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Original Article

Association of dietary diversity, genetic susceptibility, and the risk of incident dementia: A prospective cohort study

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ABSTRACT

Background: Previous studies have revealed how single foods or nutrients affect dementia, but the evidence for a potential link between dietary diversity and dementia is inconsistent.
Objectives: This study aimed to evaluate the association between dietary diversity and the risk of incident dementia.
Design, Setting and Participants: This prospective study included 104,572 white participants without dementia at baseline recruited between 2006 and 2010 from the UK Biobank.
Measurements: Dietary Diversity Score (DDS) was acquired through the Oxford WebQ's 24-hour dietary recall survey spanning from 2009 to 2012. Cox proportional hazards models were used to estimate the associations between DDS, diversity scores of food groups and the risk of incident dementia. Stratified analyses were subsequently conducted to assess the potential variations across different demographic, socioeconomic, and genetic risk groups.
Results: Over a median follow-up period of 10.44 years, 725 participants developed incident dementia. A higher DDS was associated with a lower risk of incident dementia (HR: 0.95; 95 % CI: 0.93–0.97). Stratified analyses revealed statistical significance in this association for individuals under 65 years old (HR: 0.95; 95 % CI: 0.92–0.98), and those with higher polygenic risk scores (PRS; HR: 0.92; 95 % CI: 0.89–0.95). Among five food groups, a higher diversity score for meat and protein alternatives was associated with a lower risk of dementia (HR: 0.92; 95 % CI: 0.86–0.99).
Conclusion: Enhancing dietary diversity reduces dementia risk, and is potentially influenced by genetic predisposition. Consuming a diverse range of foods may be an effective strategy against dementia.

1. Introduction

Dementia is any disorder where a significant decline from one's previous level of cognition causes interference in occupational, domestic, or social functioning [1]. With the aging population trend, the number of people living with dementia across the world is expected to rise from 55 million in 2019 to 139 million in 2050, posing a heavy economic and social burden [2]. Several environmental and lifestyle factors, including being over 65 years old, female, having hypertension or diabetes, overweight or obesity, smoking, drinking, and being physically inactive are associated with an increased risk of dementia [3]. As an important modifiable factor, diet has garnered increasing attention for its relationship with health outcomes in recent years [4]. However, the potential role of diet in the prevention of dementia remains unclear.

Deficiency of anti-oxidants, such as vitamins C, E, beta-carotene, and marine-oil-derived n-3 polyunsaturated fatty acids, has been demonstrated to increase the risk for dementia [4]. However, since foods are eaten in combination, there has been a shift from investigating single nutrients and foods towards investigating the impact of a diverse diet [5]. Longitudinal studies indicated that those who consumed a wide variety of foods had a lower risk of cognitive decline or incident demen-

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tia, and a highly diverse diet suppressed hippocampal volume loss over 2 years [6–8]. Dietary diversity, defined as the number of different food groups consumed over a given reference period [9], is assessed by calculating the Dietary Diversity Score (DDS) to evaluate nutrient adequacy and diet quality, and has been extensively validated in both developing and developed countries [10]. Previous research on food combinations has focused on dietary patterns such as the Mediterranean diet (MedDiet), Dietary Approaches to Stop Hypertension dietary pattern (DASH), and the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet [11]. However, when assessing the association between dietary patterns and dementia, it is difficult for older adults to collect food quantities using the Food Frequency Questionnaire (FFQ) [12]. In contrast, DDS is measured using a simple count of foods or food groups over a given period, offering a more feasible evaluation that is simpler and easier for respondents to complete [13]. Several studies have demonstrated the beneficial effects of a high DDS on cognitive function [4,6–8]. However, due to the small sample size [8], short follow-up time [14], homogeneity in study populations [6], and the limited capacity of dietary measurement tools to fully capture diet diversity [15], there are still some limitations in the evidence regarding the association between dietary diversity and the risk of dementia.

It has been widely accepted that dementia develops at the interface between environmental factors and inherited predisposition[16,17]. Numerous Genome-Wide Association Studies (GWASs) have recently identified a growing number of genetic variations associated with the risk of dementia [18,19], estimating disease heritability ranging from 13 % to 80 % [20]. There was evidence that a favorable lifestyle was associated with a lower dementia risk among participants with high genetic risk [21]. Recently, Peng et al. also reported that people with high genetic risk scores for Alzheimer's disease (AD) who persist in a pro-inflammatory dietary pattern may promote the risk of AD [22]. Therefore, exploring modifiable risk factors for dementia needs to consider an individual's inherent genetic susceptibility.

To obtain more comprehensive evidence, we conducted a prospective cohort study among 104,572 participants recruited from the UK Biobank to investigate the association between DDS and incident dementia, as well as how it can be influenced by genetic predisposition. Furthermore, the relationship between the scores of the five food groups constituting the DDS and the risk of dementia was evaluated, with the aim of identifying significant contributors to maintaining optimal cognitive function.

