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Original article

Dietary patterns, inflammatory biomarkers and cognition in older adults: An analysis of three population-based cohorts

Natalia Ortega [a, b, c, *], Leona Schütte [a], Tosca O.E. de Crom [d], Trudy Voortman [d, e], Olivia I. Okereke [f], Marco Vinceti [g, h], Armin von Gunten [i], Pedro Marques-Vidal [j], Nicolas Rodondi [a, l], Arnaud Chiolero [a, b, k], Patricia O. Chocano-Bedoya [a]

[a] Institute for Primary Health Care (BIHAM), University of Bern, Bern, Switzerland
[b] Population Health Laboratory (#PopHealthLab), University of Fribourg, Fribourg, Switzerland
[c] Graduate School for Health Sciences, University of Bern, Bern, Switzerland
[d] Department of Epidemiology, Erasmus MC University Medical Center Rotterdam, Rotterdam, the Netherlands
[e] Meta-Research Innovation Center at Stanford (METRICS), Stanford University, Stanford, CA, USA
[f] Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA
[g] Environmental, Genetic and Nutritional Epidemiology Research Center, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Italy
[h] Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA
[i] Service of Old-Age Psychiatry, Department of Psychiatry, Lausanne University Hospital, Lausanne, Switzerland
[j] Department of Medicine, Internal Medicine, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
[k] School of Population and Global Health, McGill University, Montreal, Canada
[l] Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

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SUMMARY

Background: Targeting effective strategies to prevent cognitive decline is key in the aging population. Some diets have been linked to a slower cognitive decline, potentially through reducing inflammation. We aimed at determining the effect of inflammatory dietary patterns (IDPs) on cognitive function in three population-based cohorts.

Methods: In this longitudinal study, we analyzed data from the Canadian Longitudinal Study of Aging, CoLaus|PsyCoLaus and Rotterdam Study. Our analytical sample included participants over 55 years old with baseline data on cognition, dietary intake, and inflammatory markers. IDPs were derived for each cohort using reduced rank regression to reflect maximal variation in three inflammatory markers. We calculated scores of consumption of the IDPs, higher scores indicating more IDP consumption. We used inverse probability of treatment and censoring weights in the marginal structural models to estimate associations of higher versus lower quarters of consumption of an IDP on general cognition (Mini-Mental State Evaluation) and four cognitive domains (memory, verbal fluency, verbal learning and processing speed and executive function) during at least 3 years of follow-up.

Results: We included 10,366 participants (mean age 68) followed-up for a mean of 5 years. Diet explained between 1 and 2% of the variation of the inflammatory markers. There were no differences in general cognition when comparing the highest to the lowest quarter of consumption of IDPs among the three cohorts. Mean differences for the four cognitive domains were of small magnitude across cohorts and not clinically relevant.

Conclusion: Diet explained low variation in inflammatory markers. Consuming IDPs was not associated with mean differences in general or domain-specific cognitive function.

1. Introduction

The growing number of people living with cognitive impairment poses a major global public health challenge [1]. Prioritizing lifestyle prevention strategies among middle-aged and older adults at the population level could be key to addressing the burden of cognitive impairment. Diet could be a target of these given that it is a ubiquitous, modifiable exposure that is related to other factors affecting cognitive function, such as cardiovascular disease. Yet evidence on diet and cognitive function remains unclear [2,3].

* Corresponding author. Mittelstrasse 43 3012 Bern, Switzerland.
E-mail address: natalia.ortega@unibe.ch (N. Ortega).

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Some diets, including the Mediterranean and DASH diets, have been suggested to reduce the risk of cognitive decline [4,5]. The Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet is a hybrid of both, designed with a focus on neuroprotective foods, and has been associated with a lower risk of cognitive decline and Alzheimer's disease [6–8], likely through anti-inflammatory pathways [9–12]. Chronic inflammation has been linked to cognitive decline [13,14]. Both the MIND and Mediterranean diets are rich in fish and long-chain omega-3 fatty acids, which help to reduce inflammation [15] and thereby the risk of cognitive decline and Alzheimer's disease [13,16]. However, these diets were not specifically constructed for their inflammatory effect.

The Dietary Inflammatory Index (DII) is the most popular and validated tool to quantify the inflammatory potential of a diet. Two recent meta-analyses [17,18] and an analysis of the UK Biobank cohort study [19] showed that higher DII was associated with a higher risk of cognitive impairment and a lower global cognitive function and verbal fluency, but not with episodic memory or executive function. Importantly, the DII score is constructed identically for all populations while they might consume different dietary patterns. This means that the DII might not reflect the dietary pattern leading to higher inflammation across populations. Additionally, the DII is a combination of micro- and macronutrients and whole foods that does not translate to a complete dietary pattern given that some nutrients may be contained in foods (e.g., tea and flavonoids) and others may be left out (fish, meat, fruits). Therefore, a data-driven method deriving population specific inflammatory scores would be appropriate.

