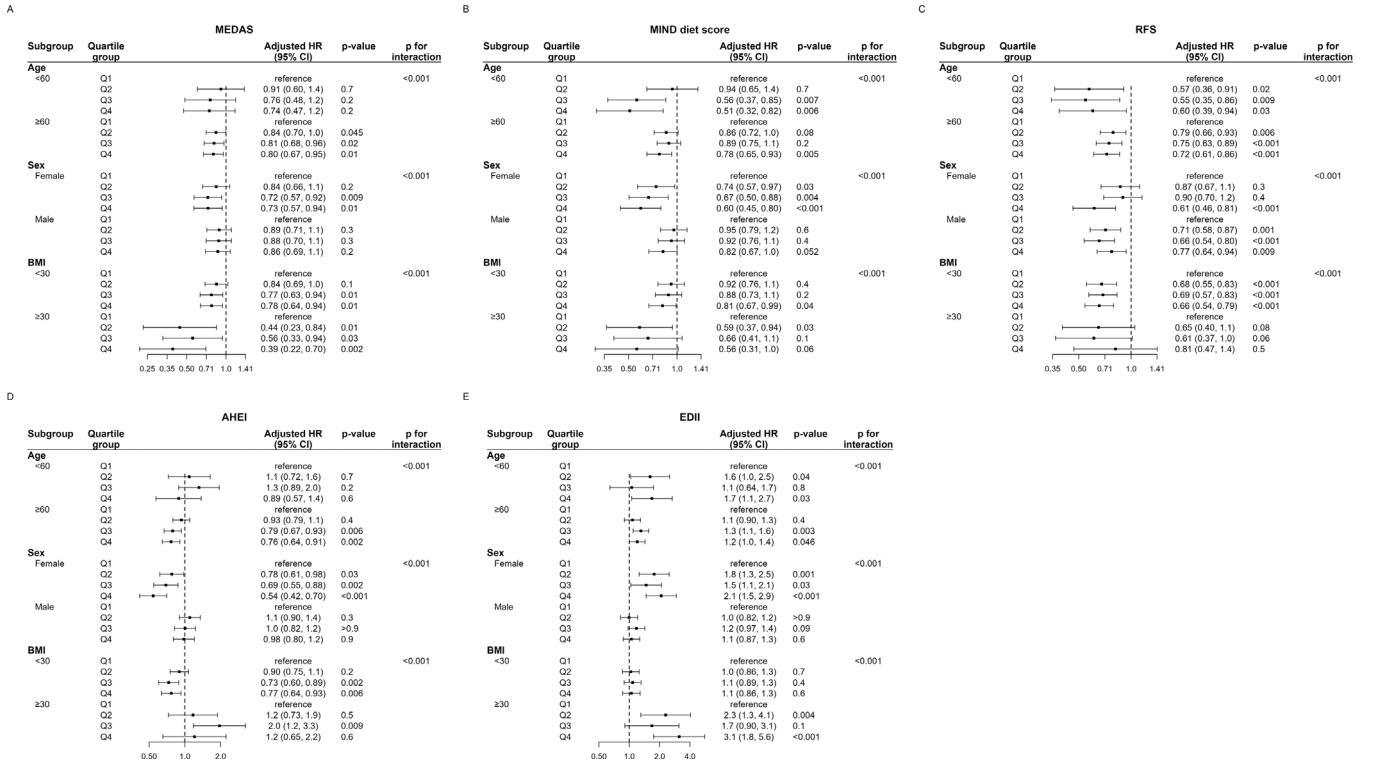

Fig. 4. Forest plot for subgroup analysis of dietary index score and dementia risk.
A: Mediterranean diet adherence screener (MEDAS), B: Mediterranean Dietary Approaches to Stop Hypertension Intervention for Neurodegenerative Delay (MIND) diet, C: Recommended Food Score (RFS), D: Alternative Healthy Eating Index (AHEI), E: Energy-adjusted Dietary Inflammatory Index (EDII). Models were exact matched for age and sex, and further adjusted for ethnicity, BMI, alcohol, smoking, physical activity, ApoEε4 genotype, and family history of dementia.

varied by follow-up duration. Only the MIND diet showed a protective effect in the early period (<5 years). Over 5–10 years, RFS, AHEI, and EDII also demonstrated significant associations, supporting the cumulative impact of diet on dementia risk [60]. After 10 years, only MEDAS and EDII remained significant, indicating that other risk factors may become more influential over time. Further research is needed to explore these long-term interactions.