2. Materials and methods

2.1. Participants

The UK Biobank is a large-scale prospective cohort that recruited over 500,000 participants (39 to 74 years old) from 22 centers in England, Scotland, and Wales from 2006 to 2010. Information on demographics, lifestyle, and health status was collected at assessment centers through touchscreen questionnaires, verbal interviews, and physical measurements at baseline visit. All available resources are listed on the UK Biobank website (http://www.ukbiobank.ac.uk/resources/). Ethical approval was granted for the UK Biobank by the North West-Haydock Research Ethics Committee (REC reference: 21/NW/0157), and participants provided written informed consent.

Among 502,521 participants, 211,031 individuals completed at least one of the five rounds of 24-hour dietary recall surveys between 2009 and 2012. Participants meeting certain criteria were excluded from this study. These criteria included individuals of non-white racial background (n = 39,280), being diagnosed with dementia by the time of recruitment or beyond December 31, 2019 (n = 89), loss to follow-up or death before December 31, 2019 (n = 8,883), and with missing data (n = 58,207). After exclusion, the final analysis included 104,572 individuals.

2.2. Assessment of DDS

Dietary information in the UK Biobank was assessed through five rounds of 24-hour dietary recall surveys conducted using the Oxford WebQ dietary questionnaire 23. This questionnaire assessed detailed dietary intake over the previous 24 and was added to the assessment centers from April 2009 to September 2010. After that, the WebQ questionnaire was administered online once every 3–4 months and repeated for a total of 4 rounds over a 16-month period from February 2011 to June 2012 for 24-hour dietary assessments.

DDS was developed by Kant et al. [24] and has been validated in other cohorts [9,15,25]. According to the United Nations' Food and Agriculture Organization food group classification guidance [26], DDS was constructed based on five major food consumption groups (eighteen subgroups) [25]: grain products (whole grains, non-whole/refined grains), vegetables (dark green leafy, vitamin A-rich, starchy tubers, other), fruits (citrus, vitamin A-rich, other), meat and protein alternatives (red meat, fish and seafood, poultry, organ meat, eggs, legumes and nuts), and milk products (yogurt, milk, cheese). The DDS was equal to the sum of points for all 18 subgroups. An increase of one unit in DDS represents an increase in participants' consumption of one food subgroup, with a range of 0–18 points. A higher DDS reflects a richer diet, which is associated with meeting the requirements for all essential nutrients (Table S1). For each food subcategory consumed by participants, the dietary diversity score increases, but diverse foods consumed within the same subcategory were not repeatedly counted. We calculated mean values for the number of repeated dietary assessments.

2.3. Assessment of incident dementia

The primary endpoint in this study was incident all-cause dementia, as defined by the UK Biobank Outcome Adjudication Group, using the International Classification of Diseases-10th Revision (ICD-10) codes F00, F01, F02, F03, and G30. Hospital inpatient data from England, Scotland, and Wales, as well as the national death registers, were utilized to identify the date of the first known dementia after the date of baseline assessment. Follow-up started from recruitment and ended at the time of incident dementia, loss to follow-up, death, or the latest data update (December 2019), whichever occurred first.

2.4. Polygenic risk scores for AD

The GWAS meta-analysis for AD published in 2019 was used as the base dataset [19], with a total of 455,258 European ancestry samples. We calculated two types of individual-level polygenic risk scores (PRS) in the UK Biobank as the target dataset, with and without the APOE4 status, to estimate the genetic susceptibility to AD. For the former, we used all SNPs in the base dataset, and for the latter, we excluded variants in the APOE region (chromosome 19, coordinates hg19: 45,020,859 to 45,844,508). The PRSice-2 software (https://www.prsice.info) was used to calculate the PRS [27].

All SNPs common between the base and target dataset were identified. These SNPs were clumped based on linkage disequilibrium with a cutoff of r^2=0.1 in a 250-kb bidirectional window to keep a set of independent SNPs. The best model was derived by testing the inclusion of SNPs from a range of P value thresholds from 5×10^{-8} to 1 with an incremental interval of 0.005, to determine which threshold gave the largest Nagelkerke's R^2 value, thereby achieving the best predictive abilities in the target data set.

2.5. Covariates

The adjustment models selected the following covariates: (1) personal characteristics, including age (continuous) and gender (male or female); and (2) lifestyle variables, including smoking status (ever smoked

Table 1
Baseline characteristics of participants in the UK Biobank cohort study.

