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Diet Inflammatory Index and Dementia Incidence: A Population-Based Study

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Abstract

Background and objectives: Aging is characterized by a functional shift of the immune system towards a proinflammatory phenotype. This derangement has been associated with cognitive decline and has been implicated in the pathogenesis of dementia. Diet can modulate systemic inflammation; thus, it may be a valuable tool to counteract the associated risks for cognitive impairment and dementia. The present study aimed to explore the associations between the inflammatory potential of diet, assessed using an easily applicable, population-based, biomarker-validated diet inflammatory index (DII), and the risk for dementia in community-dwelling older adults.

Methods: Individuals from the Hellenic Longitudinal Investigation of Aging and Diet (HELIAD) were included in the present cohort study. Participants were recruited through random population sampling, and were followed for a mean of 3.05 (SD=0.85) years. Dementia diagnosis was based on standard clinical criteria. Those with baseline dementia and/or missing cognitive follow-up data were excluded from the analyses. The inflammatory potential of diet was assessed through a DII score which considers literature-derived associations of 45 food parameters with levels of pro- and anti-inflammatory cytokines in the blood; higher values indicated a more pro-inflammatory diet. Consumption frequencies were derived from a detailed food frequency questionnaire, and were standardized to representative dietary intake normative data from 11 different countries. Analysis of dementia incidence as a function of baseline DII scores was performed by Cox proportional hazards models.

Results: Analyses included 1059 individuals (mean age=73.1 years; 40.3% males; mean education=8.2 years), 62 of whom developed incident dementia. Each additional unit of DII was associated with a 21% increase in the risk for dementia incidence [HR=1.21 (1.03 – 1.42); p=0.023]. Compared to participants in the lowest DII tertile, participants in the highest one (maximal pro-inflammatory diet potential) were 3 [(1.2 – 7.3); p=0.014] times more likely to develop incident dementia. The test for trend was also significant, indicating a potential dose-response relationship (p=0.014).

Conclusions: In the present study, higher DII scores (indicating greater pro-inflammatory diet potential) were associated with an increased risk for incident dementia. These findings might avail the development of primary dementia preventive strategies through tailored and precise dietary interventions.

1. Introduction

Population aging is poised to become one of the most significant social transformations of the twenty-first century, as indicated by the substantial increases in the proportion of older adults across most populations globally. The worldwide population aged ≥ 65 years numbered 382 million in 1980, 962 million in 2017 and is estimated to reach nearly 2.1 billion by 2050.[1] The disability burden of age-related cognitive decline and dementia is also expected to increase as a consequence of this drastic demographic transition. This is an alarming projection, considering that in the last global burden of disease study in 2010, Alzheimer's disease (AD) and other dementias were already accounting for 0.46 of total global disability-adjusted life-years.[2]

Aging is accompanied by physiological alterations in both the innate and the adaptive arms of the immune system, a process called immunosenescence.[3] One of the hallmarks of immunosenescence is the institution of a chronic low-grade subclinical systemic inflammatory state, characterized by high circulating levels of pro-inflammatory cytokines and mediators, including interleukin (IL)-1, IL-6, C-reactive protein (CRP) and tumor necrosis factor (TNF).[4] This process is mainly mediated by chronically activated macrophages and monocytes, and contributes to many aging-associated phenotypes (hence the term "inflammaging").[5,6] Brain-wise, inflammaging has been associated with cognitive impairment,[7] Alzheimer's disease (AD),[8] and cerebral small vessel disease (CSVD), a component of Vascular dementia (VaD),[9] hence potentially contributing to the most common causes of dementia and cognitive decline.

There is substantial evidence to suggest that many foods, nutrients and non-nutrient food components, can modulate the inflammatory status both acutely and chronically.[10] Therefore, diet, a modifiable lifestyle factor, might have a valuable role in combating inflammaging[11] and counteracting its associated risk for dementia and late-life cognitive impairment. From this standpoint, a method to characterize and measure the inflammatory potential of individuals' diets could help develop tailored and precise dietary interventions and cognitive health maintenance strategies. Among others, Shivappa and colleagues, proposed a dietary inflammatory index (DII), consisting of 45 items including energy, nutrients, bioactive compounds, and foods/spices.[12] These components were selected from a systematic review of studies using standard dietary assessment methods, and presented significant associations with biomarkers of inflammation,[12] providing a comprehensive way to explore associations between the inflammatory potential of diet and different health-related outcomes.