Two previous studies [20,21] used reduced rank regression (RRR), a data-driven method, to explore the association between food groups and inflammatory markers among young adults in the UK and older US women. Subsequently, they linked these findings to cognitive functioning. Both studies reported no significant association between global cognition and verbal fluency, and partly conflicting results for memory and executive function. To disentangle these conflicting results with population-specific inflammatory diet scores, we aimed at calculating mean differences in cognitive function between participants consuming highly inflammatory dietary patterns compared to those with least inflammatory dietary patterns in three geographical populations of older adults.

2. Methods

2.1. Population and study design

We used data from three population-based prospective cohorts from Switzerland (CH), Canada, and the Netherlands (NL) that collected data on dietary habits and cognitive function, and plasma samples at baseline, and that repeated cognitive function assessments at least 3 years later. The Swiss CoLaus|PsyCoLaus (PsyCoLaus) study contacted a random sample of the Lausanne population aged 35-75-years and 41% (n = 6733) agreed to participate [22]. The Canadian Longitudinal Study of Aging – Comprehensive cohort (CLSA) randomly selected households of adults aged 45–85 years and 45% (n = 30,097) participated [23]. The Rotterdam Study (RS) included three sub-cohorts, which were pooled for the current project: I (waves 5, 6 and 7 – first with nutritional data); II (waves 3, 4 and 5 – first with nutritional data); and III (waves 1, 2 and 3). In 1990, Cohort I recruited 7983 persons over 55 years old in the Ommoord district in Rotterdam, NL. In 2000, Cohort II added 3011 participants who had turned 55 or moved into the study area. Cohort III recruited 3932 younger participants (45 years and older) in the same study area. The average response rate was 72% [24]. The three study sites conducted in-person interviews, administered tests, and took physical measurements (Fig. 1). Cohorts were approved by their respective ethics authorities complying with all relevant regulations, and written informed consent was obtained from all participants including consent for further use of the data (Supplementary Material 1). The present study was approved by the Cantonal Ethics Committee for research in Bern (2022-01976).

In the current analysis, the sample included participants who met our selection criteria: over 55 years old, with complete nutritional and cognitive data, inflammatory markers, and without cognitive impairment at baseline (defined as a Mini Mental State Examination [MMSE] >24 [25] for RS and PsyCoLaus, and as a Mental Alternation Test [MAT] >15 points [26] for CLSA). We justify our early older adulthood definition to capture cognitive decline for as many adults as possible and to capture diet in this period to then observe subsequent decline. We excluded participants with <3 years follow-up from our models (Fig. 1).

2.2. Dietary intake assessment and dietary pattern identification

Dietary intake was assessed with food frequency questionnaires (FFQs) in the three cohorts. PsyCoLaus used a 97-item [27], RS a 389-item [28] and CLSA a 36-item semi-quantitative FFQ [29]. For each food item, participants self-reported how often on average they had consumed a common unit or portion size during the previous year for RS and CLSA and last four weeks in PsyCoLaus.

We identified dietary patterns explaining most variation in inflammatory markers in our study population using RRR. This method identifies linear functions of exposure variables (i.e., food groups) to maximize explained variation in disease-related response variables (i.e., inflammatory markers) [30]. We predefined 20 (CLSA) and 27 (PsyCoLaus and RS) food groups (g/day) and we selected serum hs-CRP, IL-6, and TNFα in CLSA and PsyCoLaus, and SII, NLR, PLR – inflammatory white blood cells – in RS as response variables, based on the hypothesis that dietary patterns could correlate with higher systemic inflammation. The quantification of inflammatory markers is described elsewhere [31–33]. We excluded participants with hs-CRP values corresponding to acute inflammation (over 10 mg/L) [34]. The diet and inflammatory markers were assessed cross-sectionally at baseline. One main dietary pattern was derived for each cohort separately, thus running one RRR for each cohort. We used quarters (divided by quartiles) of the inflammatory dietary pattern scores as independent variables in the marginal structural models (MSMs). In the main tables, we report results for the inflammatory dietary pattern explaining most variation of the inflammatory markers (Factor 1). Estimates from the MSMs for factors 2 and 3 are shown in Supplementary Tables.