Characteristics, mean (SD), or n (%)	Incident (n = 725)	Non-incident (n = 103,847)
Personal characteristics		
Age, years (SD)	63.96 (4.29)	56.20 (7.79)
Sex (%)		
Male	399 (55.03 %)	48,764 (46.96 %)
Female	326 (44.97 %)	55,083 (53.04 %)
Lifestyle		
BMI, kg/m^2 (SD)	26.74 (4.24)	26.73 (4.37)
Smoking status (%)		
Never	414 (57.10 %)	70,127 (67.53 %)
Ever	311 (42.90 %)	33,720 (32.47 %)
Alcohol status (%)		
Never	53 (7.31 %)	3,307 (3.18 %)
Ever	672 (92.69 %)	100,540 (96.82 %)
Physical activity	46.45 (50.19)	44.52 (53.55)
Socio-demographics		
Education (%)		
CSEs or equivalent	101 (13.93 %)	15,195 (14.63 %)
A levels/AS levels or equivalent and O levels/GCSEs or equivalent	48 (6.62 %)	6,335 (6.10 %)
NVQ or HND or HNC or equivalent and other professional qualifications	198 (27.31 %)	28,681 (27.62 %)
College or university degree	217 (29.93 %)	45,605 (43.92 %)
none of the above	161 (22.21 %)	8,031 (7.73 %)
Townsend Deprivation Index (SD)	−1.56 (2.90)	−1.89 (2.67)
Annual family income (%)		
Less than £18,000	204 (28.14 %)	12,335 (11.88 %)
£18,000 to 30,999	202 (27.86 %)	22,299 (21.47 %)
£31,000 to 51,999	106 (14.62 %)	27,604 (26.58 %)
£52,000 to 100,000	68 (9.38 %)	24,816 (23.90 %)
Greater than £100,000	17 (2.34 %)	7,409 (7.13 %)
Prefer not to answer	70 (9.66 %)	7,150 (6.89 %)
Do not know	58 (8.00 %)	2,234 (2.15 %)
Dietary habits		
Dietary diversity score (SD)	9.92 (3.11)	10.28 (3.16)
Grain products (SD)	1.62 (0.53)	1.64 (0.55)
Vegetables (SD)	2.54 (1.27)	2.58 (1.24)
Fruits (SD)	1.42 (0.84)	1.45 (0.88)
Meat and protein alternatives (SD)	2.38 (1.29)	2.62 (1.29)
Dairy products (SD)	1.94 (0.87)	1.99 (0.89)
Disease susceptibility		
PRS (SD)	−0.0005 (0.0023)	−0.0017 (0.0018)

BMI, body mass index; PRS, polygenic risk scores; CSE, Certificate of Secondary Education; GCSEs, General Certificate of Secondary Education; NVQ, National Vocational Qualification; HND, Higher National Diploma; HNC, Higher National Certificate.

or never smoked), alcohol status (ever consumed alcohol or never consumed alcohol), BMI (continuous), and physical activity (continuous); and (3) Socio-demographics, including education level (college or university degree, Advanced [A] levels/Advanced Subsidiary [AS] levels or equivalent or Ordinary [O] levels/General Certificate of Secondary Education [GCSE] or equivalent, Certificate of Secondary Education [CSE] or equivalent, National Vocational Qualification [NVQ] or Higher National Diploma [HND] or Higher National Certificate [HNC] or equivalent or other professional qualifications, and none of the above), Townsend Deprivation Index (TDI, continuous) [28], and annual family income (less than £18,000, 18,000 to 30,999, 31,000 to 51,999, 52,000 to 100,000, greater than 100,000, do not know, and prefer not to answer); and (4) genetic susceptibility, including PRS including APOE4 (continuous) and PRS excluding APOE4 (continuous).

2.6. Statistical analysis

Baseline characteristics of the samples were summarized and stratified by dementia status as percentages for categorical variables and means and standard deviations (SDs) for continuous variables. We used Cox proportional hazard models to estimate the hazard ratios (HR) and 95 % confidence intervals (CI) for the associations between DDS, scores of five major food groups, and the risk of incident dementia. Three adjusted models were performed to adjust potential confounders: Model 1 adjusted for age and gender; Model 2 adjusted for age, gender, education level, smoking status, alcohol status, BMI, physical activity, TDI and annual family income; Model 3 additionally adjusted for the PRS excluding APOE4 based on Model 2; and Model 4 additionally adjusted for the PRS including APOE4 based on Model 2. The exposure-response relationship between DDS and incident dementia was evaluated using restricted cubic spline (RCS) regressions. To ensure an optimal balance between best fitting and overfitting in the main splines utilized for incident dementia, we initially selected a range of 3–5 knots for constructing the model for DDS [29]. Akaike's Information Criterion (AIC) was then employed to determine the number of knots with the best fitting (3 knots for DDS at the 10th, 50th, and 90th) [30]. We also performed stratification analysis by age (<65 years or ≥65 years), gender (male or female), smoking status (ever smoked and never smoked), alcohol status (ever consumed alcohol and never consumed alcohol), BMI (<25 and ≥25 kg/m^2), physical activity (<28 for low and ≥28 for high), TDI (<median for low and ≥median for high), annual family income (< £52,000 for low and ≥ £52,000 for high), and PRS including and excluding APOE4 (< median for low and ≥median for high).

Sensitivity analyses were performed to assess the robustness of our study results. First, We excluded individuals who developed dementia within 2 years from baseline assessment to minimize the risk of reverse causality. Then, missing data were addressed through multiple imputations using chained equations within the "mice" package to re-

