

Food group intake and brain lesions in late-life vascular depression

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ABSTRACT

Background: Studies indicate that diet may be related to the occurrence of brain lesions. The cross-sectional association between food intake and brain lesion volumes in late-life depression was examined in a cohort of elderly individuals with current or prior depression.

Methods: Food intake was assessed in 54 elderly vascular depression subjects (vascular depression defined by presence of hyperintensities on brain MRI) using a Block 1998 food frequency questionnaire. Food and kilocalorie intake were determined. Brain lesion volumes were calculated from MRI. Subjects were aged 60 or over and were participants in a longitudinal study of major depression. All subjects received psychiatric assessment and treatment, and medical comorbidity assessments.

Results: High-fat dairy and whole grains were significantly positively correlated with brain lesion volume, while other food groups were not significantly associated with lesion volume. In multivariable analyses, controlling for age, sex, hypertension, diabetes and total kilocalories, the positive association with lesion volume remained significant for both high-fat dairy and whole grains.

Conclusions: High fat dairy and whole grain consumption may be associated with brain lesions in elderly subjects with depression.

Key words: diet, elderly, hyperintensities, MRI, dairy

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Introduction

In the etiology of late-life depression, biological and neurological changes figure at least as prominently as genetic and psychosocial factors, in contrast to early-life depression (Krishnan *et al.*, 1997). Brain lesions seen on magnetic resonance imaging (MRI) are indicative of damage to gray and white matter and are more common among those with late-life depression than those with early-life depression (Baldwin and Tomenson, 1995). “Vascular depression” is depression that is characterized by these brain lesions (Alexopoulos *et al.*, 1997; Krishnan *et al.*, 1997) which are associated with both the persistence and worsening of depressive symptoms (Steffens *et al.*, 1999; 2002). Research into the causes of these brain lesions is critical to understanding the occurrence, course and outcomes of late-life depression.

Postmortem histopathological studies of depressed subjects have found that white matter lesions are ischemic based upon evidence of increased macrophage and microglial activity, and astrogliosis (Thomas *et al.*, 2002). Intake of foods known to affect vascular disease are likely to be associated with these ischemic lesions, although few studies have examined this question. In the Nurses’ Health Study and Health Professionals’ Follow-up Study, fruit and vegetable intake was found to be protective for ischemic stroke (Joshi *et al.*, 1999). In terms of specific nutrients, serum vitamin E (or α -tocopherol) and lycopene (an antioxidant carotenoid) were found to be negatively correlated with white matter hyperintensities on MRI in 355 elderly participants of the Austrian Stroke Prevention Study (Schmidt *et al.*, 1996). These findings suggest that fruit, vegetable and whole-grain consumption may be protective for ischemic brain lesions.

Numerous studies have investigated the relationship between nutritional factors and mood; however, few have examined depression in the elderly and even fewer of the depression studies have focused on factors known to affect vascular disease. In a previous study, we reported that elderly depressed individuals were more likely than never-depressed comparison subjects to consume a diet high in saturated fat and cholesterol, while having a higher body mass index (BMI) (Payne *et al.*, 2006).

The present study was conducted in a group of geriatric individuals with depression. The goal was to determine whether certain food groups were associated with the size of brain lesions among these subjects. We predicted that the reported intakes of potentially damaging foods, such as meats and high-fat dairy products, would be positively correlated with brain lesion volume. Potentially protective foods, such as fruits, vegetables, whole grains, and low-fat dairy products, were predicted to be negatively associated with brain lesion volume.

Methods

Design

This cross-sectional project occurred within a larger longitudinal clinical study of depression in older adults (Longitudinal Study of Depression in Later Life and the Conte Center for the Neuroscience of Depression).

Sample

The sample included patients of the Duke University Psychiatric Service with a primary diagnosis of major depression at study baseline. Enrollment was restricted to those aged 60 years or older, and those who could speak and write English. Only vascular depression subjects (defined by MRI, see below) were included in analyses for this paper.

Exclusion criteria included a concurrent diagnosis of a major psychiatric or neurological illness, significant cognitive impairment (as indicated by a Mini-mental State Examination score of less than 24 out of 30), and metal in body (contra-indicated for MRI). In addition, those with severe depression symptomatology were excluded because of concerns about subject burden. This criterion did not require a specific depression rating cut-off but was instead determined by the treating psychiatrist on a case-by-case basis.

