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RESEARCH PAPER

Plant-based dietary patterns and the risk of dementia: a population-based study

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Abstract

Background: Plant-based dietary patterns are increasingly popular in western countries and are supported by many governments and health organisations for their potential beneficial role in the prevention of chronic diseases. Yet, the potential role of plant-based dietary patterns in the development of dementia remains unclear.
Objective: To evaluate the association between plant-based dietary patterns and the risk of dementia.
Methods: Dietary intake was measured at baseline in 9,543 dementia-free participants (mean age 64 years, birth years 1897–1960, 58% women) of the prospective population-based Rotterdam Study, using food frequency questionnaires. Based on these questionnaires, we calculated an overall plant-based dietary index (PDI), healthy PDI (hPDI) and unhealthy PDI (uPDI), with higher scores reflecting higher consumption of (any, healthy and unhealthy, respectively) plant-based foods and lower consumption of animal-based foods. We analysed the association of the PDIs with incident dementia using Cox proportional hazard models.
Results: During a mean follow-up of 14.5 years, 1,472 participants developed dementia. Overall, the PDIs were not associated with the risk of dementia (hazard ratio [95% confidence interval] per 10-point increase: 0.99 [0.91–1.08] for PDI, 0.93 [0.86–1.01] for hPDI, 1.02 [0.94–1.10] for uPDI). However, among men and *APOE ε4* carriers, a higher hPDI was linearly associated with a lower risk of dementia (0.86 [0.75–0.99] and 0.83 [0.73–0.95], respectively), while this association was U-shaped among *APOE ε4* non-carriers (*P* value for non-linearity = 0.01).
Conclusions: We found no strong evidence for an overall association between plant-based eating and the risk of dementia. Our findings in stratified analyses warranted further investigation.

Keywords: plant-based diet, nutrition, dementia, Alzheimer's disease, epidemiology, older people

Key Points

- Plant-based dietary patterns are increasingly popular in western countries.
- The potential role of plant-based dietary patterns in the development of dementia remains unclear.
- In this study, we found no strong evidence for an association between plant-based eating and the risk of dementia.

Introduction

Plant-based dietary patterns are increasingly popular in western countries and are supported by many governments and health organisations for their potential beneficial role in the prevention of chronic diseases [1, 2]. Indeed, diets with relatively more plant- and fewer animal-based foods have been linked to a lower risk of type 2 diabetes [3, 4] and cardiovascular diseases [5, 6], which are in turn important risk factors for dementia [7–9]. Yet, the potential role of plant-based dietary patterns in the development of dementia remains unclear.

Healthy plant-based foods like vegetables, whole grains, fruits, nuts and legumes are sources of various health-promoting nutrients that may affect the brain through their anti-inflammatory and anti-oxidative capacities [10],

along with their protective properties against metabolic abnormalities [4, 11, 12]. Moreover, although animal-based foods contain essential nutrients that may support brain health [13, 14], various animal-based foods, including meat and full-fat dairy, are also sources of saturated fatty acids, of which excessive consumption has been linked to poor brain health [15, 16].

Against this background, the Mediterranean diet has extensively been studied in relation to the risk of dementia, with most studies finding an inverse link [17, 18]. The Mediterranean diet mainly emphasises plant-based foods, but in contrast to plant-based dietary patterns, moderate consumption of fish, poultry and dairy products is also incorporated. Given these distinct characteristics, one prospective cohort study has investigated the association of plant-based eating, in the form of a vegetarian diet (i.e. consuming no meat and fish), with the risk of dementia [19]. In this Taiwanese population, vegetarians were at a lower risk of dementia compared to omnivores. Moreover, two observational studies found that diets with relatively more healthy plant- and fewer animal-based foods were associated with a slower decline in cognitive functioning [20, 21]. Yet, to date, no published studies have investigated the relative contribution of plant- and animal-based foods to the diet in relation to the risk of dementia.

We therefore aimed to evaluate the association between the degree of adhering to an overall, healthy and unhealthy plant-based dietary pattern and the risk of dementia.