However, only a limited number of studies have explored potential relationships between the DII and dementia. In two cross-sectional studies, DII scores were inversely associated with performance on cognitive tests assessing memory[13] and global cognitive function,[14] whereas, in another study, DII was not associated with global cognitive function.[15] High DII scores were also associated with increased odds for Mild cognitive impairment (MCI).[14] Another study also reported a strong inverse association between baseline DII and both global cognitive functioning as well as verbal memory evaluated 13 years later.[16] Prospective data from one study revealed that higher DII scores were associated with significantly increased risk for MCI or probable dementia and greater cognitive decline over time.[17]

The aim of the present study was to augment the relatively small body of evidence regarding the DII and its potential association with the risk for dementia, while addressing some of the limitations of the current literature. Specifically, the only prospective population-based study that has explored these relationships included only female participants, a fact that limits the generalizability of its results.[17] The present study, presents a prospective investigation of the inflammatory potential of diet, assessed through a biomarker-validated, non-population-specific DII,[12] and dementia incidence, in a non-sex-specific population of community-dwelling non-demented older adults.

2. Methods

2.1. Participants

Individuals from the Hellenic Longitudinal Investigation of Aging and Diet (HELIAD) were included in the present cohort study. HELIAD is a population-based, multidisciplinary study, designed to estimate the epidemiology of dementia and other neuropsychiatric conditions associated with aging in the Greek population. Participants are being reevaluated at intervals of approximately 3 years, repeating the baseline examination and consensus diagnosis at each follow-up; two evaluations per person have been completed so far.[18] Two centers, one located in Marousi (a suburb of Athens, Greece) and the other in the city of Larissa (part of the province of Thessaly in central Greece) took part in this study. Participants were selected through random sampling of community-dwelling individuals 65 years of age or older. More details about participant characteristics and the study design and methodology can be found in previously published work.[18–21] The participants included in the present analyses were selected

from the entire study population according to the following inclusion criteria 1) no baseline dementia, 2) available follow-up data, 3) available baseline dietary information.

2.2. Standard Protocol Approvals, Registrations, and Patients Consents

The present study protocol has been approved by the ethical standards committees of the National and Kapodistrian University of Athens and University of Thessaly, and all participants gave written informed consent prior to their participation.

2.3. Diagnostic criteria

Diagnoses were reached through diagnostic consensus meetings of all the main investigators involved in the project, both neurologists and neuropsychologists, as previously described.[21] In particular, the diagnosis of dementia, and subtypes thereof, was based on DSM-IV-TR criteria[22] and the designation of probable or possible AD was made according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer Disease and Related Disorders Association (NINCDS/ADRDA) criteria.[23] The diagnosis of vascular dementia was based on a history or clinical evidence of stroke, the presence of a clear temporal relation between stroke and the onset of dementia, and the Hachinski Ischemia Scale score.[24] Lewy body and frontotemporal dementias were diagnosed based on respective criteria.[25,26] Dementia staging was performed by the semi-structured interview of the Clinical Dementia Rating Scale (CDR), which assesses six domains of cognitive and functional performance.[27] MCI was diagnosed according to the Petersen criteria.[28]

2.4. Dietary assessment

Dietary intake was evaluated through a semi-quantitative food frequency questionnaire (FFQ) that has been validated for the Greek population.[29] Briefly, the FFQ included information on all main food groups consumed during the last month (i.e., 69 questions regarding consumption of dairy products, cereals, fruits, vegetables, meat, fish, legumes, added fats, alcoholic beverages, stimulants, sweets).[18] The questionnaire was administered by a trained dietician, and the caregiver assisted the participant during the survey when necessary. Responses were converted to daily intakes of specific food items, and were extrapolated into macro- and micro-nutrient intakes by using USDA Food composition tables and selecting items that most appropriately match foods eaten in Greece, as well as selected analyses of national recipes and local foods (see eMethods 1).

2.5. Diet Inflammatory Index

The DII was created based on evidence suggesting that dietary factors influence inflammation.[12] It consists of 45 food parameters that include various macro- and micro-nutrients, bioactive compounds (including flavonoids), and foods/spices, each associated with an inflammatory effect score. A detailed description of the DII[12] and its construct validation[30–33] have been published elsewhere.[17] Briefly, following a review of the literature, 45 foods and nutrients were found to be associated with six cardinal inflammatory biomarkers (IL-1β, IL-4, IL-6, IL-10, TNF-α, and CRP). A value was assigned to each food parameter, based on its association with these inflammatory biomarkers: +1, 0, or −1 for a positive, null, or inverse association, respectively. Scores were weighted by the characteristics of the study reporting these associations.

Weighted scores were tallied to obtain the food parameter-specific overall inflammatory effect score (see eTable 1). Dietary intake data were standardized based on mean and standard deviation values derived from a world composite database, containing data from 11 different countries, representing a wide range of diets across diverse populations globally; participant's exposure to each food parameter was then expressed as a z-score relative to the standard global mean. The standardized dietary intake estimates were then converted to centered percentiles for each DII component. Subsequently, these centered percentiles were multiplied by the corresponding component-specific inflammatory effect scores and summed to obtain the overall DII score for each individual. The DII score characterizes an individual's diet on a spectrum from maximally anti-inflammatory to maximally pro-inflammatory, with a higher score indicating a more pro-inflammatory diet, and a lower score indicating a more anti-inflammatory diet. For the purposes of the present study, 36 FFQ-derived food parameters were used for DII calculation.

