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Research Letter

Associations Between Nutrient Intake and Corresponding Nutritional Biomarker Levels in Blood in a Memory Clinic Cohort: The NUDAD Project

To the Editor:

Diet is a promising intervention target to prevent or slow Alzheimer's disease (AD).[1,2] Early (predementia) stages of AD offer a unique opportunity for dietary interventions.[2] Nutritional assessment methods to estimate nutrient intake have, however, not been validated in clinical populations. Hence, we assessed the association between nutrient intake assessed by food frequency questionnaire (FFQ) and nutrient status measured by nutritional biomarkers in blood in a clinical sample of controls, mild cognitive impairment (MCI), and patients with AD.

Methods

From the Nutrition, the Unrecognized Determinant in Alzheimer's Disease (NUDAD) study we included 90 participants: 29 patients with AD, 22 patients with MCI, and 39 individuals with subjective cognitive decline (SCD) who served as controls.[3] All participants completed a FFQ and had at least 1 nutritional biomarker measurement. Written informed consent was obtained from all participants and the local Medical Ethics Committee approved the study.

Usual dietary intake was measured using the semiquantitative 238-item HELIUS FFQ with a reference period of 4 weeks.[4] In addition, participants reported their nutritional supplement use. If the nutrient dosage could not be obtained from participants or the (online) instructions leaflet (n = 11), it was imputed with the nutrient dosage of the most frequently used comparable supplement in this study.

All nutritional biomarker were measured in fasting plasma, serum, or whole blood samples, except for folic acid and vitamin B12, which were measured in nonfasting samples, and vitamin A, which was measured in both fasting (89%) and nonfasting (11%) samples.

To investigate associations of nutrient intake with nutritional biomarker levels, we used linear regression analyses. Furthermore, we assessed whether associations differed per diagnostic group (controls/MCI/AD). Lastly, we performed sensitivity analyses excluding supplement users for each nutrient separately.

Results

Overall, mean age was 67 ± 9 years, 42 (47%) were female, and vitamin and mineral supplement use was observed in 40 (44%) participants.

Table 1 shows the associations between nutrient (diet + supplement) intake and their corresponding nutritional biomarker levels in blood. Intake and blood levels were associated for vitamin B1, vitamin B6, vitamin B12, vitamin C, folate, and eicosapentaenoic acid, and trends were observed for retinol activity equivalents, total omega-3 fatty acids, and docosahexaenoic acid (DHA). No associations were found for zinc.

Subsequently, we evaluated if associations differed per diagnostic group. Interactions ($P < .10$) were found between diagnostic group and nutrient intake for vitamin B6, vitamin C, total omega-3 fatty acids, and DHA. Stratification by diagnostic group showed associations for vitamin B6 in all diagnostic groups [B(SE) controls; 0.78 (0.06), MCI; 1.05 (0.20), AD; 0.45 (0.14), $P < .01$], for omega-3 fatty acids and DHA in controls [B(SE) controls; 0.50 (0.20), $P = .021$, 0.38 (0.13), $P = .009$, MCI; −0.38 (0.30), $P = .230$, −0.13 (0.27), $P = .646$, AD; 0.25 (0.17), $P = .166$, −0.27 (0.25), $P = .285$] and for vitamin C in AD [B(SE) controls; 0.22 (0.15), $P = .152$, MCI; 0.03 (0.27), $P = .927$, AD; 0.75 (0.11), $P < .001$].

Finally, we re-analyzed the data in the total cohort excluding supplement users for each nutrient separately. Associations remained comparable in effect size for most nutrients, but attenuated for DHA, vitamin B1, B6, and B12 [(B(SE) 0.07(0.15), −0.41(0.60), 0.31(0.23), −0.22(0.47), $P > .05$].

Discussion

The main finding of this study is that nutrient intake of omega-3 fatty acids, A, B and C vitamins, as assessed by the HELIUS FFQ and self-reported supplement use, is moderately associated with their corresponding nutritional biomarker levels in a memory-clinic cohort of controls and patients with MCI or AD. Associations were largely similar across diagnostic groups, except for total omega-3 fatty acids and DHA that were only associated in controls, and vitamin C that was only associated in AD. Almost one-half of the participants used nutritional supplements.

In the subgroup of nonsupplement users, associations between nutrient intake and nutritional biomarker levels remained largely comparable to our findings in the total cohort.

Among the strengths of this study is that we used a well characterized, clinical population with different stages of cognitive decline. A potential limitation is that the FFQ used in this study has a reference period of 4 weeks, which is relatively short to assess habitual diet. The burden of memory, however, may be less in comparison to other FFQs that use a reference period up to a year,

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Table 1
Associations between Nutrient Intake and Nutritional Biomarker Levels in Blood

Determinants	Outcome	All		
Nutrient intake	Nutritional biomarker	B(SE)	*P*	n
Retinol activity equivalents, mcg/d	Vitamin A, μmol/L	0.23 (0.12)	.057	87
Vitamin B1*, mg/d	Vitamin B1, nmol/L	0.48 (0.09)	<.001	79
Vitamin B6*, mg/d	Vitamin B6, nmol/L	0.71 (0.07)	<.001	79
Vitamin B12, mcg/d	Vitamin B12, pmol/L	0.35 (0.10)	<.001	77
Vitamin C, mg/d	Vitamin C, μmol/L	0.49 (0.09)	<.001	78
Folate equivalents, mcg/d	Folate, nmol/L	0.49 (0.09)	<.001	77
Zinc, mg/d	Zinc, μmol/L	−0.10 (0.11)	.373	79
Omega-3 fatty acids, % of total fatty acids intake	Omega-3 fatty acids, % of plasma total fatty acids	0.21 (0.12)	.101	79
DHA, % of total fatty acids intake	DHA, % of plasma total fatty acids	0.19 (0.12)	.102	79
EPA, % of total fatty acids intake	EPA, % of plasma total fatty acids	0.41 (0.11)	<.001	79

EPA, eicosapentaenoic acid; *SD*, standard deviation.
The HELIUS FFQ was not designed to measure these nutrients.
Linear regression analyses adjusted for sex, age, diagnosis, and total energy intake were used, using separate models for each nutritional biomarker. Data were log-transformed and converted to z scores before data analysis. Effect size is change of SD nutritional biomarker blood level per 1 SD increase in nutrient intake.

which could be an advantage in a cohort of cognitively impaired individuals. Moreover, most plasma and serum biomarkers reflect relatively short-term intake. Future studies should include nutritional biomarkers in adipose tissue or erythrocytes that assess longer-term intake.[5]

In conclusion, nutrient intake and nutrient status were moderately associated and largely similar across diagnostic groups. Our findings indicate that the HELIUS FFQ provides valid estimates of nutrient intake in a memory-clinic cohort.

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