Alzheimer's & Dementia 13 (2017) 1125-1132

Alzheimer's & Dementia

Featured Article

Nutrient biomarker patterns and long-term risk of dementia in older adults

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Abstract

Introduction: Several nutrients may predict dementia risk. We characterized nutrient biomarker patterns, which integrate the complexity of nutrient exposure and biodisponibility associated with long-term risk of dementia in a large cohort of older persons, the Three-City study.

Methods: We included 666 nondemented participants with plasma measurements of 22 fat-soluble nutrients at baseline, who were followed up for 12 years for dementia.

Results: A "deleterious" pattern combining lower blood status in vitamin D, carotenoids, and polyunsaturated fats and higher saturated fats was strongly associated with a higher risk of dementia. Compared with individuals in the first quintile of the pattern score, participants in the highest quintile of score had an approximately fourfold increased risk of dementia (hazard ratio = 4.53 [95% confidence interval 1.99, 10.32], *P* for trend <.001) in multivariate models.

Discussion: A blood pattern reflecting lower status in several nutrients among nondemented individuals appeared strongly associated with the long-term risk of dementia in this cohort.

Keywords: Primary prevention; Risk factors; Cohort studies; Dementia; Nutrients; Biomarkers

1. Introduction

Nutrition may represent a promising strategy for lifestyle-based preventive interventions against dementia and Alzheimer's disease (AD) [1]. Preclinical studies have established a protective effect of several individual nutrients on brain health, in particular fat-soluble nutrients including omega-3 polyunsaturated fatty acids (n-3 PUFAs), carotenoids, vitamin E, and vitamin D. Long-chain n-3 PUFAs, mainly provided by fish intake, have important structural and functional roles in neuronal membranes [2]. Carotenoids are found in colored fruits and vegetable; they are precursors of retinoids, key signaling molecules for synaptic plasticity [3]. Vitamin E, provided by seed oils and nuts, represents the major lipid-soluble antioxidant found in cells; the main function of vitamin E is to prevent the peroxidation of membrane phospholipids [4]. Vitamin D, which results from endogenous synthesis after sun exposure and to a lower extent from intake of animal products including fatty fish, eggs, and dairies, has a major role in brain development, maturation, and functioning (vitamin D receptors are present in several brain areas) [5]. Furthermore, all these fat-soluble nutrients possess potential antiamyloid effects [4] and potent anti-inflammatory and/or antioxidant properties [6], which may help lower neuroinflammation and oxidative stress associated with dementia and AD. Epidemiologic studies have found associations between higher intakes/blood levels of long-chain n-3 PUFAs, carotenoids, vitamins E, and vitamin D, and a lower risk of dementia-related outcomes [7–10]. However, inconsistent findings have also been reported [11–15], and clinical trials that have tested supplementation of individual nutrients (mostly of vitamin E and n-3 PUFAs) generally failed to demonstrate any clinical efficacy on cognition in humans [16–19].

Individual nutrients taken in isolation may not be sufficiently powerful to protect the brain of older adults, and

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http://dx.doi.org/10.1016/j.jalz.2017.01.025

global approaches of diet may be more promising [20,21]. Nutrient biomarker patterns, which better take into account the complexity of nutritional exposures, may be even more relevant to dementia risk. Compared with patterns based on intakes ascertained through questionnaires, blood patterns may be less prone to measurement error and may reflect "true" biological exposure accounting for individual variations in bioavailability and metabolism. Yet, limited cross-sectional research has explored nutrient patterns (mostly from dietary questionnaires) and brain health. A pattern characterized by higher intakes of vitamin B12, vitamin D, and zinc was associated with lower AD biomarkers [22]. Another study related a pattern rich in PUFAs and vitamin E to preserved white matter integrity [23]. Moreover, higher plasma levels of vitamins B, C, D, and E were associated with better global cognitive function, whereas profiles reflecting higher n-3 PUFAs were associated with better executive function [24].

