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Elevated brain lesion volumes in older adults who use calcium supplements: a cross sectional clinical observational study

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Abstract

Recent studies have implicated calcium supplements with elevated vascular risk, and therefore these supplements may also relate to the occurrence of brain lesions (or hyperintensities) in older adults. These lesions represent damage to brain tissue that is caused by ischaemia. This cross sectional clinical observational study examined the association between use of calcium-containing dietary supplements and lesion volumes in a sample of 227 older adults (60 years and older). Food and supplemental calcium intakes were assessed with a Block 1998 FFQ; participants with supplemental calcium intakes above zero were categorized as supplement users. Lesion volumes were determined from cranial MRI (1.5 Tesla) using a semi-automated technique; volumes were log-transformed because they were non-normal. An ANCOVA model showed that supplement users had greater lesion volumes than non-users, even after controlling for dietary food calcium, age, sex, race, education, energy intake, depression and hypertension (Calcium supplement use: $\beta = 0.34$, SE = 0.10, $F_{1,217} = 10.98$, $p = 0.0011$). The influence of supplemental calcium use on lesion volume was of similar magnitude to that of hypertension, a well-established risk factor for lesions. Among supplement users, the amount of supplemental calcium was not related to lesion volume ($\beta = -0.000035$, SE = 0.00015, $F_{1,139} = 0.06$, $p = 0.81$). This study indicates that the use of calcium-containing dietary supplements, even low dose supplements, by older adults may be associated with greater lesion volumes. Evaluation of randomised, controlled trials is warranted to determine if this relationship is a causal one.

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Conflict of interest

The authors have no conflicts of interest.

Authorship

M. E. P. designed the study, interpreted the data, and drafted the manuscript. D. R. M. analysed the data. M. E. P., D. R. M., D. C. S., and J. J. B. A. contributed to the interpretation of the data and revision of the manuscript. M. E. P. and D. C. S. financed the study.

Keywords

Calcium supplement; Brain lesions; MRI hyperintensities; Older adult

Introduction

Brain lesions, also known as hyperintensities, are areas of damage seen on brain MRI (Figure 1). These lesions are common in older adults and increase risk of devastating health outcomes, including depression, cognitive decline, dementia, stroke, physical disability, hip fracture and death([1–10]). Postmortem studies have determined that these lesions are due primarily to ischemia, especially larger lesions (> 3mm) and lesions found in depressed individuals([11]).

Our prior study showed that higher total calcium intakes were associated with greater brain lesion volumes in older adults, indicating calcium's potential as an etiological factor for lesions([12]). Given that lesions result primarily from ischaemic damage, this calcium-lesion finding is consistent with recent reports showing that excess calcium, especially that from dietary supplements, may increase one's risk of cardiovascular outcomes, including myocardial infarction, incident coronary heart disease, stroke, and ischaemic heart disease deaths([13–18]). For example, the Heidelberg cohort (N=23,980) demonstrated that calcium supplement use significantly increased risk of myocardial infarction over 11 year follow-up (HR=1.86)([19]). Supplemental calcium may be particularly harmful because of its influence upon serum calcium concentrations([20, 21]). Serum concentrations even within the normal range have been shown to be associated with arterial calcification([22, 23]) and other cardiovascular pathology([24]). It is critical to determine the contribution of supplemental calcium to lesions, given detrimental effects of lesions and the modifiable nature of calcium intake. This question is especially relevant for women's health because women are greater consumers of calcium supplements, primarily due to concerns about osteoporosis([25]). In addition, women are at greater risk for depression and dementia, conditions that are partially caused by ischaemic brain lesions([1, 5]).

The relative importance of calcium supplements, as opposed to food calcium, was not established by our prior calcium-lesion study. Therefore, the aim of this current study of older adults was to evaluate differences in lesion volumes between users and non-users of calcium-containing dietary supplements in the same study sample, while also exploring the influence of supplement dose and duration, as well as sex differences and vitamin D. We hypothesized that supplement users would have higher lesion volumes than non-users, irrespective of dietary calcium intake.