2.6. Critical evaluation of reported energy intake

The validity of reported energy intake was assessed according to the methodology proposed by Goldberg and colleagues[34] and revised by Black and colleagues.[35] Briefly, for each participant Basal Metabolic Rate (BMR) was estimated using the FAO/WHO/UNU age- and sex-specific prediction equations;[36] the ratio of the FFQ-estimated Energy Intake/BMR (EI/BMR) was then calculated. This ratio was then compared to individual-specific cut-offs, calculated based on the Physical Activity Level (PAL) of each participant, to assess for energy misreporting. If the EI/BMR ratio of a participant was below or above these cut-offs, then the reported energy intake was considered non-plausible, and these participants were classified as "nonacceptable energy

reporters", whereas the rest of the participants as "acceptable energy reporters". In the present study, the PAL of each participant was derived from a validated physical activity questionnaire (Athens Physical Activity Questionnaire—APAQ).[37]

2.7. Clinical comorbidity index

The clinical comorbidity index was calculated as the sum of the following clinical conditions: hypertension, diabetes mellitus, coronary heart disease, myocardial infraction, congestive heart failure, heart arrhythmia, other heart disease, dyslipidemia, chronic obstructive pulmonary disease or other pulmonary disease, thyroid gland disease, liver disease, renal insufficiency, peptic ulcer disease, peripheral vascular disease, cancer, arthritis, traumatic brain injury, epilepsy, B-12 deficiency, Parkinson's Disease, Huntington's disease, Multiple sclerosis, Normal pressure hydrocephalus and Down Syndrome.

2.8. Other covariates

Age at study enrollment, energy intake, baseline MCI, education, and sex, were also included in the analyses as possible confounders, as these factors have been associated with the risk of developing dementia.[38–42]

2.9. Statistical analyses

Baseline participant characteristics by availability of follow-up data, availability of dietary data, dementia incidence, DII score, and validity of reported energy intake, were compared through analysis of variance for continuous variables and Pearson's $\chi 2$ for categorical variables, respectively (followed by post-hoc Bonferroni tests in the case of multiple comparisons).

DII score was initially treated as a continuous variable. In order to explore the exposure-disease relationship for non-linearity and the potential presence of threshold effects, we also ranked DII score into tertiles, each containing a third of the study sample. In all analyses, the 1st tertile (maximal anti-inflammatory diet potential) was used as the reference and was compared to the other tertiles (i.e., 2nd and 3rd), with the last one indicating maximal pro-inflammatory diet potential. Age, years of education, energy intake, the clinical comorbidity index and the duration of follow-up interval were treated as continuous variables. Sex (female, male) and MCI (no MCI at baseline, MCI at baseline) were treated as categorical variables.

Analysis of dementia incidence as a function of DII scores was performed using Cox proportional hazards models. In these models, dementia was defined as the dichotomous outcome. The time-to-event variable was defined as time from baseline evaluation to visit of dementia diagnosis; participants who did not develop dementia were censored at the time of their last evaluation. DII score (from the baseline visit) was the main predictor (in a continuous form initially and in tertile form for trend test calculation subsequently). Covariate adjustment was conducted as follows: model 1 was unadjusted, model 2 was adjusted for age, sex, years of education, energy intake, and baseline MCI, and model 3 was further adjusted for the clinical comorbidity index. The proportionality of hazards assumption was tested through the Schoenfeld residuals method. Since the variable expressing years of education violated the proportional hazards assumption, we included its interaction with the natural logarithm of the time variable in the adjusted Cox models.[43]

2.9.1. Sensitivity analysis for acceptable energy reporting

Sensitivity analyses were performed by recomputing the unadjusted and adjusted Cox regression models, while excluding participants classified as “nonacceptable energy reporters”. Specifically, since the computation of our main predictor (DII) is influenced by energy intake,[12] and energy intake was estimated using a self-report tool (i.e., prone to reporting error),[44,45] we excluded from the analyses participants with a non-plausible energy intake. This criterion was instituted to increase the validity of energy intake estimation and DII calculation.

2.9.2. Supplementary analyses

To increase our confidence that the inflammatory potential of diet was not affected by early dementia processes, we conducted a moderator analysis, by including the DII x baseline MCI interaction term in an adjusted (for age, sex, years of education, energy intake, and baseline MCI) Cox model.