2.3. Cognitive function assessment

Our primary outcome was general cognition, assessed with the MMSE in PsyCoLaus and RS and with the MAT in CLSA. The MMSE involves spoken replies to evaluate orientation, memory and attention, the capacity to name objects, follow a verbal or written order, spontaneously write a sentence or recreate a geometric figure [35]. The MAT consists of an alternating series of numbers and letters and demands timed performance and category-switching assessing executive function. It is a valid screening tool with good discriminative power to detect cognitive impairment [26].

Our secondary outcomes assessed four domains of cognition: processing speed and executive function, verbal learning, episodic memory, and verbal fluency. Cognitive outcomes were shared by at least two cohorts. Executive function and processing speed were assessed with the Stroop test in all three cohorts [36]. Verbal

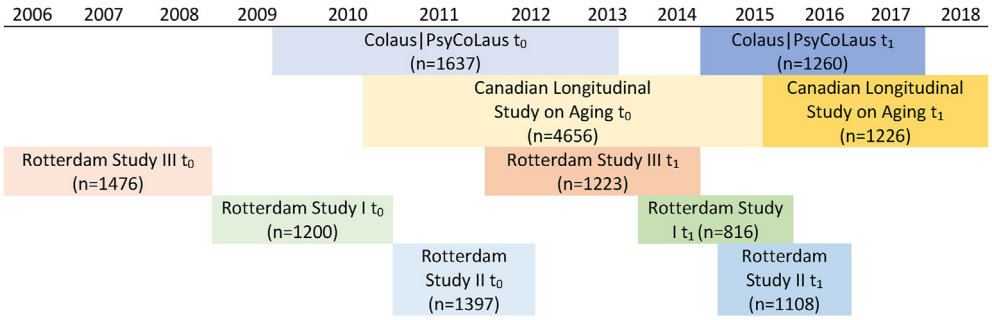

Fig. 1. Timeline of the baseline and follow-up visits in the three cohorts included in our study. n: number of eligible participants for our analyses; t_0: time 0, baseline; t_1: time 1, follow-up.

fluency was assessed with the animal naming test [37]. Episodic memory was assessed with the Free and Cued Selective Reminding Test [38] in PsyCoLaus and the Prospective Memory Task [39] in CLSA. CLSA and RS measured verbal learning with the Rey Auditory Verbal Learning Test [40]. We summarized tests' characteristics in Supplementary Table 1.

2.4. Confounders

Our causal model based on expert knowledge is depicted in a Directed Acyclic Graph (DAG) (Fig. 2, see details in Supplementary Fig. 1). We included the following set to block all the backdoor paths: age (<70, 70–74 and ≥ 75), sex, smoking status (current, former, never), alcohol consumption (never, less than 1/day and more than 1/day), past major cardiovascular events (self-reported – cardiomyopathy, congenital heart disease, valvular heart disease, heart failure, coronary artery disease, angina, myocardial infarction, stroke, percutaneous coronary intervention, coronary artery bypass graft or pacing) (yes/no), diabetes diagnosis or treatment (yes/no), education (elementary, high school or superior), body mass index (normal, overweight, obese), physical activity (tertiles), history of any major depressive disorder diagnosis (yes/no), family income (tertiles), and history of diagnosis of hypertension or self-reported use of hypertensive drugs (yes/no). The selected confounders were harmonized across cohorts to make our results comparable, except for total calories (kcal/day), that was not available in CLSA.

2.5. Statistical analysis

All analyses were performed in each of the three cohorts separately. We estimated mean differences in the outcomes as a contrast between the lowest and higher quarters of the dietary pattern score explaining most variation in inflammatory markers (i.e., Factor 1) using stabilized inverse probability weighting (IPW) of MSMs as our estimator [41]. We calculated IPW of the exposure to ensure conditional exchangeability at baseline using Generalized Linear Models in the study population including the confounders in the previous section. We truncated weights over the 99.5th percentile. To relax that missing data on the outcome was missing completely at random, we applied IPW of loss to follow-up that assumes missing at random pattern, meaning that participants were lost-to-follow-up only conditional on observed covariates at baseline. Namely, we included age, sex, occupation, BMI, smoking, past cardiovascular events, hypertension, and diabetes. Our final weight was the product between both weights and again truncated at 99.5th percentile. We fitted MSMs specifying gaussian distributions for the counterfactual continuous outcomes and estimated average marginal predicted means of the outcomes. We excluded participants with missing data on the outcomes from the MSMs. We calculated parametric 95% confidence intervals (CIs) of the estimates.