Characteristics	Cases/total	Hazard ratio (95% CI)	*P* value
General population			
Model 1	725/104,572	0.93 (0.91-0.95)	4.17×10^{-9}
Model 2	725/104,572	0.95 (0.92-0.97)	4.56×10^{-6}
Model 3	725/104,572	0.95 (0.92-0.97)	6.53×10^{-6}
Model 4	725/104,572	0.95 (0.93-0.97)	2.72×10^{-5}
Stratified analysis			
Age			
<65	339/87,969	0.95 (0.92-0.98)	2.43×10^{-3}
≥65	386/16,603	0.99 (0.96-1.02)	5.31×10^{-1}
Gender			
Male	399/49,163	0.96 (0.92-0.99)	4.96×10^{-3}
Female	326/55,409	0.95 (0.91-0.98)	2.51×10^{-3}
BMI, kg/m2			
<25	253/39,423	0.98 (0.94-1.02)	3.23×10^{-1}
≥25	472/65,149	0.93 (0.91-0.96)	2.80×10^{-6}
Smoke			
Never	414/70,541	0.93 (0.90-0.96)	1.92×10^{-5}
Ever	311/34,031	0.97 (0.94-1.01)	1.11×10^{-1}
Alcohol			
Never	53/3,360	0.90 (0.82-0.98)	1.74×10^{-2}
Ever	672/101,212	0.95 (0.93-0.98)	2.54×10^{-4}
Physical activity			
Low	352/52,324	0.97 (0.93-1.00)	5.47×10^{-2}
High	373/52,248	0.94 (0.91-0.97)	1.38×10^{-4}
TDI			
Low	344/52,291	0.93 (0.89-0.96)	1.45×10^{-5}
High	381/52,281	0.97 (0.94-1.00)	4.87×10^{-2}
Annual family income			
Low	128/9,512	0.94 (0.92-0.97)	4.55×10^{-5}
High	597/95,060	0.97 (0.92-1.02)	2.03×10^{-1}
PRS excluding APOE4			
Low	307/52,286	0.95 (0.92-0.99)	1.20×10^{-2}
High	418/52,286	0.94 (0.91-0.97)	1.47×10^{-4}
PRS including APOE4			
Low	210/52,286	1.01 (0.97-1.06)	6.25×10^{-1}
High	515/52,286	0.92 (0.89-0.95)	8.37×10^{-9}

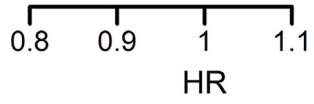

Fig. 1. Association between DDS and incident dementia and stratified analysis
The exposure unit for DDS is one food subgroup. Model 1 adjusted for age and gender; Model 2 adjusted for age, gender, education level, smoking status, alcohol status, BMI, physical activity, TDI and annual family incom; Model 3 additionally adjusted for PRS excluding APOE4; and Model4 additionally adjusted for PRS including APOE4. The stratified analysis was based on Model 4. DDS, dietary diversity score. BMI, body mass index. TDI, Townsend Deprivation Index; PRS, polygenic risk scores.

duce potential bias in the inferences. Random Forest (RF) was employed to perform 5 imputations, accounting for the inherent uncertainty in estimating missing values by producing multiple plausible datasets. All data analyses were completed using R software (version 4.3.0). Statistical significance was set at a two-sided *P*-value of less than 0.05.

3. Results

3.1. Baseline characteristics of participants

This study involved 104,572 participants (Figure S1). During a median follow-up of 10.44 years (1,109,503 person years in total), 725 cases of incident dementia were identified. The mean age at recruit-

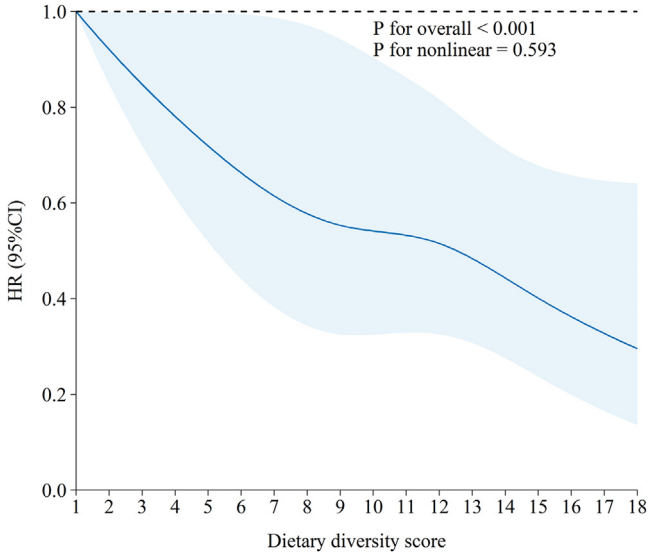

Fig. 2. Dose-response relationships between DDS and the risk of dementia
No evidence of non-linearity was supported.

ment was 56.25, and 47.01 % (49,163 /104,572) of the participants were male. The mean (SD) score of DDS was 10.28 (3.16), and the mean (SD) scores of the five major food groups (grain products, vegetables, fruits, meat and protein alternatives, and dairy products) were 1.64 (0.55), 2.58 (1.24), 1.45 (0.88), 2.61 (1.29), and 1.99 (0.89), respectively. Table 1 shows the characteristics of participants with incident dementia and those without dementia. Compared with other participants, the participants who developed dementia during follow-up were more likely to be older, male, and have a higher TDI, PRS, and a lower DDS.