Statistical analyses were conducted using STATA version 16 (College Station, TX: StataCorp LLC) and IBM SPSS version 26 (Armonk, NY: IBM Corp). Hypothesis tests were 2-sided and nominally significant α values were defined as $p \leq 0.05$.

2.10. Data availability

Anonymized data not published within this article may be shared upon request from any qualified investigator for purposes of replicating procedures and results.

3. Results

3.1. Missing data analysis

The initial HELIAD study sample consisted of 1850 non-demented participants (Figure 1). Cognitive follow-up information was available for 1072 participants (Figure 1). Compared to participants with available cognitive follow-up, participants with missing follow-up (n=778) were slightly older [mean age (SD) = 74.1 (5.5) vs 73.2 (5.0) years; p<0.001] and had higher proportions of baseline MCI [n (%) = 125 (16.1) vs. 118 (11.0); p=0.001]. There were no significant differences between participants with missing and those with available follow-up in terms of years of education, sex, or clinical comorbidity index. Most importantly, there was no difference in DII scores.

There were 1072 non-demented participants with available cognitive follow-up data; 13 of these participants were lacking baseline dietary information, so they were excluded from the analyses (Figure 1). Compared to participants with available dietary information (n=1059), participants with missing dietary information were less educated [mean years of education (SD) was 4.8 (4.1) for those with missing data vs. 8.2 (4.9) for those included; p=0.015], but did not differ with respect to any other characteristics.

3.2. Baseline clinical and sociodemographic characteristics

Among the 1059 participants who were included in the analyses, 62 participants developed incident dementia (53 of them developed AD, 5 VaD, 3 Lewy body dementia, and 1 developed dementia due to underlying psychiatric disorder) over a mean follow-up of 3.05 years (SD=0.85; range=6.08). Participants' baseline clinical and sociodemographic characteristics by dementia

incidence, as well as by the inflammatory potential of their diets (DII score tertiles) can be found in Tables 1 and 2, respectively. Individuals who developed dementia were older, less educated, had higher DII scores and were more likely to have MCI at baseline compared to those who did not, but did not differ in terms of sex, energy intake, or clinical comorbidity index. Comparison of participant characteristics by DII score tertiles revealed that participants consuming diets with greater inflammatory potential were older, less educated, and reported lower energy intakes. Moreover, compared to women, a lower proportion of men tended to consume diets with a high inflammatory potential. There was no association between DII tertile and MCI relative frequencies, or clinical comorbidity index.

3.3. DII and dementia incidence in total sample

Both unadjusted and adjusted Cox proportional hazards models revealed that greater inflammatory diet potential was associated with a significantly higher risk for incident dementia (Table 3). Specifically, in the adjusted models there was a 21% increase in the risk for dementia incidence with each additional unit of DII (Table 3; Model 2). Compared to participants in the lowest DII tertile, participants in the highest one (maximal pro-inflammatory diet potential) were 3 times more likely to develop incident dementia (Table 3; Model 2, Figure 2). Additionally, the significant test for trend was indicative of a potential dose-response relationship (Table 3; Model 2). The model further adjusted for the clinical comorbidity index revealed almost identical results (Table 3; Model 3).

Lastly, the adjusted Cox model including the DII x baseline MCI interaction, revealed a non-significant interaction term [HR=1.11 (0.88 – 1.40); p=0.363].

3.4. DII and dementia incidence in acceptable energy reporters

Nonacceptable energy reporters [n (%) = 244 (23); 105 (10) low energy reporters and 139 (13) high energy reporters] did not differ from acceptable energy reporters [n (%) = 815 (77)] in terms of age, sex, years of education, MCI relative frequencies, or DII scores. Compared to nonacceptable energy reporters, a higher proportion of men were acceptable energy reporters [n (%)= 347 (43) vs. 80 (33); p=0.006].

Both unadjusted and adjusted Cox proportional hazards models revealed that greater inflammatory diet potential was associated with a significantly higher risk for incident dementia. Specifically, in the adjusted models there was a 26% increase in the risk for dementia incidence with each additional unit of DII [HR=1.26 (1.05 – 1.52); p=0.013]. Compared to participants in the lowest DII tertile, participants in the highest one (maximal pro-inflammatory diet potential) were 3.43 times more likely to develop incident dementia [$HR_{highest\ tertile\ vs.\ lowest}$=3.43 (1.25 – 9.46); p=0.017]. In addition, the significant test for trend was indicative of a potential dose-response relationship (p_{trend}=0.017).

4. Discussion

In the present study, higher DII scores were associated with an increase in the risk for dementia incidence. The gradual risk increase for higher DII tertiles, suggests a potential dose–response relationship between the inflammatory potential of diet and the risk for incident dementia. The observed associations remained unchanged and significant even after excluding from the analyses participants who reported an energy intake that could be considered nonacceptable due to potential dietary intake misreporting.