Methods

This cross sectional clinical study occurred within a larger longitudinal cohort examination of depressed and non-depressed older adults (NeuroCognitive Outcomes of Depression in the Elderly), which began in 1994 and had ongoing enrollment until 2011([26]). Nutritional data were collected annually beginning in 1999. MRI brain scans began in 1994 and were acquired every two years. For this study, only one MRI scan and one nutritional assessment

were used for each participant. Analyses used lesion volumes from the MRI closest in time to the first available nutrition assessment.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the Duke University Institutional Review Board (IRB), Durham, North Carolina, USA. Written informed consent was obtained from all participants prior to their taking part in the study.

Sample

All participants who had both nutrition data (from food frequency questionnaire) and MRI lesion volume data were included in the current study (N = 227). We included only scans acquired with a 1.5 Tesla scanner. This sample included participants who met diagnostic criteria for major depressive disorder [according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)([27])] at study baseline, and never-depressed comparison participants recruited from the community. Participants were aged 60 years or older, and were able to speak and write in English.

Exclusion criteria included a concurrent diagnosis of a psychiatric or neurological illness, and significant cognitive impairment (as indicated by a Mini-Mental State Examination([28]) score of less than 24 out of 30). In addition, participants with severe depression symptomatology were excluded because of concerns about 1) subject burden, given the length and difficulty of the food frequency questionnaire, and 2) memory difficulty, common with severe depression, which could impact accuracy of the reporting. This criterion was evaluated by the treating psychiatrist on a case-by-case basis, an approach used because that clinician was most familiar with a patient's limitations. Comparison participants (controls) were required to have no evidence of a depression diagnosis or lifetime history of depression.

Treatment

Depressed participants received individualized treatment from a psychiatrist, who followed them throughout the study. Most depressed participants received antidepressant medication.

Nutrition Assessment

The nutrition protocol has been described previously([29]). The 1998 Block FFQ (NutritionQuest; Berkeley, CA) was self-administered to assess dietary intake over the previous year. For approximately 90% of participants, the nutrition assessment year either preceded or overlapped with the MRI acquisition. The 1998 Block is an updated version of the FFQ developed by Gladys Block at the National Cancer Institute([30]), and has been validated against other nutrition assessment instruments([31]). Returned questionnaires were checked for completeness and excluded if more than 15 food items were skipped. The 1998 version of the Block FFQ included duration and frequency items on use of dietary supplements, including calcium supplements and mineral-containing multivitamins. Intake estimates included total energy (kilojoules), calcium (mg), and vitamin D (mcg). Calcium and vitamin D intakes were calculated from both foods and dietary supplements. Participants with supplemental calcium intakes greater than zero were categorized as calcium

supplement users, while those with zero intake were categorized as non-users. Duration of supplement use included 6 levels (less than 1 year, 1 year, 2 years, 3–4 years, 5–9 years, 10 or more years).

Lesion Volumes

Participants 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([32]). The MR images were processed for lesion volumes by blinded (to all identifying information, including depression diagnosis and dietary intake) analysts in the Neuropsychiatric Imaging Research Laboratory (NIRL).

A dual-echo fast spin-echo axial acquisition was used for volumetric measurement of brain structures, including gray and white matter lesions. NIRL image processing procedures have been described previously([32]). 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 then selected based upon a set of rules that allow trained analysts to reliably select lesion regions. Periventricular lesions were defined as regions that were contiguous with the lateral ventricles 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. Lesion volumes were derived by multiplying the lesion area on each slice by the slice thickness (3 mm), and then summing lesion volumes from all slices. Total lesion volume included both gray matter lesions and white matter lesions, although white matter lesions predominated. For purposes of this study, only total lesion volume was examined.

Statistical Analyses

All statistical analyses were performed using SAS software, version 9.3 TS (Serial # 70007112; SAS Institute, Cary, NC, USA). Significance was defined at $p < 0.05$ level; very significant was defined at $p < 0.01$.