3.2. Associations between DDS and incident dementia

The association between DDS and the risk of incident dementia was estimated in four adjusted models (Fig. 1). When adjusting for age and gender, higher DDS was associated with a lower risk of dementia (HR: 0.93; 95 % CI: 0.91–0.95; $P = 4.17 \times 10^{-9}$; Model 1). The results remained robust when further adjusting for personal characteristics, lifestyle, and socioeconomic factors (HR: 0.95; 95 % CI: 0.92–0.97; $P = 4.56 \times 10^{-6}$; Model 2) and additionally adjusting for PRS of AD (PRS excluding APOE4: 0.95, 95 % CI: 0.92–0.97, $P = 6.53 \times 10^{-6}$; PRS including APOE4: HR: 0.95, 95 % CI: 0.93–0.97, $P = 2.72 \times 10^{-5}$). In Fig. 2, we used RCS to model and visualize the relation of DDS with incident dementia. The dose-response curve indicated that higher levels of DDS were consistently associated with a lower risk of incident dementia, with no evidence of non-linearity observed ($P = 0.593$).

The stratified analysis results of Model 4 (Fig. 1) revealed statistical significance in this association for individuals under 65 years old (HR: 0.95; 95 % CI: 0.92–0.98; $P = 2.43 \times 10^{-3}$), both male(HR: 0.96; 95 % CI: 0.92–0.99; $P = 4.96 \times 10^{-3}$) and female(HR: 0.95; 95 % CI: 0.91–0.98; $P = 2.51 \times 10^{-3}$), those with a BMI greater than or equal to 25 kg/m^2 (HR: 0.93; 95 % CI: 0.91–0.96; $P = 2.80 \times 10^{-6}$), non-smokers (HR: 0.93; 95 % CI: 0.90–0.96; $P = 1.92 \times 10^{-5}$), individuals with higher physical activity (HR: 0.94; 95% CI: 0.91-0.97; $P = 1.38 \times 10^{-4}$), and those with lower annual family income (HR: 0.94; 95 % CI: 0.92–0.97; $P = 4.55 \times 10^{-5}$). Compared to individuals who consumed alcohol and those with high TDI, the protective effect of DDS against dementia is more pronounced in individuals who never consumed alcohol and those with lower TDI (Fig. 1). Meanwhile, the associations were significant for individuals with high genetic susceptibility to AD, as measured by the PRS (PRS excluding APOE4: 0.94, 95 % CI: 0.91–0.97, $P = 1.47 \times 10^{-4}$; PRS including APOE4: HR: 0.92; 95 % CI: 0.89–0.95; $P = 8.37 \times 10^{-9}$).

3.3. Association between diversity scores of five food groups and incident dementia

Among five food groups, association between diversity score of meat and protein alternatives and the risk of dementia was significant in four adjusted models. As shown in Fig. 3, a higher diversity score of meat and protein alternatives was associated with a lower risk of incident dementia (HR: 0.92; 95 % CI: 0.86–0.99; $P = 1.58 \times 10^{-2}$; model 4). However, diversity scores for grain products (HR: 0.99; 95 % CI: 0.86–1.13; $P = 0.847$; model 4), vegetables (HR: 0.97; 95 % CI: 0.90–1.03; $P = 0.305$; model 4), fruits (HR: 0.96; 95 % CI: 0.88–1.05; $P = 0.399$; model 4), and dairy products (HR: 0.95; 95 % CI: 0.87–1.03; $P = 0.208$; model 4) were not associated with the risk of dementia. The results across the four adjusted models remained identical (Fig. 3).

In stratified analysis, a significant association between diversity score of meat and protein alternatives and incident dementia was observed in individuals under 65 years old (HR: 0.89; 95 % CI: 0.80–0.98; $P = 1.50 \times 10^{-2}$), male (HR: 0.89; 95 % CI: 0.82–0.98; $P = 1.40 \times 10^{-2}$), those with BMI greater than or equal to 25 kg/m^2 (HR: 0.90; 95 % CI: 0.83–0.97; $P = 9.95 \times 10^{-3}$), non-smokers (HR: 0.86; 95 % CI: 0.80–0.95; $P = 2.06 \times 10^{-3}$), those who consumed alcohol (HR: 0.93; 95 % CI: 0.87–0.99; $P = 3.80 \times 10^{-2}$), individuals with higher physical activity (HR: 0.90; 95 % CI: 0.82–0.99; $P = 2.90 \times 10^{-2}$), those with higher annual family income (HR: 0.86; 95 % CI: 0.77–0.99; $P = 4.10 \times 10^{-2}$), and those with higher PRS (PRS excluding APOE4: 0.87, 95 % CI: 0.80–0.95, $P = 1.67 \times 10^{-3}$; PRS including APOE4: HR: 0.83; 95 % CI: 0.76–0.90; $P = 2.62 \times 10^{-6}$). Fig. 4 presents the result of stratified analysis. All these associations are negative correlations.

3.4. Sensitivity analysis

The results were not much altered compared with those from initial analyses when we repeated analyses after excluding participants with dementia during the first 2 years of follow-up (Table S2) and conducting multiple imputation by chained equations (Table S3). The exposure-response curves between DDS and incident dementia in sensitivity analysis are shown in Figures S2–3, with no evidence of non-linearity being observed. The associations of DDS and scores for meat and protein alternatives with dementia remained significant, with a higher DDS or score for meat and protein alternatives associated with a lower risk of developing dementia.