We performed sensitivity analyses to test the robustness of our results to the main assumptions in our analysis. We collapsed 7 food groups (grains, fish, fruits, vegetables, and vegetable fats, and eliminated coffee and tea) in PsyCoLaus and RS to match the ones in CLSA and repeated the RRR to evaluate how the grouping might have affected our model estimates. We repeated the main analyses using the Mediterranean diet score, as an a priori measure of diet quality in PsyCoLaus as a positive control exposure that has been related to cognitive function to detect unmeasured confounding. We also repeated the main analysis in adults over 65, typically considered "older adults" and with the continuous exposure.

We reported standardized mean differences (SMD) in Supplementary Table 2 to quantify the differences in baseline characteristics and covariate balance before IPW, defined as the difference in the characteristic between exposure groups divided by the standard deviation of the characteristic among all participants. We considered SMDs <0.01 to be well-balanced across quarters of consumption of an inflammatory dietary pattern. We performed the RRR using the PLS procedure in the SAS software (SAS Institute, Inc., Cary, North Carolina) and all other analyses in R version 4.3.1 (2023-06-10) using the tidyverse [42], MASS [43], ggpubr [44], and geepack [45] packages. The code and outputs were developed and using Jupyter Notebook and can be found in Supplementary File 2.

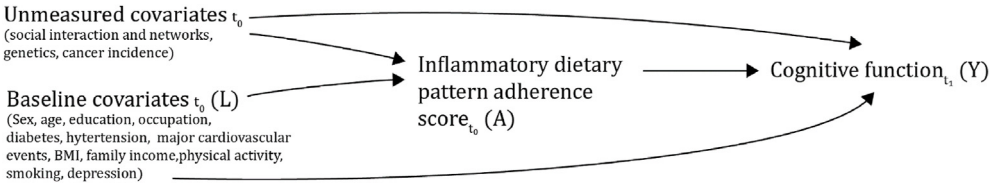

Fig. 2. Simplified Directed Acyclic Graph (DAG) depicting our assumptions for the role of confounders in the association between inflammatory dietary patterns and cognitive function. A detailed DAG is provided in Supplementary Fig. 1. BMI: Body Mass Index.

3. Results

A total of 10,597 participants (male from 42% in RS to 51% in CLSA) with a mean age ranging from 66.9 in CLSA to 69.8 in RS were included at baseline and mean follow-up times from 3.0 years in CLSA to 5.2 in RS (Table 1). Differences for levels of consumption of an inflammatory dietary pattern are presented in Supplementary Table 2.

In the RRR, we obtained three Factor 1 scores (i.e., one per cohort) representing three dietary patterns explaining most variation in inflammatory markers. Factor 1 explained 1.2, 2.0 and 2.1% of the variation in of the set of inflammatory markers for CLSA, PsyCoLaus and RS, respectively; and they explained 16.5, 11.6 and 15.2 % of variation in food intake (Supplementary Table 3). Factor 1 from PsyCoLaus and RS had positive response score coefficients across all inflammatory markers, suggesting that an elevated Factor 1 score corresponds to higher levels of all three inflammatory markers (Supplementary Table 4). Factor 1 for CLSA corresponds to higher CRP and IL6 and lower TNFα, with a small coefficient. Therefore, we describe/interpret all identified patterns as "inflammatory dietary patterns". Factor 1 predominantly explained variation of CRP in CLSA and PsyCoLaus (2.7 and 1.6%, respectively), and NLR and SII in RS (2.0 and 1.9%, respectively). Factor 1 was positively correlated with the intake of processed and red meat, eggs, vegetable fats and sauces (meaning higher inflammatory markers) and negatively correlated (lower inflammatory markers) with fruits, vegetables, legumes, whole grains, fish, and nuts in the three cohorts (Table 2). See Supplementary Figs. 5 and 6 for the dietary patterns and explained variation of Factors 2 and 3.

Table 1
Baseline characteristics of the participants in the three cohorts.