Methods

Study population

This study was embedded within the Rotterdam Study, a prospective population-based cohort study in the Netherlands, of which details have been described previously [22]. Briefly, the original study (RS-I) started in 1990 with 7,983 participants aged ≥55 years (birth years: 1897–1938), residing in the district Ommoord, a suburb of Rotterdam. The study was extended in 2000 (RS-II), with 3,011 participants who moved into the study area or reached the age of 55 years (birth years: 1906–1944). In 2006, the study was further enlarged (RS-III), with 3,932 participants aged ≥45 years (birth years: 1918–1960). Participants are invited for follow-up examination rounds every 3 to 6 years.

Participants from all three sub-cohorts contributed to the current analysis. However, out of the 14,926 participants, 5,189 lacked data on dietary habits at study entry due to the implementation of dietary assessment after a pilot round ($n = 271$), prevalent dementia in combination with the lack of caregiver assistance to recall dietary habits ($n = 393$) or undocumented reasons ($n = 4{,}525$). We further excluded participants who had unreliable dietary data (i.e. energy intake of <500 or >5,000 kcal/day) ($n = 38$), had dementia at baseline ($n = 38$), were not sufficiently screened for dementia ($n = 58$) or did not sign informed consent for follow-up monitoring ($n = 60$), leaving 9,543 participants eligible for the current study.

Plant-based dietary index

Dietary intake was assessed at baseline using validated food frequency questionnaires (FFQs). The approach used to quantify dietary intake for sub-cohort RS-I and RS-II was slightly different from sub-cohort RS-III. For sub-cohorts RS-I and RS-II, participants first completed a checklist in which they indicated whether they consumed any of the 170 pre-defined food items at least twice a month within the past year. Next, participants underwent a structured interview conducted by trained dieticians to specify food items and identified in which frequencies and amounts the food items were consumed. For sub-cohort RS-III, responses to a self-administered FFQ including questions on the consumption of 389 food items over the past month was used to assess dietary intake. Both FFQs have been validated against other dietary assessment methods, which showed that based on these FFQs, participants can be ranked adequately according to their food and nutrient intake [23–25].

From the obtained dietary data, we derived an overall plant-based dietary index (PDI), a healthy PDI (hPDI) and an unhealthy PDI (uPDI). These indices are based on previously created indices [3] and slightly modified to reflect Dutch dietary habits [4]. Food items were divided into 22 food categories, among which 7 were healthy plant based (fruits, vegetables, whole grains, nuts, legumes, tea and coffee, vegetable oils), 4 unhealthy plant based (refined grains, potatoes, sugary beverages, sweets) and 11 animal based (low-fat milk, low-fat yogurt, full-fat milk, full-fat yogurt, cheese, fish, eggs, animal fat, unprocessed lean meat, processed and red meat, dessert and sugary dairy). Food items that were not clearly animal or plant based were categorised in a miscellaneous category, which was similar to alcohol consumption not included in the PDIs, but included in the statistical models to account for potential confounding. Participants' intake for each food category were scored 0–4, based on cohort-specific distribution in quintiles, with 0 representing the lowest and 4 representing the highest consumption levels of the respective food group. The PDI was created by summing scores of both healthy and unhealthy plant-based food groups and inverse scores of animal-based food groups (Supplementary Table 1, available in *Age and Ageing* online). The hPDI was calculated by summing scores of healthy plant-based food groups and inverse scores of unhealthy plant-based and animal-based food groups. The uPDI was calculated by summing scores of unhealthy plant-based food groups and inverse scores of healthy plant-based and animal-based food groups. This resulted in a final score theoretically ranging from 0 to 88, with higher scores reflecting better adherence to the respective PDI.

Dementia

Participants were screened for dementia at baseline and every 3 to 6 years during follow-up examinations using the Mini-Mental State Examination (MMSE) and the Geriatric Mental Schedule (GMS) organic level. Those with an MMSE <26 or a GMS >0 were further examined using the Cambridge Examination for Mental Disorders in the Elderly diagnostic interview. Participants were also monitored for dementia on a continuous basis through an electronic link between the study database and medical records from general practitioners and the regional institute of outpatients mental health care. The final diagnosis was established by a consensus panel led by a neurologist, according to standard criteria for dementia (DSM-III-R), and for sub-diagnosis of Alzheimer's disease (NINCDS-ADRDA). Follow-up was completed until 1 January 2020 for 96% of the potential person-years.

