NUTRIENT PATTERNS AND BRAIN BIOMARKERS OF ALZHEIMER’S DISEASE IN COGNITIVELY NORMAL INDIVIDUALS

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Abstract: Objectives: Epidemiological evidence linking diet, one of the most important modifiable lifestyle factors, and risk of Alzheimer’s disease (AD) is rapidly increasing. However, there is little or no evidence for a direct association between dietary nutrients and brain biomarkers of AD. This study identifies nutrient patterns associated with major brain AD biomarkers in a cohort of clinically and cognitively normal (NL) individuals at risk for AD. Design: Cross-sectional study. Setting: Manhattan (broader area). Participants: Fifty-two NL individuals (age 54±12 y, 70% women, Clinical Dementia Rating=0, MMSE>27, neuropsychological test performance within norms by age and education) with complete dietary information and cross-sectional, 3D T1-weighted Magnetic Resonance Imaging (MRI; gray matter volumes, GMV, a marker of brain atrophy), 11C-Pittsburgh compound-B (PiB; a marker of fibrillar amyloid-β, Aβ) and 18F-fluorodeoxyglucose (FDG; a marker of glucose metabolism, METglc) Positron Emission Tomography (PET) scans were examined. Measurements: Dietary intake of 35 nutrients associated with cognitive function and AD was assessed using the Harvard/Willet Food Frequency Questionnaire. Principal component analysis was used to generate nutrient patterns (NP) from the full nutrient panel. Statistical parametric mapping and voxel based morphometry were used to assess the associations of the identified NPs with AD biomarkers. Results: None of the participants were diabetics, smokers, or met criteria for obesity. Five NPs were identified: NP1 was characterized by most B-vitamins and several minerals [VitB&Minerals]; NP2 by monounsaturated and polyunsaturated fats, including ω-3 and ω-6 PUFA, and vitamin E [VitE&PUFA]; NP3 by vitamin A, vitamin C, carotenoids and dietary fibers [Anti-oxidants&Fibers]; NP4 by vitamin B12, vitamin D and zinc [VitB12&D]; NP5 by saturated, trans-saturated fats, cholesterol and sodium [Fats]. Voxel-based analysis showed that NP4 scores [VitB12&D] were positively associated with METglc and GMV, and negatively associated with PiB retention in AD-vulnerable regions (p<0.001). In addition, both METglc and GMV were positively associated with NP2 scores [VitE&PUFA], and negatively associated with NP5 scores [Fats] (p<0.001), and METglc was positively associated with higher NP3 scores [Anti-oxidants&Fibers] (p<0.001). Adjusting for age, gender, ethnicity, education, caloric intake, BMI, alcohol consumption, family history and Apolipoprotein E (APOE) status did not attenuate these relationships. The identified ‘AD-protective’ nutrient combination was associated with higher intake of fresh fruit and vegetables, whole grains, fish and low-fat dairies, and lower intake of sweets, fried potatoes, high-fat dairies, processed meat and butter. Conclusion: Specific dietary NPs are associated with brain biomarkers of AD in NL individuals, suggesting that dietary interventions may play a role in the prevention of AD by modulating AD-risk through its effects on Aβ and associated neuronal impairment.

Key words: Alzheimer’s disease, nutrition, aging, Positron Emission Tomography (PET), Magnetic Resonance Imaging (MRI).

Introduction

There is increasing evidence to suggest that diet, one of the most important modifiable lifestyle factors, may play a role in preventing or delaying cognitive decline and Alzheimer’s disease (AD), a major public health problem (1–7). AD is the most common cause of dementia and is associated with presence of amyloid-beta (Aβ) plaques, neurofibrillary tangles and neuronal loss. As pharmacological treatments for AD are limited, there is a growing interest in understanding how diet could mitigate AD risk and progression (8, 9). Despite studies showing protective effects of several nutrients against AD, the overall picture remains equivocal (10). These studies would greatly benefit from biomarkers for early AD pathology and associated neuronal injury, which are needed to assess the impact of diet on brain health and to monitor treatment efficacy (10), especially during the recently conceptualized preclinical period of AD (11). In vivo biomarkers are needed to clarify how nutrition promotes healthy brain aging (10), and can therefore be protective against AD, which is critical prior to implementing dietary recommendations for prevention and treatment.

There are very few studies that examined the relationships between dietary nutrients and brain biomarkers of AD in cognitively normal (NL) individuals. A few Magnetic Resonance Imaging (MRI) studies investigated the relationship between ω3 polyunsaturated fatty acids (PUFA) and brain volumes in non-demented elderly, and showed a correlation between higher baseline ω3-PUFA levels and lower atrophy rates over time (12-14). However, according to current
hypothetical models of AD progression, structural MRI changes are secondary to Aβ deposition and neuronal hypometabolism (11), and previous studies included only individuals of age >65 y. To our knowledge, there are no published studies that examined the the associations of dietary nutrients with brain Abeta and metabolic activity in NL individuals.