Our objective was to characterize nutrient biomarker patterns (based on plasma measurements of 22 candidate fat-soluble nutrients including 12 fatty acids, six carotenoids, 25-hydroxy vitamin D [25(OH)D], α and γ tocopherols [i.e., two main forms of vitamin E], and retinol [i.e., vitamin A]) associated with the long-term risk of dementia in a large cohort of older subjects, the Three-City (3C) study.

2. Methods

2.1. Study population

The 3C study is a French prospective cohort initiated in 1999 to 2000 to study vascular risk factors for dementia, including 9294 noninstitutionalized community dwellers aged ≥65 years from three French cities: Bordeaux (n = 2104), Dijon (n = 4931), and Montpellier (n = 2259) [25]. The protocol of 3C was approved by the Consultative Committee for the Protection of Persons participating in Biomedical Research at Kremlin-Bicêtre University Hospital, Paris, France, and all participants provided written informed consent. The baseline data collection recorded during in-person interviews included sociodemographic and lifestyle characteristics, symptoms and complaints, main chronic conditions, medication use, and a battery of neuropsychological tests. Furthermore, anthropometric and blood pressure measurements and fasting blood samples were collected. Five follow-up examinations were performed 2, 4, 7, 10, and 12 years after baseline examination.

In Bordeaux, a comprehensive, in-person nutritional survey was conducted in 2001 to 2002 by trained dieticians among 1811 participants. Furthermore, nutrient biomarkers were determined in subsamples using the blood biobank constituted at baseline. Of the 674 participants with measurements of all candidate nutrients, none was demented at baseline, and all were followed at least once for cognition and dementia. Among them, we excluded eight participants with missing data for the main covariates (age, gender, level of education, apolipoprotein E ε4 genotype [*APOE* ε4], and blood lipid levels). Our study sample thus included 666 participants from 3C Bordeaux free of dementia at baseline (Fig. 1). Among them, 98 participants deceased between baseline and the last visit in 2011 to 2012.

2.2. Diagnosis of dementia

The diagnosis of dementia was based on a three-step procedure [25]. Trained psychologists administered a battery of neuropsychological tests at baseline and at each follow-up visit. The participants who were suspected of dementia based on their neuropsychological performances were secondarily examined by a neurologist to establish a diagnosis. Finally, an independent committee of neurologists examined all potential cases of dementia to obtain a consensus on the diagnosis and etiology, based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition [26]. Dementia cases were classified as probable or possible AD according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association. No one involved in the diagnosis of dementia had access to fat-soluble nutrient assessment at any time during the study.

2.3. Assessment of plasma nutrient biomarkers

Fasting serum, plasma, and DNA samples collected at baseline were stored at −80°C in a biobank. The concentrations of 22 fat-soluble nutrients of interest were determined in total plasma, using methodologies described in details in previous publications [8,27,28]. Briefly, we determined 12 plasma fatty acids using gas chromatography, with concentrations expressed in percentage of total fatty acids. The six major carotenoid species found in human diet (α carotene, β

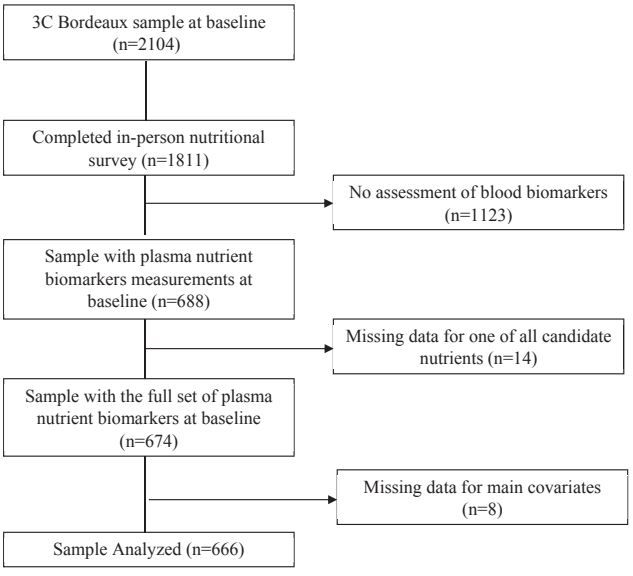

Fig. 1. Flow chart of the study sample in the Three-City study, Bordeaux.