Covariates

A detailed description is available in Supplementary Methods 1, available in *Age and Ageing* online.

Statistical analysis

We investigated the association of the PDI, hPDI and uPDI per 10-point increase with incident dementia, using Cox proportional hazard models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). We confirmed that the proportional hazard assumption was not violated by visual inspection of the Schoenfeld residuals. To test for potential non-linear associations, we included splines with 2 knots to the indices and tested whether this improved the fit of the model using ANOVA and studied the association per quintile of the dietary indices. We used follow-up time in years as time scale and repeated analyses using age as time scale to verify that this did not affect our results. In order to obtain cause-specific HRs, participants were censored when they were diagnosed with dementia, died, were lost to follow-up or at the end of follow-up, whichever came first. All analyses were adjusted for sub-cohort, age, sex and energy intake (model I) and further for educational attainment, alcohol intake, the miscellaneous food category, smoking status, physical activity and *APOE* ε4 status (model II, main model). To reduce the risk of residual confounding, we further adjusted in an additional model for cardiometabolic risk factors that could act as a confounder or mediator, namely, body mass index, diabetes, total cholesterol, high-density lipoprotein cholesterol, systolic and diastolic blood pressure, and use of blood pressure- and lipid-lowering medication (model III). We repeated the analyses considering Alzheimer's disease as only outcome. To explore effect modification by sex, age and *APOE* ε4 status, we included an interaction term between each of these covariates and the PDIs, and we performed stratified analyses (i.e. women versus men, <70 versus ≥70 years, and *APOE* ε4 carrier versus non-carrier). Moreover, we repeated the analyses after excluding participants with an MMSE <26 to address potential recall bias due to cognitive impairment and after excluding the first 5 years of follow-up to address potential reverse causality. In addition, we repeated the analyses considering the healthy plant-based, unhealthy plant-based and animal-based food category scores individually as exposure to explore if one of those individual categories explains potential associations. To provide insight into the role of competing risk by mortality, we visually assessed Kaplan–Meier survival curves with age as underlying timescale, per age, sex and sub-cohort-specific quintile of the PDIs.

Missing data on covariates (18.6% for physical activity, 5.3% for *APOE* ε4 status and <5% for all other covariates) were imputed using five-fold multiple imputation. Analyses were performed on the five datasets and pooled HRs with their corresponding 95% CIs are provided. Statistical analyses were conducted using the 'survival', 'splines' and 'mice' packages from R Statistical Software version 4.0.3.

Results

Baseline characteristics of the study population are provided in Table 1. Participants were on average 64.1 years old (standard deviation: 8.6) and 58% of the participants were women. Participants with a higher PDI were less likely to be women, had a higher daily energy and lower alcohol intake (Supplementary Table 2, available in *Age and Ageing* online), while participants with a higher hPDI and uPDI were more likely to be women and had a lower energy intake (Supplementary Tables 3 and 4, available in *Age and Ageing* online). The uPDI was higher among lower educated and older participants. As expected, participants with a higher PDI consumed more healthy and unhealthy plant-based foods and less animal-based foods (Supplementary Table 5, available in *Age and Ageing* online). Moreover, participants with missing data on dietary intake for reasons unrelated to dementia were somewhat older and lower educated compared to those with data on dietary intake (Supplementary Table 6, available in *Age and Ageing* online).

The PDI was positively correlated with the hPDI (r = 0.56) and uPDI (r = 0.25), while no correlation between the hPDI and uPDI was observed (r = 0.06).

During a mean follow-up of 14.5 years (range: 0.0–29.7), 1,472 participants developed dementia (incidence rate 10.6 per 1,000 person-years). Overall, the PDI, hPDI and uPDI were not significantly associated with the risk of dementia (HR [95% CI] per 10-point increase: 0.99 [0.91–1.08] for PDI, 0.93 [0.86–1.01] for hPDI and 1.02 [0.94–1.10] for uPDI; Table 2). Analysing the PDIs in quintiles showed that the association for the hPDI was suggestively U-shaped, but this was not confirmed by non-linear analysis (P = 0.08; Supplementary Figure 1, available in *Age and Ageing* online). No evidence for a non-linear association was observed for the PDI and uPDI (P = 0.90 and 0.37, respectively).