A prospective US population-based study of 7085 women aged 65-79 years, revealed that higher DII scores were associated with higher risk of MCI or probable dementia, and with greater cognitive decline and earlier onset of cognitive impairment.[17] The present results replicate and expand these previous findings, supporting their generalizability to a non-sex-specific population of non-demented older adults; however, their validity and reproducibility need to be further explored and ascertained by future research.

Studies that have evaluated cognitive performance as a function of DII score have reported findings consistent with the present results. Specifically, higher baseline DII scores were associated with lower cognitive performance evaluated 13 years later in a French cohort of 3080 individuals with a mean age (SD) of 52.0 (4.6) years.[16] Furthermore, two cross-sectional studies, one conducted in a Korean population of 316 older adults aged 65 years or older, and the other in a representative sample (n=1723) of US older adults, aged 60-85 years, reported inverse associations between DII scores and global cognitive function, verbal memory,[14] episodic memory, working memory, and semantic memory.[13]

On the other hand, in a cross-sectional study conducted in 641 participants from Tasmania, Australia, with a mean age (SD) of 69.8 (7.4), no association was observed between DII scores and global cognitive function.[15] However, the relationship between the predictor (DII score) and the outcome (global cognitive function) was evaluated at a single timepoint, whereas the evaluation of the rate of change of the outcome as a function of the predictor over time might had yielded different findings. Mathematically, if the former analysis is based on a function estimating the change of the outcome variable with respect to the change of the predictor variable, the latter analysis is based on the time derivative of that particular function. In other

words, although one individual with a high DII score and one with a low DII score might have the same cognitive performance at a specific timepoint, the first individual might also exhibit a more rapid cognitive decline over the course of time that eventually reaches the threshold of clinical dementia.

After approximately 40 years of age, similar to other systems of the body, the immune system undergoes senescence, and certain immune system features begin to reveal effectual decline.[7] Additionally, the immune system begins to adversely affect human aging, possibly contributing to the development and clinical course of age-related conditions such as cardiovascular, metabolic and neurodegenerative diseases.[46] Immunosenescence can be considered an example of antagonistic pleiotropy, where the beneficial effects of the immune system, attributed to the neutralization of harmful agents earlier in life, become detrimental later in life, due to recent advances in life expectancy, not foreseen by evolution.[47]

A hallmark feature of immunosenescence is the increase in cellular production of proinflammatory mediators, such as CRP, TNF-α, IL-6 and IL-1β, that contribute to the institution of a chronic systemic subclinical inflammatory state, a process that is collectively referred to as inflammaging. Systemic pro-inflammatory cytokines may reach the central nervous system and lead to reduced brain-derived neurotrophic factor (BDNF) levels, glutamatergic activation (excitotoxicity), oxidative stress, and induction of apoptosis,[48] which constitute some of the mainstream neuroinflammatory and neurodegenerative pathways involved in the development of dementia.

Inflammaging, has been associated with cognitive decline and has been implicated in the pathophysiology of AD, VaD and Parkinson's disease (PD), which account for the vast majority of dementia cases worldwide. Proinflammatory mediators, especially CRP, have been associated with cognitive impairment in the elderly,[46] and increased plasma levels have also been observed in individuals with PD and cognitive impairment.[49] In addition, Inflammaging is increasingly being recognized as a risk factor for age-related CSVD, which is most prevalent among the elderly and contributes to the high global disease burden of stroke and VaD in this population.[9]

Although immunosenescence and inflammaging are aging-related processes present in the majority of individuals, genetic, environmental, lifestyle, and nutritional factors are responsible for their interindividual heterogeneity.[50] Increasing evidence has revealed that complex interactions between food components and histone modification, DNA methylation, non-coding RNA expression, and chromatin remodeling, influence the inflammaging phenotype. Therefore, dietary interventions might prove a valuable tool in decreasing the risk for dementia and late-life cognitive impairment by counteracting inflammaging and modulating its phenotypic expression, through epigenetic and other mechanisms.[11] Towards this direction, the development of a widely-applicable and reliable method to characterize individuals' diet based on their inflammatory potential is an important priority in the pursuit of healthy aging and cognitive health maintenance strategies.