Characteristics	PsyCoLaus	CLSA	RS
Number of participants	1637	4656	4073
Sex (% Male)	695 (42.5)	2353 (50.5)	1724 (42.3)
Age (%)			
Below 70	1006 (61.5)	956 (20.5)	1235 (30.3)
Between 70 and <75	358 (21.9)	3059 (65.7)	1959 (48.1)
75 or older	273 (16.7)	641 (13.8)	879 (21.6)
Education (%)			
Elementary	1112 (67.9)	363 (9.2)	2005 (49.9)
High school	261 (15.9)	1383 (35.1)	1208 (30.1)
Higher education	264 (16.1)	2193 (55.7)	806 (20.1)
Body Mass Index			
Normal (<25)	619 (38.2)	1368 (29.4)	1164 (28.6)
Overweight (25–30)	682 (42.0)	1281 (27.5)	967 (23.8)
Obese (>30)	321 (19.8)	2001 (43.0)	1934 (47.6)
Smoking (%)			
Never	683 (41.9)	2063 (44.3)	621 (15.3)
Former	711 (43.6)	2258 (48.5)	2165 (53.2)
Current	238 (14.6)	335 (7.2)	1282 (31.5)
Cardiovascular events[a](% Yes)	336 (20.6)	640 (13.7)	56 (1.4)
Hypertension (% Yes)[b]	1096 (67.0)	1933 (41.5)	3069 (75.5)
Alcohol use (%)			
Never	383 (25.7)	652 (14.0)	1534 (37.7)
Less than one per day	707 (47.5)	2992 (64.3)	1637 (40.2)
One per day or more	398 (26.7)	1012 (21.7)	902 (22.1)
Depression (%)	181 (12.1)	610 (13.1)	260 (6.4)
Income (%)[c]			
Low	421 (39.4)	1670 (35.9)	1025 (28.2)
Medium	500 (46.8)	1258 (27.0)	675 (18.5)
High	148 (13.8)	1728 (37.1)	1939 (53.3)
Diabetes (% Yes)	185 (11.3)	805 (17.3)	642 (16.1)
Physical Activity			
Low	279 (19.4)	1306 (28.9)	1331 (34.7)
Medium	653 (45.4)	1545 (34.2)	1257 (32.7)
High	507 (35.2)	1664 (36.9)	1252 (32.6)
MAT/MMSE[d] mean (SD)	29.4 (1.1)	27.8 (6.7)	28.1 (1.5)

CLSA: Canadian Longitudinal Study on Aging, RS: Rotterdam Study, MAT: Mental Alternation Test, MMSE: Mini-Mental State Examination, SD: Standard deviation.
[a] Cardiomyopathy, congenital heart disease, valvular heart disease, heart failure, coronary artery disease, angina, myocardial infarction, stroke, percutaneous coronary intervention, coronary artery bypass graft or pacing. In RS it only includes stroke.
[b] Past diagnosis of hypertension or use of hypertensive drugs.
[c] Income in CLSA and CoLaus corresponds to tertiles of family income, while in RS corresponds to tertiles of individual monthly income.
[d] CLSA performed the MAT, while RS and PsyCoLaus performed MMSE.

General cognitive function was not associated with higher quarters of Factor 1 scores (i.e., higher inflammation). Mean differences in MMSE and MAT were 0.04 (95% CI -0.2 to 0.3), 0.2 (95% CI -1.1 to 1.5), and 0.03 (95% CI -0.3 to 0.3) for PsyCoLaus, CLSA and RS, respectively, when comparing extreme quarters. No dose–response trend was observed with intermediate quarters (Table 3). We obtained similar results for Factors 2 and 3 in all cohorts (Supplementary Table 7). None of the specific cognitive domains were associated with higher quarters of Factor 1 scores (i.e., higher inflammation) in PsyCoLaus and CLSA. However, mean differences in processing speed, verbal learning and verbal fluency were lower for higher Factor 1 score quarters compared to the lowest quarter in RS. For instance, the immediate and delayed recalls for verbal learning were 0.5 (95% CI 0.3–0.8) and 0.4 (95% CI 0.2–0.7) points lower, respectively, comparing the highest to the lowest quarter. Similarly, participants in the highest quarter of an inflammatory diet were able to recall 0.5 (95% CI 0.2–0.8) less words per minute compared to the lowest. Processing speed was 2.7 (95% CI 0.2–5.2) seconds slower in the highest quarter of an inflammatory diet compared to the lowest (Table 3).