Our study also has some limitations. First, dietary intake was assessed using a self-reported 24-h food recall method, which, despite its feasibility and cost-effectiveness in large-scale epidemiological studies, is subject to recall bias. Participants' ability to accurately recall and report their food consumption may vary, leading to potential misestimation of nutrient intake. Additionally, this method has inherent limitations, including underreporting or overreporting of food intake due to social desirability bias, day-to-day variability in dietary habits, portion size estimation errors, and reduced accuracy in specific populations. Second, there might be possibilities of regression dilution bias as in a long-term prospective cohort study. The result of this study regarding the association between dietary patterns and dementia risk might have been underestimated because of the combined effects of measurement errors and long-term fluctuations within individuals [61]. Third, the study population was limited to UK participants aged 40–69 years at baseline with 13.5 years of follow-up, which may restrict the generalizability of our findings to populations with different ethnic, cultural, or age characteristics. Moreover, the observed relationship between diet patterns and dementia risk may vary across different age groups and follow-up durations [62]. Future research should further investigate these factors with diverse age cohorts and varying follow-up periods. Fourth, the dietary index scores were calculated based on the average data collected between 2011 and 2012 without accounting for potential changes in participants' dietary habits over the follow-up period. As dietary patterns can evolve over time, this could limit our ability to fully assess the long-term impact of diet on dementia risk, as the scores might not accurately reflect participants' eating behaviors throughout the entire study period. In future studies, it would be valuable to explore the impact of dietary changes over time on dementia incidence to gain a more comprehensive understanding of this relationship. Fifth, one limitation of exact matching in our study is that the estimated effect can only be generalized to a small population and lacks precision, typically due to the sample left over after matching. Future studies should consider alternative matching strategies that might better preserve sample size while effectively controlling confounding variables. Lastly, despite matching key covariates and adjusting for multiple potential confounders, residual confounding may persist and influence dietary choices and dementia risk. Future research considering more confounding factors can help with a more comprehensive understanding of dietary intervention for dementia.

In conclusion, our study highlights that greater adherence to the Mediterranean and MIND diets and maintenance of an overall high diet quality is significantly associated with a reduced risk of dementia. Additionally, adherence to the MIND diet, RFS, and AHEI were also linked to a lower incidence of MCI, a key risk factor for dementia. In contrast, diets with high inflammatory potential, as reflected by higher EDII scores, were associated with an increased risk of dementia. These findings emphasize the crucial role of diet as a modifiable lifestyle factor in preventing dementia. Considering the limited treatment options for dementia, promoting dietary interventions targeting nutrient-dense and anti-inflammatory foods could be a valuable strategy to reduce the incidence of dementia at the population level.

5. Conclusion

Higher adherence to the Mediterranean diet, MIND diet, high-quality diet, and anti-inflammatory diet has been associated with a reduced risk of dementia. Notably, the protective effects of these dietary patterns vary

depending on age, sex, obesity status, ApoEε4 status, underscoring the importance of considering population-specific characteristics when designing dietary interventions. Future research should investigate the biological mechanisms underlying these associations further and validate these results in more diverse populations to strengthen the evidence for dietary recommendations for preventing dementia.

CRediT authorship contribution statement

JEY, YJL, YJK, SJH, and JWL contributed to the conception and design of the work; acquisition, analysis, and interpretation of data; and drafting of the manuscript. All the authors critically revised the manuscript, provided final approval, and are accountable for all aspects of the study, ensuring its integrity and accuracy.

Declaration of Generative AI and AI-assisted technologies in the writing process

This paper was written without the use of AI or AI assistive technology.

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Data availability

Researchers can register and apply for data access from UK biobank at https://www.ukbiobank.ac.uk/. Other additional information can be provided by request from the corresponding author.

Declaration of competing interest

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.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jnha.2025.100564.

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