Nevertheless, the present results should be interpreted in view of potential limitations. A significant number of study participants were lost to follow-up (n=689), and while they did not differ in terms of the main predictor (DII score), this might still pose a threat to the internal

validity of the study by introducing informative censoring (e.g., compared to participants who developed dementia, cognitively healthy individuals may be more likely to drop out as they do not feel the need to be further examined). Dementia diagnosis was based only on clinical criteria, so the possibility of disease misclassification bias cannot be entirely excluded. In addition, the relatively short follow-up of the present study (mean= 3.05 years; SD=0.85), raises the possibility of reverse causality. To further investigate this issue, we conducted a moderator analysis. The relationship between DII score and incident dementia was not moderated by the presence of MCI at baseline. Assuming that neuropathological alterations related to early dementia processes would have been present in individuals with MCI, these results decrease the likelihood that reverse causality accounts for our findings. Moreover, assessment of dietary intake by an FFQ may be subject to measurement error,[21] including dietary misreporting due to social desirability and/or cognitive deficits, which might lead to differential exposure misclassification. However, all the necessary precautions to limit food consumption misreporting were taken, including the administration of questionnaires by trained dietitians, and the contribution of participant's caregiver in data collection when deemed necessary. Additionally, to increase our confidence that the observed exposure-disease relationship had not been affected by potential measurement errors related to energy intake, we conducted sensitivity analyses restricting the sample to only acceptable energy reporters. Of note, potential errors might also arise from the fact that the USDA food database was applied to Greek foods for dietary intake estimation; however, selected analyses of local foods were also considered for estimation of daily intakes. Serum levels of inflammatory biomarkers were not available to directly characterize the systemic inflammatory status of study participants.

Nonetheless, based on previous validation studies exploring the associations of DII with several inflammatory biomarkers among different and diverse populations, we assumed that DII scores accurately reflect the underlying inflammatory state. Furthermore, repeated measurements of DII were not available, therefore, the temporal stability of the score could not be ascertained. However, in a previous large-scale study the average change of the DII score in a 3-year period was -0.36, representing approximately 2% of the index range. In the present study, data on eugenol, ginger, onion, turmeric, garlic, oregano, pepper, rosemary and saffron were not available; therefore, these components were not considered during DII calculation. Because all of these food parameters are anti-inflammatory, the DII scores in this study likely underestimate the anti-inflammatory potential of participants' diets.

On a different note, the longitudinal design of the present study instills confidence in our findings and sheds some light on the temporal relationship between the inflammatory potential of diet and dementia incidence. The diagnosis of dementia was reached through expert consensus meetings using widely acceptable published criteria. The inflammatory potential of diet was evaluated using a literature-derived, biomarker-validated, population-based DII.[12] Finally, study participants were selected through random population sampling of community-dwelling individuals, which together with the use of a non-population-specific DII, increases external validity and generalizability.

5. Conclusion

Aging-related immune system changes result in the institution of a chronic low-grade subclinical inflammatory state (inflammaging). This process has been implicated in the

pathological processes of Alzheimer's disease and Vascular dementia, possibly contributing to a significant proportion of late-life cognitive impairment and dementia disease burden worldwide. Accruing evidence supports that diet plays a central role in the regulation of chronic inflammation, and dietary modulation of inflammaging might be a valuable preventive strategy for dementia and cognitive decline. In the present study, we were able to demonstrate that the inflammatory potential of diet, assessed using an easily applicable tool,[12] was positively associated with the risk for dementia in community-dwelling non-demented older adults. Although the validity and reproducibility of these associations need to be ascertained by further studies, they contribute substantial information to the present literature and might assist the efforts for the development of population-level dietary guidelines and effective healthy aging strategies.

eMethods-http://links.lww.com/WNL/B626

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LEGENDS:

Table 1: Participants' baseline clinical and sociodemographic characteristics by incidence of dementia.

Table 2: Participants' baseline clinical and sociodemographic characteristics by Diet Inflammatory Index tertile.

Table 3: Unadjusted and adjusted Cox regression models. Results from the associations between baseline Diet Inflammatory Index scores and the hazard ratio for dementia incidence.

Figure 1: Flowchart describing sample.