In the sensitivity analyses, the estimates of the MSMs did not change substantially after collapsing foods into the CLSA grouping (Supplementary Table 8). Factor 1 captured more food variability but explained less of the inflammatory response variability (Supplementary Table 9). In the main analysis, Factor 1 explained 3.6 and 5.5% of the variation for the food groups in PsyCoLaus and RS, whereas in the CLSA grouping in the sensitivity analysis explained up to 4.3 and 7.4%, respectively. Conversely, Factor 1 in the main analysis explained around 2% of the variation for the inflammatory response in PsyCoLaus and RS, whereas the grouping in the sensitivity analysis explained around 1%. Factor 1 was similar to the main analysis including fruits, vegetables, whole grains and fish being negatively correlated with inflammation and processed meat and eggs positively correlated (Supplementary Table 10). Increasing quarters of consumption of a Mediterranean diet were not associated with general cognitive function in PsyCoLaus with a mean difference of −0.1 (95% CI -0.4 to 0.2) for the comparison between the highest and lowest quarters (Supplementary Table 11). When performing the analysis excluding participants under 65, we found similar mean differences for general cognition (small magnitude even in the extremes of the CI) in the three cohorts. Among secondary outcomes, small estimates were also found across cohorts with the same trends for verbal fluency and verbal learning in RS. Processing speed was again slower for increasing inflammatory diet score quarters in RS [Q4 vs. Q1 4.4 (95% CI 0.9–7.8) seconds] (Supplementary Table 12). Coding the inflammatory diet score as a continuous variable revealed coherent results with our main analysis. Beta coefficients were of small magnitude and uninformative CIs for the primary and most secondary outcomes, except for verbal learning in RS, for which higher inflammation led to average lower scores (Supplementary Table 13).

4. Discussion

We identified dietary patterns based on their explained variation of inflammatory markers and assessed their association with cognitive function in older adults in three cohorts. These inflammatory dietary patterns were not associated with lower general cognitive function at follow-up in our study. Men over 74, overweight, with diabetes and hypertension consumed more

Table 2
Factor loadings (Pearson correlation coefficients) for Factor 1 food groups to inflammatory dietary pattern scores derived by reduced rank regression for each of the cohorts. We highlight coefficients below −0.2 and above 0.2.

	PsyCoLaus (n = 1637)	CLSA (n = 4656)	RS (n = 4073)
Tomatoes	−0.05	–	**−0.33**
Green leafy vegetables	−0.06	**−0.31**	**−0.32**
Other vegetables	−0.11	−0.12	**−0.40**
Potatoes	0.13	0.10	0.10
Legumes	−0.15	**−0.36**	−0.15
Berries	0.05	–	−0.07
Fruits[a]	**−0.27**	**−0.31**	0.08
Red meat	0.19	**0.21**	0.09
Chicken	−0.11	**0.26**	**−0.27**
Eggs	**0.40**	**0.25**	−0.03
Fermented dairy	0.05	–	0.05
Non-fermented dairy	−0.10	–	0.04
Olive oil	−0.01	–	0.12
Other vegetable fats	**0.33**	0.16	0.04
Coffee, tea	**−0.24**	–	−0.05
Sugary snacks	0.15	**−0.32**	0.11
Processed meats	0.08	**0.29**	−0.01
Wine	0.08	−0.19	**−0.29**
Alcohol	−0.07	–	−0.09
Refined grains	0.10	–	−0.16
Whole grains	**−0.33**	**−0.20**	**−0.34**
Fish	–	**−0.21**	–
White fish	**−0.37**	–	−0.15
Fatty fish	**−0.30**	–	−0.06
Shellfish	0.10	–	−0.12
Mixed meals	0.02	–	**−0.36**
Savory snacks	0.00	−0.05	−0.12
Sauces	**0.30**	−0.08	−0.19
Nuts	–	**−0.36**	−0.07

[a] Canadian Longitudinal Study on Aging (CLSA) includes Berries. CoLaus|PsyCoLaus (PsyCoLaus); RS: Rotterdam Study.

inflammatory diets. As expected, dietary patterns with lower inflammatory scores correlated with higher intake of fruits, whole grains, and fish. Vegetables were negatively correlated with inflammatory scores in CLSA and RS but not in PsyCoLaus.

After reweighting population characteristics at baseline, there were small mean differences in general cognitive function in participants in the highest versus the lowest inflammatory diet quarters, and no consistent or clinically relevant differences in domains of cognitive functioning across the three cohorts. We can conclude this for general cognitive function considering a 1-point difference in the MMSE as the lower bound for a minimally clinically relevant effect [46,47]. We are not aware of a cutoff for MAT. Similarly, executive function (Stroop Color test) sets a clinically relevant difference of 5.5 points (seconds) as an effect for healthy participants at baseline [47], while the extremes of the CIs of our estimates were between −1.3 and 5.2 s. The extremes of the CIs for the mean differences in verbal fluency, between −2.1 and 1.4, were also far the minimally relevant clinical difference set to 2.9 points [47]. Our results in the sensitivity analyses were overall consistent with these findings. Interestingly, when analyzing the dietary score as a continuous exposure, we found that higher inflammatory scores led to lower verbal learning [−0.2 (95% CI -0.29 to −0.11), −0.26 (95% CI -0.35 to −0.18)] in RS, but not in CLSA, a cohort with potentially more selection bias. Nonetheless, this cut offs for clinical relevance are thought for individuals as cut offs at the population were not available but are better suited for epidemiological studies where we present population average estimates.