Risk estimates were similar when considering Alzheimer's disease as only outcome (Figure 1). In analyses stratified

Table 1. Baseline characteristics of the study population

Characteristics	Study population (*N* = 9,543)
Women	5,530 (58)
Age, years	64.1 (8.6)
Education attainment	
Primary	1,463 (15)
Lower	3,900 (41)
Intermediate	2,662 (28)
Higher	1,463 (15)
Energy intake, kcal/day	2,099 (595)
Alcohol intake, g/day	11.9 (16.2)
Miscellaneous food intake, g/day	59.2 (64.9)
Smoking status	
Never	2,231 (23)
Former	4,152 (44)
Current	3,114 (33)
Physical activity, MET-hours/week	75.9 (49.4)
APOE ε4 status	
No allele	6,482 (72)
1 allele	2,353 (26)
2 alleles	205 (2)
Body mass index, kg/m^2	26.8 (4.0)
Diabetes	728 (8)
Systolic blood pressure, mmHg	137.7 (21.4)
Diastolic blood pressure, mmHg	76.9 (11.7)
Use of blood pressure-lowering medication	2,754 (29)
Total cholesterol, mmol/L	6.3 (1.2)
High-density lipoprotein cholesterol, mmol/L	1.4 (0.4)
Use of lipid-lowering medication	911 (10)
Overall plant-based dietary index (PDI)	44.7 (6.5)
Healthy plant-based dietary index (hPDI)	45.1 (7.0)
Unhealthy plant-based dietary index (uPDI)	46.9 (7.4)

Data are shown for non-imputed data and are presented as mean (standard deviation) for continuous variables and number (percentages) for categorical variables. *Abbreviations*: MET, metabolic equivalent of task; N, number of participants.

by sex, age and *APOE ε4* carriership, the hPDI was linearly associated with a lower risk of dementia among men (HR [95% CI]: 0.86 [0.75–0.99]) and *APOE ε4* carriers (HR [95% CI]: 0.83 [0.73–0.95]). Among *APOE ε4* non-carriers, a U-shaped association between the hPDI and the risk of dementia was observed (*P* value for non-linearity = 0.01; Supplementary Figure 1, available in *Age and Ageing* online). Nevertheless, none of the interactions investigated were significant (*P* values for interaction > 0.05).

Risk estimates for the PDI, hPDI and uPDI remained similar after excluding participants with an MMSE score <26, and after excluding the first 5 years of follow-up (data not shown). Furthermore, the healthy plant-based, unhealthy plant-based and animal-based food categories were individually not associated with the risk of dementia (Supplementary Table 7, available in *Age and Ageing* online). Finally, individuals in the lowest quantile of the PDI and hPDI had a somewhat lower survival than those in the highest quintile, while participants in the lowest quantile of the uPDI had a higher survival compared to those in the highest quintile (Supplementary Figure 2, available in *Age and Ageing* online).

Discussion

In this population-based study, we found no association between the PDI—regardless of whether an overall, healthy or unhealthy PDI was defined—and the risk of dementia. Our findings in stratified analyses, including an inverse association between the hPDI and the risk of dementia among men and *APOE ε4* carriers and the suggestion of a non-linear association among *APOE ε4* non-carriers, warrant further investigation in future studies.

To our knowledge, we are the first to report on the relative contribution of plant- and animal based foods to the diet in relation to the risk of dementia. Previous studies, however, investigated the risk of dementia by various dietary patterns that are dominated by plant-based foods, such as the Mediterranean diet [17, 18, 26] and Mediterranean-Dietary Approaches to Stop Hypertension Intervention for Neurodegenerative Delay (MIND) diet [27–29]. While most studies, including one in the Rotterdam Study [27], have reported a positive association [17, 18, 26, 28, 29], others reported no link [17, 18]. Moreover, a study among 5,710 Taiwanese participants found that vegetarians were at a lower risk of dementia compared to omnivores [19]. These findings support a role of (healthy) plant-based eating in the development of dementia, which contrasts the overall null findings observed in our study. Our findings also contradict a previous study among Chinese participants that linked a hPDI to a lower odds of mild cognitive impairment (defined as an MMSE <24) [20]. Another study found a link between the hPDI and a slower rate of cognitive decline among African American but not among white participants from the United States [21]. Notably, the composition of the diets substantially differed between African Americans and white participants, despite similar hPDI scores. For instance, compared to white participants, African Americans consumed more whole grains and sugar-sweetened beverages, and fewer animal fat and dairy products. This may suggest that differences in diet composition explain contrasting findings across studies, but genetic variability and differences in lifestyle factors may also play a role.