4. Discussion

In this large prospective cohort study, we found that a higher DDS was associated with a lower risk of incident dementia, and such association was influenced by age and PRS. In addition, among the five food groups, a higher diversity score for meat and protein alternatives was associated with a lower risk of dementia.

Although many studies have found an association between diet and dementia or cognitive impairment, research on dietary diversity and subsequent dementia has been limited [4,5]. Our findings supported that higher DDS was related to a lower risk of accident dementia, in accordance with previous studies [6–8]. Zheng et al. reported that dietary diversity might attenuate the rate of cognitive decline and decrease the risk of cognitive impairment in older individuals, particularly in low-income and middle-income countries [15]. Song et al. suggested large declines in DDS within two years among oldest-old was associated to an increased risk of cognitive impairment [13]. However, most previous studies focused on elderly cohorts (≥65 years old) [7,13,14] and/or had a short follow-up time [14,16]. This could introduce a high risk of reverse causality in studies conducted among older adults [5], given the long latency period for the onset of dementia, and result in an insufficient assessment of the association between early-midlife dietary habits and the risk of subsequent dementia [6]. Therefore, our study enrolled participants from midlife to old age and conducted a long-term

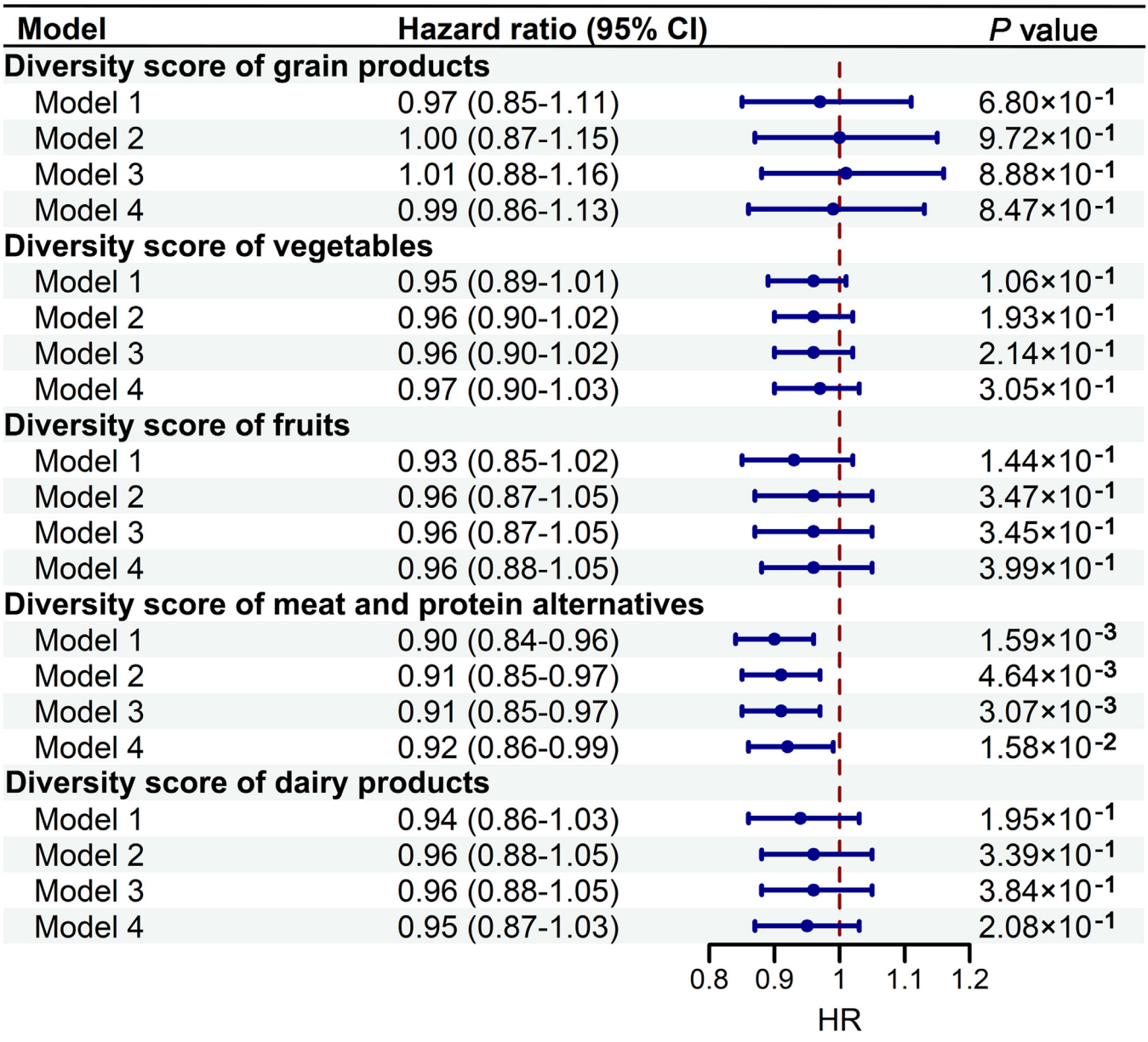

Fig. 3. Association between diversity scores of five food groups and incident dementia
The exposure unit for the diversity scores of the five food groups is one food subgroup. The cases/total were 725/104,572 in all models. Model 1 adjusted for age and gender; Model 2 adjusted for age, gender, education level, smoking status, alcohol status, BMI, physical activity, TDI and annual family income; Model 3 additionally adjusted for PRS excluding APOE4; and Model4 additionally adjusted for PRS including APOE4.

follow-up with a median of 10.44 years. We found that a diverse diet is associated with a reduced risk of subsequent dementia, and this impact is evident from early midlife.