Two previous longitudinal studies using RRR to derive an inflammatory dietary pattern to study its association with cognitive function [20,21] found comparable inflammatory dietary patterns to ours, except for a different direction for legumes and peas. They describe negative correlations between inflammatory markers and whole grains and positive correlations with red and processed meat, fried foods and legumes [21], while we found legumes to be negatively correlated. None of them reported the explained variance in inflammatory biomarkers, so comparisons on that regard are not possible. Participants consuming diets with higher inflammatory potential were also older, more frequently men, smokers, living with diabetes and hypertension. After around 6- and 10-year follow-ups in more than 20,000 participants, both studies also found small estimates for general cognitive function, in disagreement with studies using the DII [17,18]. Notably, they did not find an association with verbal fluency [21] and verbal memory [20], in agreement with our results in PsyCoLaus and CLSA, but they did find differences in verbal and mathematical reasoning, for which we did not have a measure. We found null associations between the inflammatory diet score and memory for all the cohorts and executive function in PsyCoLaus and CLSA, indicating that the conflicting results in studies using the DII could be due to a real null association. On the one hand, this could imply that another mechanism may be underlying the protective association between the MIND and Mediterranean diets and cognitive decline. Foods high in antioxidants, such as olive oil, vegetables, and berries, could be another reason that could support protective effects on brain health and improve cognitive function [48]. On the other hand, these results could be biased given that dietary patterns only explained between 1 and 2% of the variation in the inflammatory response and while previous studies showed consistent effects of the Mediterranean diet on cognitive function [6–8], we found null effects.

Our study included a comprehensive set of cognitive function measures that evaluate general cognition, memory, verbal fluency, verbal learning and executive function and processing speed. Because dietary behaviors and their relation to inflammation may differ across geographic populations, we assessed diets at the cohort-level. By applying a data-driven method based on what

Table 3
Mean differences (95% confidence intervals) for cognitive function measures according to quarters of the identified dietary patterns explaining most variation in inflammatory markers (Factor 1) derived by reduced rank regression compared to the lowest quarter. Values are obtained from inverse probability weighted marginal structural models.

	PsyCoLaus (n = 1260)			CLSA (n = 1226)			RS (n = 3147)		
	Q2	Q3	Q4	Q2	Q3	Q4	Q2	Q3	Q4
General cognitive function (MAT/MMSE/MMSE)	0.03 (−0.2 to 0.3)	0.1 (−0.2 to 0.3)	0.04 (−0.2 to 0.3)	−0.6 (−1.9 to 0.7)	−0.8 (−2.0 to 0.5)	0.2 (−1.1 to 1.5)	0.1 (−0.2 to 0.4)	0.01 (−0.3 to 0.3)	−0.03 (−0.3 to 0.3)
Processing speed, executive function (Stroop)	−0.1 (−0.4 to 0.2)	−0.4 (−0.8 to −0.1)	−0.4 (−0.8 to −0.03)	0.3 (−1.3 to 1.9)	1.1 (−0.4 to 2.7)	0.4 (−1.3 to 2.1)	0.5 (−2.6 to 3.6)	1.8 (−0.7 to 4.3)	2.7 (0.2–5.2)
Verbal learning	–	–	–	−0.1 (−0.4 to 0.3)	−0.02 (−0.4 to 0.3)	−0.02 (−0.4 to 0.4)	−0.2 (−0.4 to 0.1)	−0.5 (−0.7 to −0.2)	−0.5 (−0.8 to −0.3)
Immediate recall (RAVLT)									
Verbal learning	–	–	–	−0.1 (−0.5 to 0.3)	0.04 (−0.3 to 0.4)	0.1 (−0.3 to 0.6)	−0.04 (−0.3 to 0.2)	−0.04 (−0.3 to 0.2)	−0.4 (−0.7 to −0.2)
Delayed recall (RAVLT)									
Memory test (TMT/FCSRT)	0.8 (−0.3 to 1.7)	−0.1 (−1.3 to 1.1)	0.2 (−1.0 to 1.3)	−0.1 (−0.2 to 0.1)	−0.1 (−0.3 to 0.04)	−0.2 (−0.4 to −0.1)	–	–	–
Verbal fluency (Animal Naming)	−0.3 (−2.1 to 1.5)	0.5 (−1.1 to 2.2)	−0.3 (−2.1 to 1.4)	0.2 (−0.7 to 1.1)	−0.1 (−1.0 to 0.7)	0.03 (−0.9 to 0.9)	−0.3 (−0.6 to 0.1)	−0.4 (−0.9 to −0.04)	−0.5 (−0.9 to −0.2)

PsyCoLaus: CoLaus|PsyCoLaus; CLSA: Canadian Longitudinal Study on Aging, RS: Rotterdam Study.

people "usually eat", we could account for the variability in populations and acknowledge the potentially different inflammatory diets depending on diverse combination of foods. Another strength of our study is that we coded the exposures, outcomes and confounders equally to compare our estimates across cohorts. Lastly, grouping participants into quarters of consumption of inflammatory diets offered an easy-to-understand comparison of high versus low consumers with relation to the risk of cognitive decline.