While we did not find statistically significant evidence to support an association of consuming relatively more plant- and fewer animal-based foods with the risk of dementia, our HR of 0.93 (95% CI: 0.86–1.01) for the hPDI cannot rule out a subtle beneficial effect of healthy plant-based eating on the brain. A subtle effect seems especially feasible as we found that individuals with a lower hPDI had a somewhat lower survival rate, suggesting that mortality as competing event may have diluted the association towards the null.

Several mechanisms have been proposed that may explain a potential beneficial effect of healthy plant-based eating on dementia. Healthy plant-based diets consist of foods rich in various health-promoting nutrients, such as fibres, antioxidants and unsaturated fatty acids [1]. These nutrients may affect the brain through their anti-inflammatory and antioxidative capacities [10], and favourable effects on metabolic functions [3, 4, 12].

Table 2. Plant-based dietary indices and the risk of dementia

		Hazard ratio (95% confidence interval)		
	n/*N*	Model I	Model II	Model III
Overall plant-based dietary index				
Per 10-point increase	1,472/9,543	1.04 (0.96–1.13)	0.99 (0.91–1.08)	0.99 (0.91–1.08)
Per quintile:				
Quintile $1_{(22–39)}$	283/2,084	1.00	1.00	1.00
Quintile $2_{(39–43)}$	295/2,093	0.95 (0.80–1.11)	0.99 (0.84–1.17)	1.01 (0.85–1.19)
Quintile $3_{(43–46)}$	272/1,711	1.03 (0.87–1.22)	1.07 (0.90–1.27)	1.09 (0.92–1.30)
Quintile $4_{(46–50)}$	314/1,902	1.04 (0.88–1.22)	0.99 (0.84–1.17)	1.01 (0.85–1.20)
Quintile $5_{(50–73)}$	308/1,753	1.12 (0.95–1.33)	1.03 (0.86–1.22)	1.04 (0.87–1.24)
Healthy plant-based dietary index				
Per 10-point increase	1,472/9,543	0.94 (0.87–1.02)	0.93 (0.86–1.01)	0.93 (0.75–1.01)
Per quintile:				
Quintile $1_{(16–39)}$	280/2,059	1.00	1.00	1.00
Quintile $2_{(39–43)}$	293/1,866	0.91 (0.77–1.08)	0.94 (0.80–1.12)	0.94 (0.80–1.12)
Quintile $3_{(43–47)}$	326/2,117	0.85 (0.73–1.00)	0.84 (0.71–0.99)	0.84 (0.71–1.00)
Quintile $4_{(47–51)}$	274/1,755	0.79 (0.66–0.93)	0.78 (0.65–0.93)	0.77 (0.65–0.92)
Quintile $5_{(51–73)}$	299/1,746	0.90 (0.76–1.07)	0.90 (0.75–1.07)	0.89 (0.74–1.06)
Unhealthy plant-based dietary index				
Per 10-point increase	1,472/9,543	1.03 (0.95–1.11)	1.02 (0.94–1.10)	1.02 (0.94–1.10)
Per quintile:				
Quintile $1_{(19–41)}$	266/2,248	1.00	1.00	1.00
Quintile $2_{(41–45)}$	276/1,868	1.09 (0.92–1.30)	1.13 (0.95–1.35)	1.15 (0.96–1.37)
Quintile $3_{(45–49)}$	321/1,966	1.08 (0.92–1.28)	1.12 (0.94–1.33)	1.13 (0.95–1.34)
Quintile $4_{(49–53)}$	304/1,656	1.23 (1.03–1.45)	1.23 (1.03–1.46)	1.25 (1.05–1.50)
Quintile $5_{(53–74)}$	305/1,805	1.05 (0.88–1.25)	1.04 (0.86–1.24)	1.05 (0.87–1.26)