There are several potential mechanisms that may explain the relationship between dietary diversity and the risk of dementia. First, DDS serves as a valuable proxy indicator of nutrient adequacy in the older population [31]. Inadequate dietary diversity may indicate malnutrition, characterized by poor nutrient intake, less energy reservoir, and some adverse effects [32], while malnutrition was proven to predict a decline in cognitive function [33,34]. Second, the action of many nutrients is dependent on the presence of other nutrients from various food groups. Implementing a diversified diet helps to increase the variety of nutrients consumed, including various vitamins and antioxidants, which can reduce oxidative stress levels in the brain and decrease neuroinflammation, thus protecting brain cells from damage [35]. Third, the various components of a diet may enhance cognitive performance by altering synaptic plasticity and/or synaptic membrane fluidity [36]. Finally, dietary diversity is conducive to maintaining a healthy gastrointestinal microbiome [37], which is reported to impact brain function and mental health via the gut-brain axis [38–40]. Given that dementia remains an incurable disease, enhancing dietary diversity may have important public health implications for preventing dementia. It is recommended to include a variety of nutrient-dense foods not only across different food groups but also within them, to promote nutrient adequacy, high dietary quality, and maintain optimal health [41].

In addition, we observed a significant association between the high diversity score of meat and protein alternatives and the low risk of dementia, indicating that the more diverse the intake of this group of foods, the lower the risk of incident dementia. The calculated score for meat and protein alternatives includes red meat, fish and seafood, poultry, organ meat, eggs, legumes, and nuts. These foods have been demonstrated in previous research to contribute to protecting cognitive function and

Characteristics	Cases/total	Hazard ratio (95% CI)	*P* value
Age			
<65	339/87,969	0.89 (0.80-0.98)	1.50×10^{-2}
≥65	386/16,603	0.95 (0.87-1.03)	2.22×10^{-1}
Gender			
Male	399/49,163	0.89 (0.82-0.98)	1.40×10^{-2}
Female	326/55,409	0.95 (0.86-1.05)	3.06×10^{-1}
BMI, kg/m2			
<25	253/39,423	0.94 (0.84-1.05)	2.47×10^{-1}
≥25	472/65,149	0.90 (0.83-0.97)	9.95×10^{-3}
Smoke			
Never	414/70,541	0.86 (0.80-0.95)	2.06×10^{-3}
Ever	311/34,031	0.97 (0.87-1.07)	4.89×10^{-1}
Alcohol			
Never	53/3,360	0.81 (0.61-1.09)	1.65×10^{-1}
Ever	672/101,212	0.93 (0.87-0.99)	3.80×10^{-2}
Physical activity			
Low	352/52,324	0.94 (0.86-1.03)	2.07×10^{-1}
High	373/52,248	0.90 (0.82-0.99)	2.90×10^{-2}
TDI			
Low	344/52,291	0.91 (0.83-1.01)	6.74×10^{-2}
High	381/52,281	0.92 (0.84-1.01)	7.97×10^{-2}
Annual family income			
Low	128/9,512	0.94 (0.87-1.01)	9.60×10^{-2}
High	597/95,060	0.86 (0.77-0.99)	4.10×10^{-2}
PRS excluding APOE4			
Low	307/52,286	0.96 (0.87-1.06)	4.15×10^{-1}
High	418/52,286	0.87 (0.80-0.95)	1.67×10^{-3}
PRS including APOE4			
Low	210/52,286	1.13 (1.00-1.27)	4.96×10^{-2}
High	515/52,286	0.83 (0.76-0.90)	2.62×10^{-6}