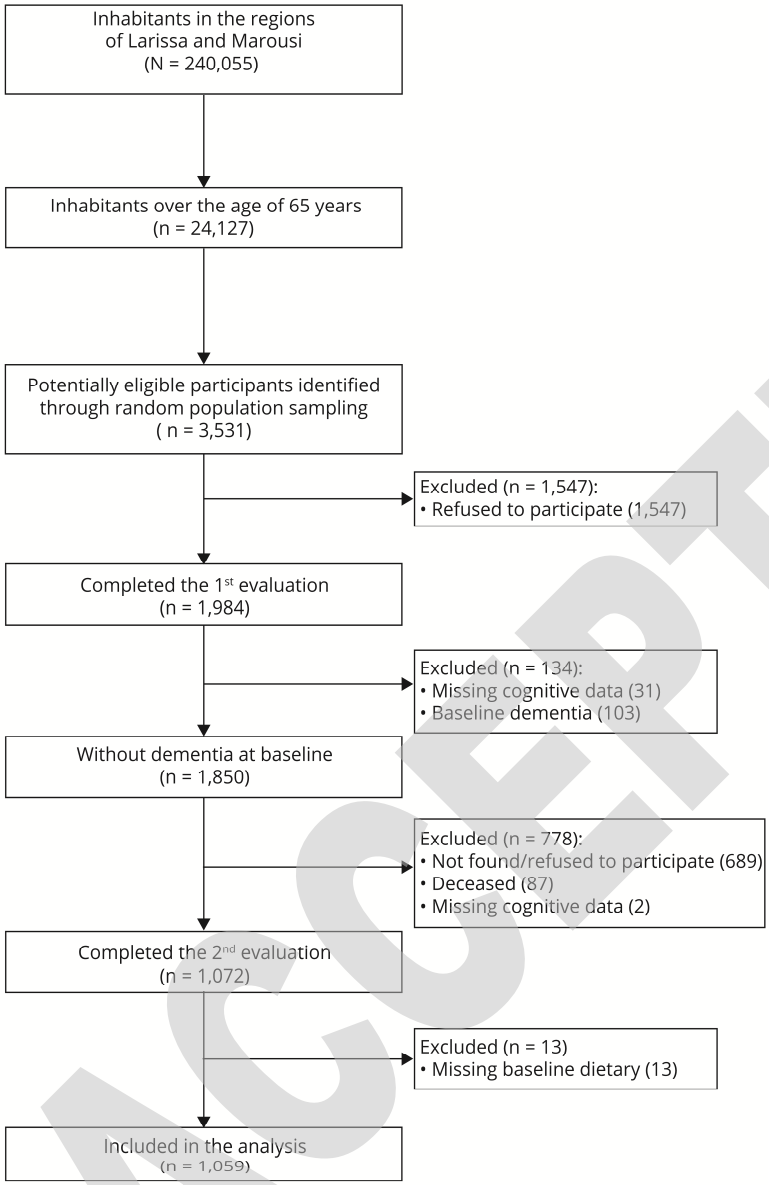

Figure 2: Survival curves based on Cox regression comparing cumulative dementia incidence in participants belonging to each Diet Inflammatory Index tertile (p for trend = 0.014). The figure is derived from a model that is adjusted for age, sex, years of education, energy intake and baseline MCI.

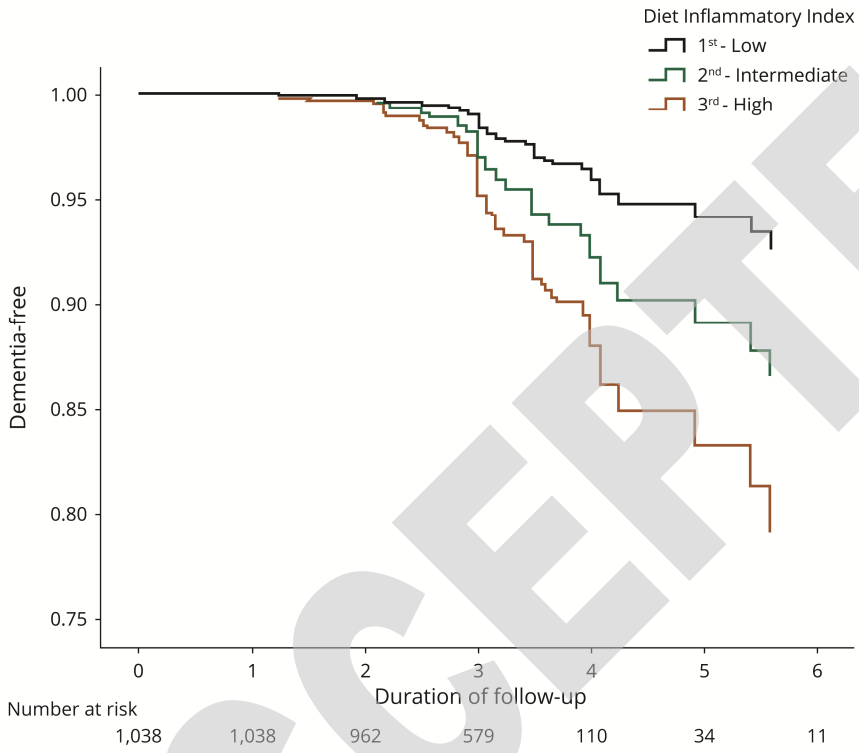

Table 1: Participants' baseline clinical and socio-demographic characteristics by incidence of dementia.