Model I is adjusted for sub-cohort, age, sex and energy intake. Model II is further adjusted for educational attainment, alcohol intake, miscellaneous food intake, smoking status, physical activity and *APOE* $\varepsilon 4$ status. Model III is further adjusted for body mass index, diabetes, total cholesterol, high-density lipoprotein cholesterol, use of lipid-lowering medication, systolic blood pressure, diastolic blood pressure and use of blood pressure-lowering medication. *Abbreviations*: *n*, participants with incident dementia; *N*, participants at risk of dementia at baseline.

Although not confirmed based on non-linear analysis, we found that the association between healthy plant-based eating and the risk of dementia is somewhat U-shaped. This may suggest that an excessive reduction of animal-based products from the diet may no longer be beneficial, possibly as a result of deficiencies [30]. Animal-based foods are major sources of certain macro- and micronutrients, including vitamin B_{12}, iron, long-chain $n-3$ fatty acids and proteins, which are crucial for brain health [13, 14]. Adequate consumption of these nutrients is particularly important for older adults, as requirements of nutrients increase with age, while energy needs decrease [31, 32]. Given that women in the present study generally had a higher hPDI, deficiencies may also explain our findings of a linear inverse association for the hPDI among men, which tended to be U-shaped among women.

That we found a linear inverse association among carriers of the *APOE* $\varepsilon 4$ allele, but not among *APOE* $\varepsilon 4$ non-carriers, suggests that healthy plant-based eating may counteract with pathological changes associated with the *APOE* gene. The *APOE* gene is a key regulator of lipid metabolism and the *APOE* $\varepsilon 4$ allele has been linked to an unfavourable lipid profile [33], which has subsequently been linked to an increased risk of dementia [34]. *APOE* $\varepsilon 4$ carriers may benefit more from consuming predominantly healthy plant-based products that contain limited amounts of saturated fatty acids. Moreover, the *APOE* $\varepsilon 4$ allele is mainly thought to affect the risk of dementia through impaired amyloid-β clearance, but also via susceptibility to neuro-inflammation, mitochondrial dysfunction and blood–brain barrier permeability [32]. Anti-inflammatory and anti-oxidative capacities of a healthy plant-based dietary pattern may diminish these effects [10].

Strengths of this study include the population-based setting, large sample size and long follow-up for incident dementia. Moreover, the use of indices to determine the relative contribution of plant- and animal-based foods to the diet allowed us to study potential health effects on the brain beyond adopting a priori-defined vegetarian diets that are based on exclusion of specific animal-based food groups from the diet.

Certain limitations also need to be considered. First, none of the participants in this study were vegan and the majority of the participants in the highest PDI quintile consumed animal-based foods on a daily basis. This makes it impossible to extrapolate our findings to higher levels of plant-based eating. Second, dietary habits may change over time, but our data were too limited to take this into account. Long-term exposure could thus not be assured, which may have biased our findings. Third, information on supplementation use of certain vitamins and minerals that are mainly present in animal-based products was inadequate and could thus not