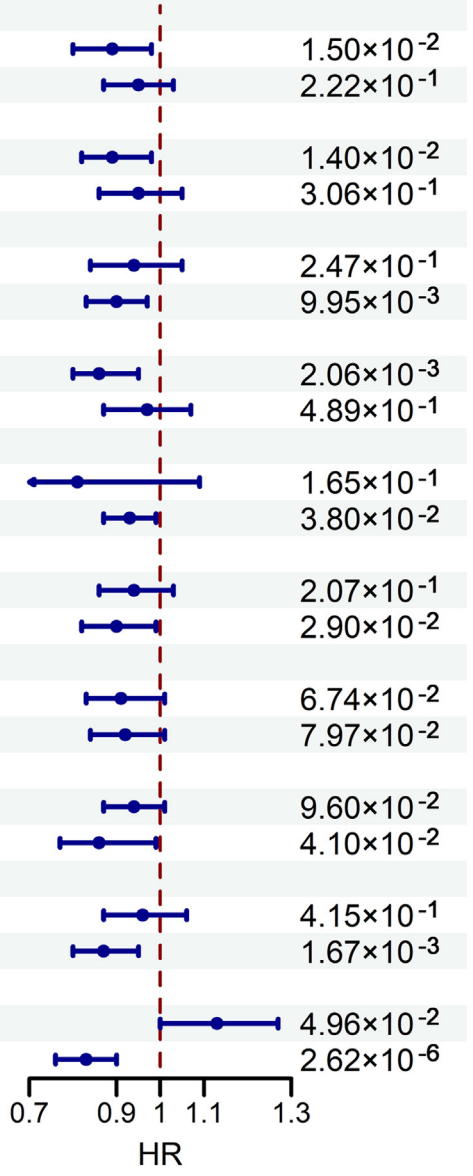

Fig. 4. Stratified analysis of association between diversity score of meat and protein alternatives and incident dementia
The exposure unit for the diversity scores of the five food groups is one food subgroup. BMI, body mass index; TDI, Townsend Deprivation Index; PRS, polygenic risk scores.

reducing the risk of dementia: the consumption of meat is relevant to maintain the integrity of neuronal membranes and brain cells [42]; Fish and seafood contain dodecahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which have protective effects against neurodegeneration [43]; eggs provide bioactive compounds, such as lutein, choline, zeaxanthin, and high-value proteins may have beneficial effects on inflammation [44]; legumes contain phytoestrogen and isoflavones (such as daidzein and genistein), which exert antioxidant, anti-inflammatory, and mitochondrial apoptosis inhibitory effects [45]; and nuts contribute bioactive compounds that support the function of brain neurons [46].

In our study, the association between DDS and dementia showed no difference between males and females but was significant in individuals under 65 years old. A plausible explanation is that the preventive effects of a healthy diet on dementia may require a prolonged process to be observed [6]. Additionally, the intake and absorption functions, compromised due to advanced age, impact the intake of various nutritional substances in older individuals [47]. This suggests the critical importance of cultivating healthy dietary habits in early-midlife for dementia prevention.

An intriguing finding was that in individuals with higher PRS, the association of higher DDS and the diversity scores of meat and protein substitutes with lower risk of dementia is significant. These protective effects were particularly pronounced in the high-risk group for PRS that includes APOE4, indicating higher genetic susceptibility, especially carrying the APOE4 allele, influenced the association between DDS and dementia risk. This finding reinforced evidence from some previous studies [48–50]. It has been suggested that APOE4 carriers may have compromised brain reserves or poor brain protection and repair mechanisms, making them more vulnerable to beneficial factors, such as the intake of long-chain n-3 fatty acids [51]. Additionally, the APOE gene has been shown to be related to the composition of microbiota in human dementia models [5]. A diverse diet may protect cognitive func-

tion and reduce the risk of dementia by influencing the synthesis and secretion of brain-derived neurotrophic factors and gut microbial-derived metabolites [52–54]. Therefore, individuals carrying the APOE4 allele may gain greater benefits from their diet through the gut microbiome [55]. Additionally, our results found that in the low-risk group for PRS including the APOE4, higher diversity scores of meat and protein substitutes were associated with an increased risk of dementia. This may be attributed to iron accumulation from red meat consumption and high sodium content in processed meats, both of which can impair cognition and increase the risk of dementia [56]. Further research is needed to validate this result.

Strengths of this study include a prospective design, a large sample size, a long follow-up time, and an exploration of DDS and genetic susceptibility. This study also has several limitations. We calculated DDS based on whether individuals consumed those 18 food subgroups, regardless of their quantitative dietary intake. This may not reflect the real dietary diversity status and changes in total calorie intake. In addition, despite adjusting for as many potential confounders as possible, such as personal characteristics, lifestyle, socio-demographics, and genetic susceptibility, residual and unmeasured confounding could not be completely ruled out in this observational study.

5. Conclusions

In conclusion, we found that a higher DDS and diversity score for meat and protein alternatives were associated with a reduced risk of incident dementia. A notable association between DDS and dementia manifests prominently in individuals exhibiting heightened genetic predisposition. Thus, more efforts are needed to promote widespread availability to a healthy and varied diet to prevent dementia, especially in vulnerable populations.

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Data availability

The data that support the findings of this study are available from the UK Biobank, but restrictions apply to the availability of these data, which were used under license for the current study and so are not publicly available. The UK Biobank resources are, however, available and can be accessed through applications on their website (https://www.ukbiobank.ac.uk/). Analytic codes are available upon reasonable request.

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.

CRediT authorship contribution statement

Boyue Zhao: Writing – original draft, Methodology, Formal analysis, Conceptualization. **Bolun Cheng:** Writing – original draft, Visualization, Formal analysis. **Xinyang Li:** Visualization, Formal analysis. **Jinyu Xia:** Writing – original draft, Formal analysis. **Yifan Gou:** Methodology. **Meijuan Kang:** Methodology, Formal analysis. **Jingni Hui:** Writing – original draft, Conceptualization. **Ye Liu:** Supervision, Data curation. **Ruixue Zhou:** Methodology, Conceptualization. **Chen Liu:** Methodology. **Bingyi Wang:** Supervision, Data curation. **Panxing Shi:** Supervision, Data curation. **Feng Zhang:** Writing – review & editing, Methodology, Funding acquisition.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100078.

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