The goal of this study was to examine the relationships between dietary nutrient patterns (NPs) and three major AD-biomarkers: brain Aβ load (i.e., a hallmark of AD pathology) assessed using 11C-Pittsburgh Compound-B (PiB) Positron Emission Tomography (PET), glucose metabolism (METglc, i.e. a proxy for neuronal activity) assessed using 18F-fluorodeoxyglucose (FDG) PET, and gray matter volumes (GMV, a marker of brain atrophy) on MRI in a cohort of young to late middle aged NL individuals. Using these imaging techniques, several studies have shown preclinical biomarker abnormalities in non-demented individuals several years, if not decades, prior to AD symptoms (11).

Given the interactive nature of nutrient action and metabolism, in this study we used principal component analysis (PCA) to generate NPs from a panel of 35 nutrients which have been related to AD or cognitive function or which are known to interact with those AD-related nutrients. NPs are advantageous as they capture the interactive effect of nutrients in combination (15-17). The present multi-modality brain imaging study uses voxel-based analysis techniques such as Statistical Parametric Mapping and Voxel-Based Morphometry to simultaneously examine Aβ deposition, METglc and GMV to define which NPs are protective against AD (as reflected in lower brain Aβ, higher metabolic activity and larger GMV among NL individuals, controlling for AD-risk factors such as age, gender, education, ethnicity, BMI, alcohol consumption, family history of AD, and Apolipoprotein E (APOE) genotype.

Methods

Participants

Among a larger pool of clinically and cognitively normal (NL) individuals participating in longitudinal brain imaging studies at New York University (NYU) Langone School of Medicine, this study focused a sub-set of 65 NL participants who were invited to participate in a lifestyle survey between 2013-2014. This study examined 52 participants who completed all clinical, MRI, PiB- and FDG-PET exams and dietary questionnaires within 6 months of each other. Of the remaining 13 subjects, 9 did not receive either the PiB or the FDG scan, and 4 returned only partially completed dietary questionnaires and were excluded from this examination. Subjects were derived from multiple community sources, including individuals interested in research participation, family members and caregivers of impaired patients. Informed consent was obtained from all subjects for participation in this NYU institutional review board-approved study.

Individuals with medical conditions or history of conditions that may affect brain structure or function, i.e. stroke, diabetes, head trauma, any neurodegenerative diseases, depression, hydrocephalus, intracranial mass, and infarcts on MRI, and those taking psychoactive medications were excluded. Subjects were 25-72 y of age, with education>12 y, Clinical Dementia Rating (CDR)=0, Global Deterioration Scale (GDS)<2, Mini Mental State Examination (MMSE)>28, Hamilton depression scale<16, Modified Hachinski Ischemia Scale<4 and normal cognitive test performance for age and education (18). A family history of late-onset AD that included at least one 1st degree relative whose AD onset was after age 60 was elicited using standardized questionnaires (18-20). APOE genotypes were determined using Polymerase Chain Reaction (PCR) using standardized protocols (21).

Dietary assessments

Dietary data regarding average food consumption over the prior year were obtained using the 116-item version of Harvard/Willett’s semi-quantitative food frequency questionnaire (SFFQ) (22, 23). Trained interviewers administered the SFFQ in English. The SFFQ has been validated for determination of nutrient intake in the elderly and young adults (22, 23) and against plasma measurements (24-26). The validity (using two 7-day food records) and reliability (using two 3-month frequency assessments) of various components of the SFFQ was replicated by several studies (3, 4, 27, 28). The food items were categorized into 30 food groups based on similarities in food and nutrient composition, and intake (g/day) of each food group was calculated by summing the intakes of member food items. The daily intake of nutrients from food sources was computed by multiplying the consumption frequency of each portion of every food by the nutrient content of the specified portion (22). The daily total caloric intake (kilocalories) was included as a confound.

A panel of 35 nutrients that have been associated with cognitive function and AD was examined, including fats: monounsaturated fatty acid (MUFA), ω-3 polyunsaturated fatty acid (PUFA), ω-6 PUFA, other PUFA, saturated fatty acid (SFA), trans-saturated fats and cholesterol (6, 29-34); vitamins and precursors: α- and β-carotene, β-cryptoxanthin, β- γ- and δ-tocopherol, vitamin A, B vitamins including B1, B2, B3, B6, B9 (folate) and B12, vitamin C, vitamin D, vitamin E, lycopene, lutein and zeaxanthin (7, 27, 35-41); minerals: calcium, copper, iron, magnesium, phosphorus, potassium, selenium, and zinc (8, 42); and dietary fibers (43). As moderate alcohol drinking may be protective against dementia (28), alcohol intake (g/day) was also calculated.

Brain imaging

All subjects received volumetric 1.5 T MRI (124 slice T1-weighted Fast-Gradient-Echo, 1.2 mm sections, no interslice gaps), PiB- and FDG-PET scans following standardized procedures (18-20, 44, 45). For PET, subjects were positioned in the scanner 60 min after injection of 15