After complete description of the study to the subjects, written informed consent was obtained. This research protocol has been reviewed and approved by the Duke University Medical Center Institutional Review Board.

Treatment

Depression subjects received individualized treatment from a psychiatrist. Most received antidepressant medication; some received electroconvulsive treatment or psychotherapy.

Measures

Assessments included psychiatric, medical, nutrition and imaging measures. At baseline and yearly thereafter a trained interviewer administered the Duke Depression Evaluation Schedule (DDES) (Landerman *et al.*, 1989) in person to each subject. The DDES, a composite diagnostic interview instrument, included sections of the NIMH Diagnostic Interview Schedule which assesses depression, and was enriched with items on physical health (Robins *et al.*, 1981). Clinical assessments, including the Montgomery-Asberg Depression Rating (MADRS), were performed at study baseline and quarterly thereafter (Montgomery and Åsberg, 1979). Nutrition assessments were administered annually. Brain MRI was performed every two years, starting at study baseline.

Nutrition protocol

The 1998 Block Food Frequency Questionnaire (FFQ), which estimates the components of a person's total dietary intake over the preceding year, was used for nutrition assessment. It has been validated against and shows moderate correlation with other nutrition assessment instruments (Subar *et al.*, 2001). The Block FFQ is a semi-quantitative assessment in that the respondent is asked to estimate both the frequency of consumption of listed food items and the typical serving size of that food.

Returned questionnaires were checked for completeness and rejected if more than 15 food items were skipped. Automated FFQ results included the following dietary variables: energy and servings per day of fruits, vegetables and whole grains. In addition, servings per day of high and low-fat dairy products and meats were calculated from individual food items on the FFQ. The meat estimate included only mammalian and poultry sources. This measure of meat consumption differs from that typically estimated using the U.S. Department of Agriculture Food Guide Pyramid which incorporates other non-dairy concentrated protein sources, such as eggs, peanut butter, beans and seafood.

Magnetic resonance imaging (MRI)

Subjects were imaged with a 1.5 Tesla whole-body MRI system (Signa, GE Medical Systems, Milwaukee, WI) under an IRB-approved protocol. The pulse sequence parameters have been described previously (Payne *et al.*, 2002). The MR images were analyzed for lesion volumes by the Neuropsychiatric Imaging Research Laboratory (NIRL). In addition, the scans were qualitatively assessed for the presence of lesions by a neuroradiologist.

LESION ASSESSMENT (QUALITATIVE)

Both T1- and T2-weighted pulse sequences were visually examined for incidental findings and lesion ratings. Lesion ratings performed for this study have been described previously (Payne *et al.*, 2002). Ratings included the following Coffey scale items:

Deep white matter hyperintensity (lesion-intense regions within the white matter tracts of cerebrum): 0 = absent; 1 = punctate foci; 2 = beginning confluence of foci; 3 = large confluent areas

Subcortical gray matter hyperintensity (lesion-intense regions within the basal ganglia and other subcortical gray matter structures): 0 = absent; 1 = punctate; 2 = multi-punctate; 3 = diffuse

Subjects who received a rating of 2 or higher on either subcortical gray or deep white lesions were categorized as having vascular depression (Krishnan *et al.*, 1997); otherwise, they were categorized as having non-vascular depression and excluded from analyses for this paper. Depression subtype was defined by baseline MRI, if possible.

QUANTITATIVE BRAIN ASSESSMENTS (INCLUDING LESION VOLUMES)

A dual-echo fast spin-echo axial acquisition was used for volumetric measurement of brain structures, including gray and white matter lesions. NIRS image processing procedures have been described previously (Payne *et al.*, 2002). The method is a supervised, semi-automated method that uses the multiple MR contrasts available to identify different tissue classifications through a “seeding” process wherein a trained analyst manually selects pixels in each tissue type that are to be identified (such as gray matter, white matter, cerebrospinal fluid, lesions, background). Gray and white matter lesion areas were selected based upon a set of rules that allow trained analysts to select lesion regions reliably. Periventricular lesions were defined as regions that were contiguous with lateral ventricle and did not extend into the white matter tracts. These lesions were classified as white matter lesions. Deep white matter lesions were located in the white matter tracts and may or may not have adjoined periventricular lesions. Subcortical gray matter lesions were defined as lesions within the basal ganglia or thalamus. Total lesion volumes were comprised of both gray matter lesions and white matter lesions, although white matter lesions were predominant.

