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Mediterranean diet and preserved brain structural connectivity in older subjects

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Abstract

Introduction: The Mediterranean diet (MeDi) has been related to a lower risk of Alzheimer's disease; yet, the underlying mechanisms are unknown. We hypothesized that protection against neurodegeneration would translate into higher gray matter volumes, whereas a specific association with preserved white matter microstructure would suggest alternative mechanisms (e.g., vascular pathways).

Methods: We included 146 participants from the Bordeaux Three-City study nondemented when they completed a dietary questionnaire and who underwent a 3-T magnetic resonance imaging at an average of 9 years later, including diffusion tensor imaging.

Results: In multivariate voxel-by-voxel analyses, adherence to the MeDi was significantly associated with preserved white matter microstructure in extensive areas, a gain in structural connectivity that was related to strong cognitive benefits. In contrast, we found no relation with gray matter volumes.

Discussion: The MeDi appears to benefit brain health through preservation of structural connectivity. Potential mediation by a favorable impact on brain vasculature deserves further research.

Keywords: Neuroimaging; Diffusion tensor imaging; Voxel-based morphometry; Mediterranean diet; Prospective studies; Risk factors in epidemiology

1. Introduction

The traditional Mediterranean diet (MeDi) is characterized by an abundant consumption of plant foods, a moderate intake of fish and alcohol, and low intakes of meats and dairy products, with monounsaturated fatty acids as the main fat source provided by olive oil. The beneficial effect of the MeDi on cardiovascular mortality is well established [1]. Adherence to the MeDi has also been associated with a lower risks of Alzheimer's disease (AD) dementia and cognitive

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decline [2–5], stroke, and depression [6], which all appear to have a strong vascular component [7–9]. The protective effect of the MeDi on stroke was confirmed in a large intervention study [10], and the MeDi was related to less cerebral infarcts at magnetic resonance imaging (MRI) [11]. However, mediation by vascular comorbidities was not evidenced in studies of dementia or cognitive decline [4,12], suggesting that nonvascular mechanisms (e.g., neurodegenerative pathways) may also be involved. Hence, more research is needed to elucidate the neurobiological basis of the relation of the MeDi to brain health.

Examining how the MeDi relates to the preservation of brain structure (i.e., gray matter [GM] volume and white matter [WM] connectivity) is critical to understand these pathways. Indeed, on the one hand cerebrovascular disease has been associated with alterations of WM microstructure [13,14], which may start decades before brain ischemic injury visible at MRI [15], and on the other hand GM atrophy in the medial temporal lobe is a typical early feature of AD [16]. Hence, we hypothesized that an association of the MeDi with higher GM volumes in AD regions may indicate involvement of neurodegenerative mechanisms and that a specific relationship with preserved WM microstructure (with no relation to GM volumes) would be suggestive of mechanisms partly independent of AD-related neurodegeneration, including possibly vascular pathways. Our objective was to examine the association between higher adherence to the MeDi and preserved brain GM volume and WM microstructure at an average of 9 years later, in older individuals from the Three-City (3C) study.

2. Methods

2.1. Study population

The 3C study is a prospective cohort initiated in 1999–2000 with the objective to study vascular risk factors of dementia. In total, 9294 noninstitutionalized community dwellers aged ≥65 years were included in three French cities (Bordeaux [N = 2104], Dijon [N = 4931], and Montpellier [N = 2259]) [17]. The protocol of 3C study 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. Data collected at baseline included sociodemographic and lifestyle information, symptoms and medical complaints, blood pressure and anthropometric measurements, and neuropsychological testing and a blood biobank. Five follow-up examinations were performed at 2, 4, 7, 10, and 12 years after baseline examination. At each visit, all potential dementia cases were identified based on their neuropsychological performances and reviewed by an independent committee of neurologists to obtain a consensus on its diagnosis and etiology according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition* [18].

In 2001–2002, a comprehensive dietary survey was conducted among 1811 participants in Bordeaux (94% of those still alive included at baseline), of whom 1712 had no missing dietary data. We excluded 31 individuals with dementia at the time of dietary assessment. Of the 1681 remaining nondemented individuals, 351 died and 1044 were reexamined at the 10-year follow-up visit in 2010–2011 (Supplementary Fig. 1). Among them, 225 participants were invited to an MRI examination using a 3-T machine, allowing accurate investigation of WM microstructure through diffusion tensor imaging (DTI; We primarily selected participants included in a previous MRI substudy and enriched our sample with individuals with cognitive deficits suggestive of dementia at the 10-year visit; to ensure that such selection of "at risk" participants did not bias results, we conducted sensitivity analyses, as detailed in the "Methods" Section 2.6.3 subsequently). The present study is based on the 146 Bordeaux 3C study nondemented participants who provided information on their diet in 2001–2002, underwent brain MRI in 2010–2011 including DTI, were free of tumor or major cerebrovascular pathologies at MRI, and had no missing data for main potential confounders.

2.2. Dietary assessment and the MeDi score

The dietary survey was conducted at home by a specifically trained dietician who administered a food frequency questionnaire (FFQ) and a 24-hour dietary recall [19,20]. Data from these questionnaires were validated in an independent 3C study subsample [21]. In the FFQ, frequency of consumption of 148 foods and beverages was recorded in 11 classes, converted into a number of servings per week, and then aggregated into 20 food per beverage groups, as detailed previously [19]. The groups considered to be a part of a MeDi were identified: vegetables; fruits; legumes; cereals including bread, pasta, and rice; fish; meats; dairy products; and alcohol. The 24-hour recall was used to estimate nutrient and total energy intake and the ratio of monounsaturated-to-saturated fatty acids.

We computed a MeDi 9-point score [4] based on the original score as described by Trichopoulou et al. [22], which included nine components. For components supposed to be beneficial to health (vegetables, fruits, legumes, cereals, fish, and a higher monounsaturated-to-saturated fatty acid ratio), 1 point was given if individual consumption was greater than the sex-specific median in our population and 0, otherwise. For alcohol, of which "moderate" consumption is considered beneficial, 1 point was given for consumption between 4 and 15 glasses/wk in men and 0 and 2 glasses in women (i.e., the second quartile of intake in our population). For components hypothesized to be detrimental (i.e., meats and dairy products), 1 point was given for a consumption less than the sex-specific median and 0, otherwise. A