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Original article

Dietary pattern, inflammation and cognitive decline: The Whitehall II prospective cohort study

Mio Ozawa [a,*], Martin Shipley [a], Mika Kivimaki [a], Archana Singh-Manoux [a,b], Eric J. Brunner [a]

[a] Department of Epidemiology and Public Health, University College London, London, UK
[b] INSERM, U1018, Centre for Research in Epidemiology and Population Health, Villejuif, France

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SUMMARY

Background & aims: Low-grade inflammation appears to play an etiological role in cognitive decline. However the association between an inflammatory dietary pattern and cognitive decline has not been investigated. We aimed to investigate dietary patterns associated with inflammation and whether such diet is associated with cognitive decline.

Methods: We analyzed 5083 participants (28.7% women) from the Whitehall II cohort study. Diet and serum interleukin-6 (IL-6) were assessed in 1991–1993 and 1997–1999. We used reduced rank regression methods to determine a dietary pattern associated with elevated IL-6. Cognitive tests were performed in 1997–1999 and repeated in 2002–2004 and 2007–2009. The association between dietary pattern and cognitive decline between ages 45 and 79 was assessed using linear mixed models.

Results: We identified an inflammatory dietary pattern characterized by higher intake of red meat, processed meat, peas and legumes, and fried food, and lower intake of whole grains which correlated with elevated IL-6 both in 1991–1993 and 1997–1999. A greater decline in reasoning was seen in participants in the highest tertile of adherence to the inflammatory dietary pattern (−0.37 SD; 95% confidence interval [CI] −0.40, −0.34) compared to those in the lowest tertile (−0.31; 95% CI −0.34, −0.28) after adjustment for age, sex, ethnicity, occupational status, education, and total energy intake (p for interaction across tertiles = 0.01). This association remained significant after multivariable adjustment. Similarly for global cognition, the inflammatory dietary pattern was associated with faster cognitive decline after multivariable adjustment (p for interaction across tertiles = 0.04). Associations were stronger in younger participants (<56 years), reducing the possibility of reverse causation.

Conclusions: Our study found that a dietary pattern characterized as higher intake of red and processed meat, peas, legumes and fried food, and lower intake of whole grains was associated with higher inflammatory markers and accelerated cognitive decline at older ages. This supports the case for further research.

1. Introduction

The number of people with dementia worldwide was estimated at 35.6 million in 2010. It is predicted to reach 65.7 million in 2030, and 115.4 million in 2050 [1]. When symptoms of neurodegeneration appear, changes in the brain have already started and it may be too late to take steps to prevent or delay disease onset. Therefore, it is important to identify potential early interventions. Success in this objective would reduce dementia prevalence and increase the proportion of older people able to live independently in the community.

Inflammation has been recognized as a risk factor for age-related neurodegenerative diseases including cognitive impairment, Alzheimer's disease, and vascular dementia [2,3]. In epidemiological studies higher levels of circulating inflammatory markers, especially interleukin-6 (IL-6) are associated with greater cognitive decline [4,5]. Diet influences the function of immune

Abbreviation: IDP, inflammatory diet pattern.

* Corresponding author. Department of Epidemiology and Public Health, University College London, 1 – 19 Torrington Place, London WC1E 6BT, UK. Tel.: +44 (0) 20 7679 1680; fax: +44 (0)20 3108 3354.

E-mail addresses: mio.ozawa@ucl.ac.uk (M. Ozawa), martin.shipley@ucl.ac.uk (M. Shipley), m.kivimaki@ucl.ac.uk (M. Kivimaki), a.singh-manoux@ucl.ac.uk (A. Singh-Manoux), e.brunner@ucl.ac.uk (E.J. Brunner).

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systems. High consumption of vegetables and fruit or a diet rich in antioxidants, for example, has been shown to reduce systemic inflammation [6]. In contrast, dietary patterns characterized by higher intakes of red and processed meats, sweets, desserts, french fries, and refined grains, appear to increase inflammation [7]. The role of diet as a determinant of age-related cognitive decline and dementia however remains uncertain.

A recent randomized controlled trial showed improved or maintained cognitive function in the intervention group (diet, exercise, cognitive training and vascular risk monitoring), compared to the control group [8]. This finding is encouraging but because the trial involved a multi-factorial intervention, the contribution of the dietary component is indeterminate. Observational studies suggest that a Mediterranean-type dietary pattern confers advantage but, as in the trial, the active ingredients and mechanisms responsible for cognitive protection across the spectrum of severity remain unknown [9].

In this study, our aim was to examine the associations of diet pattern with inflammatory markers and changes in cognitive function within a single analytic setting. We hypothesized that a dietary pattern related to increased IL-6 concentration in midlife predicts accelerated cognitive decline in a large sample of middle-aged population.