Inter-rater reliability (2 raters) demonstrated intraclass correlation coefficients (ICCs) of 0.99 for both white and gray matter lesion volumes.

Analyses

All statistical analyses were run using JMP software (Cary, NC). Statistical analyses used lesion volumes from the MRI closest to the time of the nutrition assessment. This meant that for most subjects the MRI and nutrition assessments were separated by less than one year. In order to minimize the time interval, either assessment could precede the other. Self-report of hypertension and diabetes was obtained from the closest annual DDES instrument. Analyses first assessed the potential for responder bias. Bivariate comparisons were made between individuals with acceptable FFQs (“responders”) and those who either did not return a questionnaire or who returned an unacceptable one (together categorized as “nonresponders”). Variables of interest included sex, age, baseline depression score, lesion volume, and reported hypertension and diabetes.

Bivariate analyses were performed to examine the characteristics of the sample by total lesion volume. T-tests were used for categorical independent variables, including sex, hypertension and diabetes. Simple regression models were used for continuous independent variables, including age and all nutritional variables. To examine lesion volume by food group intake, controlling for potential confounders, we ran six separate multivariable regression models using servings of vegetables, fruits, whole grains, meats, and high and low-fat dairy products, as the primary independent variables. To control for potential confounding, each

model contained a set of covariates. All models included age, sex, hypertension (yes/no), diabetes (yes/no), and total energy (kcal) as control variables.

Results

A total of 160 depression subjects were determined to be eligible to receive an FFQ questionnaire. Seventy-nine subjects (of 160) were classified as having vascular depression, of whom 54 successfully completed the FFQ (68%). The earliest FFQ assessment was used for all except three subjects (6%). For those three subjects who had returned an unacceptable initial questionnaire (more than 15 food items missing), the second FFQ was used. Nonrespondents (those who did not return an FFQ or returned an unacceptable one) did not differ from respondents in terms of age, sex, baseline MADRS depression score, lesion volume, or self-reported hypertension or diabetes. All subjects had complete data.

Sample characteristics for the vascular depression group ($n = 54$) are shown in Tables 1 and 2. Mean lesion volume (\pm standard deviation) was 9.76 mL

Table 1. Sample characteristics: demographics, medical comorbidity, and lesions^a

CHARACTERISTIC	MEAN (\pm SD)
Age	71.5 (\pm 6.6)
Sex	53.7% female
Race	92.1% white
Hypertension	50.0%
Diabetes	14.8%
Lesion volume (mL)	9.8 (\pm 10.7)
Log ^b lesion volume	1.9 (\pm 0.9)
Geometric mean of lesion volume (mL) ^c	6.6 (\pm 2.3)

Notes: ^aVascular depression sample ($n = 54$).

^bNatural logarithm (ln).

^cGeometric mean = $e^{(\text{mean of } \log_{\text{lesion}})}$, and has same units (mL) as lesion volume.

Table 2. Sample characteristics – nutritional variables^a

INTAKE VARIABLE	MEAN (\pm SD)
Total energy (kcal)	1837.3 (\pm 858.5)
Meats ^b	1.1 (\pm 1.1)
High-fat dairy ^b	1.1 (\pm 1.0)
Low-fat dairy ^b	0.4 (\pm 0.7)
Vegetables ^b	2.9 (\pm 1.9)
Fruits ^b	1.8 (\pm 1.2)
Whole grains ^b	1.8 (\pm 1.7)

Notes: ^aVascular depression sample ($n = 54$).

^bIntake in servings per day.