This study has some limitations. First, the generalizability of our study to our target population is limited because participants who participate in a cohort represent a highly motivated subset of the population who tend to be more health-conscious, so our study sample may not represent the initial target population from the selected cohorts even though we tried to mitigate it by weighting participants for their probability to be lost to follow-up. Additionally, only a few severely impaired participants participated in the studies at follow-up, so our results apply to a relatively healthy cognitive population of older adults and should be interpreted with caution out of these ranges. Second, nutrition exposure assessment is highly influenced by measurement bias, but since we restricted our sample to healthy participants at baseline, measurement bias in the exposure should be non-differential. FFQs were administered by professional dieticians in RS and CLSA, but self-administered in PsyCoLaus, being more prone to measurement error. The dietary assessment was limited to the past month or year and may not represent longer-term average exposure during younger-adulthood years. Third, we cannot exclude residual confounding. CLSA did not have information on total calorie consumption, therefore participants are not exchangeable in that respect, and we acknowledge that genetics, social and family networks and unmeasured time-varying confounders could be affecting our estimates. Fourth, we had a short follow-up for CLSA and the lower age limit of 55 years old is young, limiting the effect on cognition that we can observe. However, estimates were in line with studies with longer follow-ups and the sensitivity analysis in >65 years old showed similar trends in the estimates. Fifth, we did not model interaction or effect modification by the variables in the model, thus assuming that the association is constant for different levels and combinations of the covariates. Sixth, we must highlight that if we wanted to test the effect of one of the derived diets, we would need to validate the dietary pattern and its adequacy to predict inflammation and afterwards, compute its effect on cognition.

5. Conclusion

We derived dietary patterns explaining most variation in inflammatory markers in three population-based cohorts. However, the explained variation of the diets on these markers was low and we found no association between these dietary patterns and general cognition. Executive function, verbal learning and fluency could be diminished in a small magnitude by inflammatory dietary patterns. These trends would need to be confirmed by further studies.

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Author contributions

Conceptualization and design: NO, LS and PCB; Analysis and interpretation of the data: NO, LS; Drafting of the article: NO, LS; Editing and Final approval of the article: NO, LS, AC, AvG, NO, LS, OIO, TV, TdC, PMV, PCB, NR; Provision of study data: TdC, PMV, TV.

Data availability statement

The data of the CoLaus|PsyCoLaus study used in this article cannot be fully shared as they contain potentially sensitive personal information on participants. According to the Ethics Committee for Research of the Canton of Vaud, sharing these data would be a violation of the Swiss legislation with respect to privacy protection. However, coded individual-level data that do not allow researchers to identify participants are available upon request to researchers who meet the criteria for data sharing of the CoLaus|PsyCoLaus Datacenter (CHUV, Lausanne, Switzerland). Any researcher affiliated to a public or private research institution who complies with the CoLaus|PsyCoLaus standards can submit a research application to research.colaus@chuv.ch or research.psycolaus@chuv.ch. Proposals requiring baseline data only, will be evaluated by the baseline (local) Scientific Committee (SC) of the CoLaus and PsyCoLaus studies. Proposals requiring follow-up data will be evaluated by the follow-up (multicentric) SC of the CoLaus|PsyCoLaus cohort study. Detailed instructions for gaining access to the CoLaus|PsyCoLaus data used in this study are available at www.colaus-psycolaus.ch/professionals/how-to-collaborate/. Data from the Rotterdam Study cannot be made publicly available because of restrictions based on privacy regulations and informed consent of the participants. Proposals for data access can be directed to the management team of the Rotterdam Study (secretariat.epi@erasmusmc.nl), which has a protocol for approving data requests. Data are available from the Canadian Longitudinal Study on Aging (www.clsa-elcv.ca) for researchers who meet the criteria for access to de-identified CLSA data. We provide detailed code and pooled results in Supplementary File 2.

Conflict of interest

The authors report that there are no disclosures relevant to this publication.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2024.08.027.

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