2. Materials and methods

2.1. Study populations

The Whitehall II cohort is an ongoing study established in 1985 among 10,308 (67% men) British civil servants. The detail of the cohort and follow-up has been described previously [10]. Briefly, all participants aged 35–55 years in 20 Civil Service departments in London, UK, were invited to participate in this study. Of those invited, 73% participants agreed to participate in the baseline survey which involved a clinical examination and self-administered questionnaire. Subsequent follow-up clinical examinations have taken place in 1991–1993 (phase 3), 1997–1999 (phase 5), 2002–2004 (phase 7), and 2007–2009 (phase 9).

2.2. Cognitive function measurement

3 clinical examinations over 10 years were administered for the cognitive test battery (in 1997–1999, 2002–2004, and 2007–2009), and consisted of 4 standard tasks: Alice Heim 4-I, short-term verbal memory, phonemic fluency, and semantic fluency [11]. The Alice Heim 4-I is consisted of a series of 65 verbal and mathematical reasoning items of increasing difficulty [12]. It tests inductive reasoning, measuring the ability to identify patterns, and to infer principles and rules. 10 min were given to do this section. Short term verbal memory was assessed with a 20 word free recall test. Participants listened to a list of 20 single- or double-syllable words at 2 s intervals and then had to recall and write them down in 2 min. We used two measures of verbal fluency: phonemic and semantic fluency [13]. Participants were asked to recall in writing as many ‘S’ words and as many animal names as they could in 1 min. Global cognitive score was created to provide a summary score of these 3 tests by taking a mean of the z scores of each test. This method has been shown to minimize problems due to measurement error on the individual tests [14]. The Mini-Mental State Examination (MMSE) was administered in 2002–2004 and 2007–2009. MMSE is a measure of global cognitive function with a 30-point range.

2.3. Nutritional survey

Dietary intake was assessed by using a 127-item food frequency questionnaire. The validation of this questionnaire with 7-day diary has been reported previously [15]. For each of the food items, participants self-reported how often on average they had consumed a common unit or portion size in 1 of 9 categories during the previous year. To reduce misclassification, we used the data collected in 1991–1993 and 1997–1999, and calculated the average intake of each food and nutrient. Each food group was adjusted for energy intake using the density method.

2.4. Inflammatory markers

In 1991–1993 and 1997–1999, fasting serum was collected between 8 AM and 1 PM and stored at −80 °C. IL-6 was measured with a high-sensitivity ELISA (R&D Systems, Oxford, UK). Values lower than the detection limit (0.08 pg/mL) were set to half the detection limit.

2.5. Covariates

Demographic variables included age, sex, ethnicity, education, and total energy intake. Health related variables included body mass index (kg/m2), diabetes mellitus, hypertension, smoking, and leisure time physical activity. Ethnicity (white, south-Asian, black, other), occupational position (6 levels), education (less than primary school, lower secondary school, higher secondary school, university, and higher university degree), smoking history (never, ex-smoker, or current), and leisure time physical activity (physically active corresponds to more than 2.5 h/wk of moderate physical activity or more than 1/wk of vigorous physical activity) were based on self-report. Body weight and height were measured, dressed in a cloth gown and underclothes, in standardized fashion and body mass index (kg/m2) was calculated. Diabetes mellitus was defined by fasting glucose ≥7.0 mmol/L or a 2 h post load glucose ≥11.1 mmol/L, self-reported physician-diagnosed diabetes, or use of diabetes medication. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or use of antihypertensive drugs. Since alcohol consumption was included as one of the food components in our dietary pattern, we did not include alcohol in covariates.

2.6. Statistical analysis

The dietary pattern associated with cognitive decline was assessed using reduced rank regression [16]. This method identifies linear functions of food groups, i.e. the dietary pattern, to maximize explained variation in one or more intermediate response variables. We selected serum IL-6 measurements in 1991–1993 and 1997–1999 as response variables on the basis of the known direct association of circulating IL-6 level with cognitive decline in our study and others [4,5]. The dietary pattern related to IL-6 level was derived based on 37 predefined food groups [17]. The scores for dietary pattern were categorized in tertiles.

A linear mixed model was used to estimate the association between dietary pattern and cognitive decline over 10 years [18]. This method uses all available data over the 10 years of follow up, including participants with an incomplete set of values for cognitive tests, and takes into account the correlation of the repeated measurements on the same individual. In our analyses, age in years was used as the time variable. We included intercept and slope as random effects to allow individuals to have a different cognitive function score at baseline and different rate of cognitive decline during follow-up. Analyses were adjusted for demographic