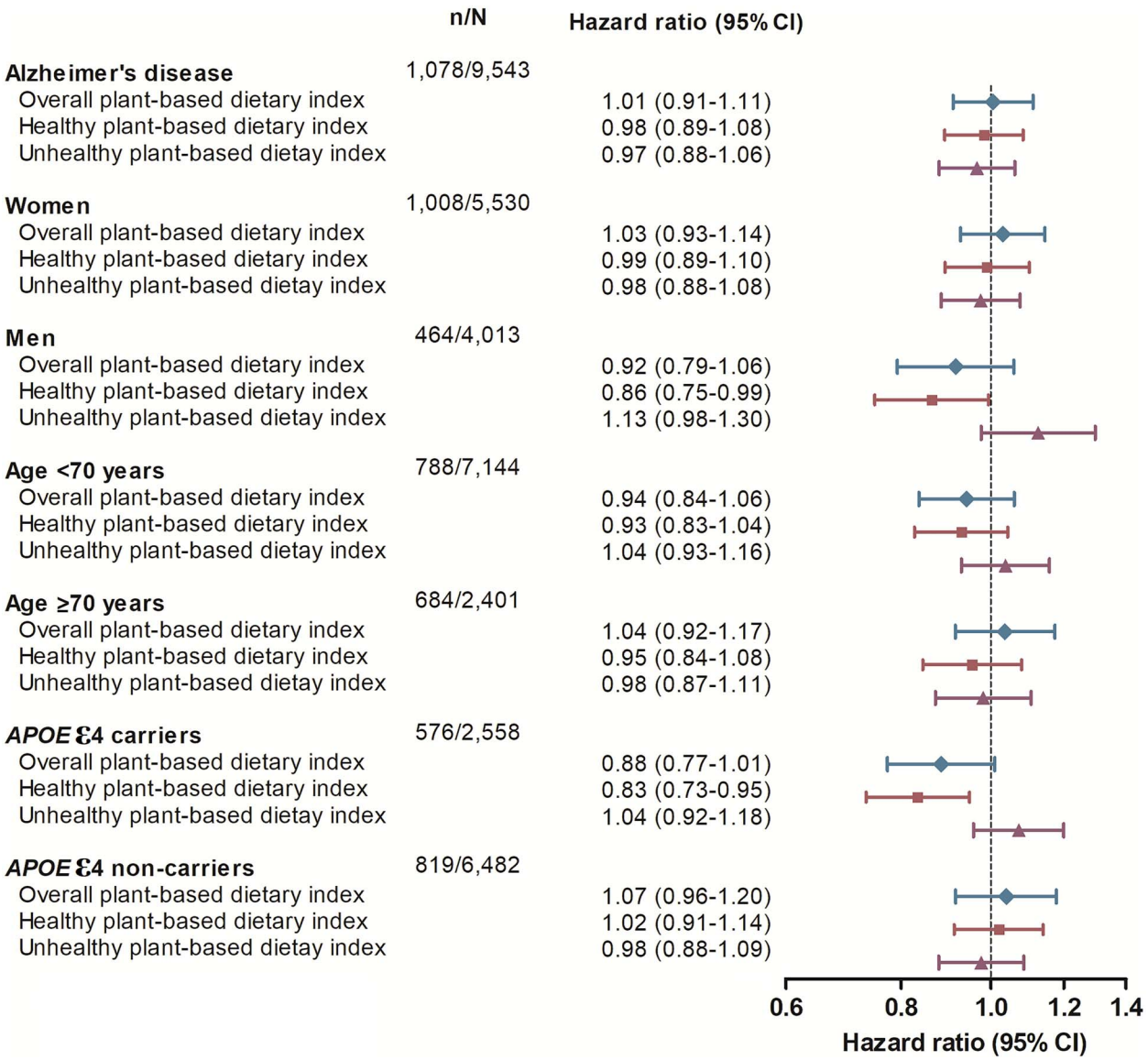

Figure 1. Subgroup analyses for the association of the plant-based dietary indices with the risk of dementia. Hazard ratios represent the association between the plant-based dietary indices per 10-point increase and the risk of dementia. Models are adjusted for sub-cohort, age, sex, energy intake, educational attainment, alcohol intake, miscellaneous food intake, smoking status, physical activity and *APOE* ε4 status (corresponding to model II in Table 2). None of the interaction terms reached statistically significance ($P < 0.05$). *Abbreviations*: CI, confidence interval; *n*, participants with incident dementia; *N*, participants at risk of dementia at baseline.

be taken into account. Last, participants excluded from the study population due to missing data on dietary intake were somewhat older and lower educated. With both factors being related to poor diet quality and a higher risk of dementia [35], this could have caused an underestimation of the true association on population level.

In conclusion, we found no strong evidence for an association between plant-based eating and the risk of dementia, regardless of whether the diet was dominated by healthy or unhealthy plant-based foods. Further studies that include participants with a greater variety in the proportion of plant- and animal-based foods in their diets are warranted to further evaluate the association of plant-based diets with the risk of dementia, and to disentangle the role of sex and the *APOE* gene in this association.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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Declaration of Conflicts of Interest: None.

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Data Availability: Because of data protection standards of the informed consent procedure of the Rotterdam Study, data cannot be made freely available in publicly available repositories.

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