Table 3. Predicted ratio of lesion volumes (geometric means) by intake level

INTAKE VARIABLE ^a	25 TH PERCENTILE	75 TH PERCENTILE	RATIO OF GEOMETRIC MEANS OF LESION VOLUME (75 TH:25 TH) ^b	CONFIDENCE INTERVAL FOR RATIO
Meats	0.5	1.6	1.0	(0.7, 1.4)
High-fat dairy ^c	0.3 ^c	1.8 ^c	1.5 ^c	(1.1, 2.2)
Low-fat dairy	0	0.2	1.0	(1.0, 1.1)
Vegetables	1.6	3.7	1.2	(1.0, 1.5)
Fruits	0.7	2.8	1.0	(0.7, 1.5)
Whole grains ^c	0.5 ^c	2.4 ^c	1.5 ^c	(1.1, 2.0)

Notes: ^aIntake in servings per day.

^bRatio = $e^{(\beta * \text{intake}_{75})} / e^{(\beta * \text{intake}_{25})}$ where β = parameter estimate from logLESION model for that intake variable, intake₇₅ = amount consumed at 75 percentile of intake, intake₂₅ = amount consumed at 25 percentile of intake.

^cFactor was significant in multivariable model ($p < 0.05$).

(± 10.68), with a range of 1.45 to 61.31. A Shapiro-Wilks test for normality was performed for total lesion volume. It indicated that lesion volume was not normally distributed ($W = 0.69$, $p < 0.0001$). A new variable for the logarithmic transformation (natural log) of lesion volume (logLESION) was created, for which we could not reject the null hypothesis of normality ($W = 0.96$, $p < 0.2055$). Geometric mean for lesion volume was included in Table 1 as a measure of central tendency that is less prone to distortion from outliers. In addition, geometric means may be easier to interpret than logarithmic values given that they have the same units as the original variable (lesion volume). Bivariate analyses between logLESION and demographic, medical comorbidity, and nutritional variables were performed. Age ($\beta = 0.059$, $SE = 0.016$, $t = 3.70$, $p = 0.0005$) and intake of high-fat dairy ($\beta = 0.329$, $SE = 0.108$, $t = 3.04$, $p = 0.004$) and whole grains ($\beta = 0.137$, $SE = 0.066$, $t = 2.07$, $p = 0.044$) were significantly (at $p < 0.05$) positively associated with logLESION.

Multivariable models examined the association between logLESION and each of the six food group variables, while controlling for age, sex, hypertension, diabetes and total caloric intake. A typical model was as follows: $\text{logLESION} = \beta_0 + \beta_1 \text{Meats} + \beta_2 \text{Age} + \beta_3 \text{Sex} + \beta_4 \text{Hypertension} + \beta_5 \text{Diabetes} + \beta_6 \text{Calories} + \varepsilon$. Servings of high-fat dairy ($\beta = 0.283$, $SE = 0.125$, $t = 2.26$, $p = 0.028$) and whole grains ($\beta = 0.197$, $SE = 0.079$, $t = 2.49$, $p = 0.016$) retained significance in multivariable models for their positive association with lesion volumes. No other foods were identified as statistically significant ($p < 0.05$). Age retained statistical significance in all models ($0.0004 < p < 0.0017$). Table 3 shows lesion volume (predicted geometric mean) ratios between the 75th and 25th percentile of intake for each nutritional factor, based upon multivariable analyses. For

example, individuals consuming 1.8 servings per day of high-fat dairy products (75th percentile of intake) had 1.5 times greater lesion volume than those consuming 0.3 servings (25th percentile). The 25th and 75th percentiles were chosen to represent “high” and “low” intake levels for this sample.

Discussion

This investigation found that intakes of high-fat dairy and whole grains were significantly positively associated with brain lesion volume among individuals with current or prior vascular depression, while there were no significant associations for the other four food groups (vegetables, fruits, meats, and low-fat dairy products). After controlling for potential confounders, including age, sex, total energy, diabetes, and hypertension, high-fat dairy and whole grain intakes remained significantly associated with lesion volume.

The finding of an association between high-fat dairy products and brain lesions is consistent with the ischemic nature of brain lesions seen in late-life depression, given that saturated fat, a prominent component of fatty dairy foods, is known to be a cardiovascular risk factor (Hu *et al.*, 1997). The medium-chain saturated fatty acids found in dairy products may be more atherogenic than other saturated fatty acids, such as the long-chain fatty acids found in meats (Kris-Etherton and Yu, 1997).