	Total (1059)	***No dementia at follow-up (997)***	***Dementia at follow-up (62)***	***P value***
Age (years)	73.1 (5.0)	72.9 (4.9)	77.5 (4.7)	**<0.001**
Sex [n (%) males]	427 (40.3)	401 (40.2)	26 (41.9)	0.789
Education (years)	8.2 (4.9)	8.3 (4.9)	6.1 (4.8)	**<0.001**
Energy intake (kcal)	1987 (539)	1987 (540)	1998 (541)	0.876
Clinical comorbidity index	2.1 (1.5)	2.1 (1.5)	2.0 (1.3)	0.499
DII score	-0.66 (2.19)	-0.70 (2.20)	-0.06 (1.85)	**0.027**
MCI [n (%)]	117 (11.0)	88 (8.8)	29 (46.8)	**<0.001**
Amnestic single-domain	23 (2.2)	17 (1.7)	6 (9.7) [a]	
Amnestic multi-domain	50 (4.7)	35 (3.5)	15 (24.2) [a]	
Non-amnestic single-domain	21 (2.0)	16 (1.6)	5 (8.1) [a]	
Non-amnestic multi-domain	23 (2.2)	20 (2.0)	3 (4.8)	

Values are presented as means (SD) or relative frequencies (%) for continuous and categorical variables, respectively. Statistically significant findings at $p \leq 0.05$ are indicated in bold. Abbreviations: SD=Standard Deviation.

[a] indicates statistically significant difference compared to the value in of the "No dementia at follow-up" column after adjustment for multiple comparisons.

Table 2: Participants' baseline clinical and socio-demographic characteristics by Diet Inflammatory Index tertile.

	Total (1059)	**Diet Inflammatory Index tertile**			
		1st (353)	***2nd (353)***	***3rd (353)***	***P value***
DII score (min, max)	(-5.83, 6.01)	(-5.83, -1.76)	(-1.76, 0.21)	(0.21, 6.01)	
Age (years)	73.1 (5.0)	72.2 (4.3) [b,c]	73.2 (5.3) [a]	74.0 [a]	**<0.001**
Sex [n (%) males]	427 (40.3)	160 (45.3) [c]	146 (41.4)	121 (34.3) [a]	**0.010**
Education (years)	8.2 (4.9)	9.6 (5.0) [b,c]	8.0 (4.7) [a,c]	7.1 (4.6) [a,b]	**<0.001**
Energy intake (kcal)	1987 (539)	2380 (534) [b,c]	1970 (388) [a,c]	1607 (369) [a,b]	**<0.001**
Clinical comorbidity index	2.1 (1.5)	2.0 (1.4)	2.1 (1.5)	2.1 (1.4)	0.355
MCI [n (%)]	117 (11.0)	32 (9.1)	45 (12.7)	40 (11.3)	0..290
Amnestic single-domain	23 (2.2)	7 (2.0)	8 (2.3)	8 (2.3)	
Amnestic multi-domain	50 (4.7)	12 (3.4)	16 (4.5)	22 (6.2)	
Non-amnestic single-domain	21 (2.0)	7 (2.0)	9 (2.6)	5 (1.4)	
Non-amnestic multi-domain	23 (2.2)	6 (1.7)	12 (3.4)	5 (1.4)	

Values are presented as means (SD) or relative frequencies (%) for continuous and categorical variables, respectively.
Statistically significant findings at $p \leq 0.05$ are indicated in bold. Abbreviations: SD=Standard Deviation.
[a] indicates statistically significant difference compared to value in the 1st tertile of Diet Inflammatory Index.
[b] indicates statistically significant difference compared to value in the 2nd tertile of Diet Inflammatory Index.
[c] indicates statistically significant difference compared to value in the 3rd tertile of Diet Inflammatory Index.

Table 3: Unadjusted and adjusted Cox regression models. Results from the associations between baseline Diet Inflammatory Index scores and the hazard ratio for dementia incidence.

Model	At Risk, n	DII score as a continuous variable		DII score as tertiles			
		HR (95% CI)	P value	Tertile	HR (95% CI)	P value	P for trend
1[a]	1059	1.18 (1.06 – 1.32)	**0.002**	1st	Reference		**0.002**
				2nd	2.19 (1.09 – 4.41)	**0.028**	
				3rd	2.97 (1.50 – 5.87)	**0.002**	
2[b]	1039	1.21 (1.03 – 1.42)	**0.023**	1st	Reference		**0.014**
				2nd	1.92 (0.89 – 4.11)	0.095	
				3rd	3.01 (1.24 – 7.26)	**0.014**	
3[c]	1025	1.20 (1.02 – 1.41)	**0.031**	1st			**0.018**
				2nd	1.89 (0.88 – 4.03)	0.101	
				3rd	2.89 (1.20 – 6.96)	**0.018**	

Statistically significant findings at $p \leq 0.05$ are indicated in bold. Abbreviations: HR=Hazard Ratio; CI=Confidence Interval.

[a] Model 1 is unadjusted.

[b] Model 2 is adjusted for age, sex, years of education, energy intake, and baseline MCI.

[c] Model 3 is adjusted for age, sex, years of education, energy intake, baseline MCI and clinical comorbidity index.