The association found between brain lesions and whole-grain consumption was in the opposite direction of that predicted. The known beneficial effects of whole grains on cardiovascular morbidity and mortality would seem to indicate their possible protective qualities for ischemic brain lesions (Jacobs *et al.*, 1998; Liu *et al.*, 1999; 2000). However, components in whole-grain products may have negative health consequences, including phytate, a compound found in the outer husk of grains, and certain dietary fibers which may impair the intestinal absorption of minerals including iron and zinc, potentially leading to deficiencies of those minerals (Hurrell *et al.*, 1992). It is possible that whole grains were correlated with brain lesions because of their association with inadequate mineral status, but this is purely speculative. Finally, whole grains vary in their components. The whole grains consumed by subjects in this project may have had a high glycemic index which could have detrimental cerebrovascular effects (Liu *et al.*, 2001).

The paucity of research into the association between food intake and brain lesions, especially in depression, provides only a limited framework within which to interpret the current results. The high-fat dairy finding is consistent with previous work showing that saturated fat and cholesterol were associated with late-life depression (Payne *et al.*, 2006). In terms of other foods, fruit and vegetable consumption has been negatively associated with brain disease

(Joshiyura *et al.*, 1999). This finding was not supported by the present study. The failure to detect these and other predicted associations may have been due to the focus on depression subjects, sample size, differing nutrition assessment methodologies, or to a combination of factors. If certain foods are found to be associated with late-life depression but not with brain lesions, this may indicate that the relationship between atherogenic nutrients and depression is mediated by other factors in addition to ischemic brain lesions. A cross-sectional study may be unlikely to detect an association between nutritional factors and lesions because individuals with known vascular disease have already changed their diets. Alternatively, lesions in certain brain regions such as the basal ganglia and hypothalamus may have led to changes in dietary behavior.

The present study has a number of limitations, including the modest sample size and multiple comparisons. The cross-sectional design precludes confirmation of an etiological effect of diet on brain lesions. The length of time likely required for development of brain lesions combined with a lack of historical dietary data make interpretation of any association even more difficult. The Block FFQ may be insufficient to detect dietary differences in individuals across the spectrum of brain lesion volumes, due to problems associated with self-reporting and the inherently high intra-individual to inter-individual variation of human diets. In addition, the whole-grain findings should be interpreted with caution given that the Block 1998 FFQ is not optimal for measuring whole-grain consumption because of lack of specificity about food items. Finally, we recognize that our results may be generalizable only to geriatric individuals with depression who have received psychiatric treatment.

In conclusion, significant evidence of a positive association between brain lesion volume and consumption of both high-fat dairy and whole grains among individuals with vascular depression was found. No significant associations were found between brain lesion volume and other food groups (fruits, vegetables, meats, and low-fat dairy). These findings, however, need to be confirmed in a larger sample. The dairy finding may indicate an association between saturated fat and lesions. If the nutrient intake differences observed in this study reflect long-term dietary patterns, then a greater high-fat dairy consumption may have contributed to an increased volume of lesions. However, a longitudinal study will be needed before any etiological conclusions can be drawn between diet and brain lesions in depression. Finally, the authors speculate that an atherogenic diet may be related to late-life depression via other mechanisms in addition to the development of brain lesions.

Conflict of interest

None.

Description of authors' roles

M. Payne designed the study, supervised the dietary data collection and image analysis, analyzed the data, and wrote the paper. P. Haines assisted with study design, statistical analyses, and critical revisions of paper. L. Chambless guided the statistical analyses, and assisted with the design and writing. J. Anderson assisted in the design and writing. D. Steffens supervised all data collection, and assisted in the design and writing.

Acknowledgments

This project was funded by the following National Institute of Mental Health grants: MH40159, MH54846, MH60451, and MH70027. The authors wish to thank the participants of this research project for their dedication to furthering knowledge of late-life depression. The authors also acknowledge the following individuals from Duke University Medical Center for their assistance with subject recruitment and assessment: Ms. Denise F. Messer, Ms. Cortnee N. Willetts, and Ms. Carrie B. Dombeck. The authors also thank Ms. Messer for the lesion volume measurements. Dr. Payne acknowledges the generous contributions of her dissertation committee members, including Dr. Alice S. Ammerman at the University of North Carolina at Chapel Hill, and Dr. Judith C. Hays at Duke University.

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