Covariates of interest were demographic variables (age, sex, race), years of education, group (depression vs. comparison), and hypertension. Hypertension ("high blood pressure") was included with self-reported physical health items from the National Institute of Mental Health (NIMH) Diagnostic Interview Schedule([33]) portion of the Duke Depression Evaluation Schedule (DDES), which was administered annually. BMI (kg/m^2) was calculated from self-reported weight and height at time of FFQ.

Statistical analyses used lesion volumes from the MRI closest to the time of the nutrition assessment. For most participants 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 was obtained from the closest annual DDES instrument. Given relatively small numbers of minority participants, race was dichotomized as White vs.

non-White. Since lesion volumes were non-normal, values were log-transformed prior to use in statistical models (LogLesion).

For bivariate analysis, t-tests were performed on continuous level variables and Chi-square tests were performed on categorical variables testing for differences between calcium supplement users and non-users. ANCOVA models were fit to test differences between supplement users and non-users upon lesion volume while controlling for covariates. Covariates included age, sex, race, education, hypertension, depression, total energy intake, and food calcium. BMI was omitted from model because it was not significant in prior calcium-lesion study([12]). Secondary analyses used the main ANCOVA model in order to examine potential for sex differences (addition of interaction term [sex*supplement use]), as well as influence of vitamin D intake (inclusion of total vitamin D intake).

The approximate power of the main model was 0.908 (based on a Type III F-test for multiple regression using PROC POWER considering 9 predictors and 227 observations, controlling for a Type I error of 0.05).

Results

Participant Characteristics

A total of 285 participants had a 1.5 Tesla MRI scan and were asked to complete an FFQ. Of these, 227 individuals completed the FFQ. A comparison of FFQ responders and non-responders found no differences in age, sex, race, education, hypertension or lesion volume, but non-responders were more likely to be in the depression group (N = 45 depression vs. N = 13 non-depressed; $\chi 2 = 23.02$, df = 1, $p < 0.0001$). This study sample (N = 227) was almost the same as the sample from prior study (N = 232) ([12]); small differences were due to addition of new participants, as well as removal of a few participants' data from the study archive, which occurred after prior study was completed.

Of the 227 older adults participants (see Table 1), 149 were categorized as users of calcium-containing dietary supplements (range of daily supplemental intake: 37 to 1,130 mg) and 78 were non-users (i.e., supplemental intake = 0 mg). Supplement users were more likely to be female ($\chi 2 = 14.22$, df = 1, $p = 0.0002$), and to have more years of education ($t = -3.04$, df = 128.96, $p = 0.0029$) than non-users. Groups also differed by race, as White participants were more likely to be supplement users, while non-Whites were more likely to be non-users ($\chi 2 = 6.12$, df = 1, $p = 0.01$). In addition to higher intake of supplemental calcium, users had significantly higher intake of food and beverage calcium ($t = -2.69$, df = 225, $p = 0.0076$), total calcium ($t = -13.56$, df = 223.53, $p < 0.0001$), and total vitamin D ($t = -13.97$, df = 221.19, $p < 0.0001$) than non-users. Users had significantly higher lesion volumes ($t = -3.63$, df = 209.5, $p = 0.0004$) than non-users. Geometric mean for lesion volume was included in Table 1 as a measure of central tendency that is less prone to distortion from outliers, and also may be easier to interpret than logarithmic values given that geometric means have the same units as the original variable (i.e., ml for lesion volume).

ANCOVA Models

To examine the effect of calcium supplement use (yes/no) on LogLesion while controlling for potential confounders, we performed an ANCOVA model. This model showed that users of calcium-containing supplements had significantly higher LogLesion values than non-users, after controlling for dietary calcium intake (food calcium), age, sex, race, education, energy intake, depression and hypertension (Table 2). Significant covariates in the model were age, hypertension, and depression. Food calcium was not significant in the model. Table 3 shows lesion volume (predicted geometric mean) ratios between groups for each of the significant categorical predictor variables, based upon the full multivariable model. Calcium supplement users had 1.4 times greater lesion volume than those who were non-users. Among users of calcium-containing supplements, the amount of supplemental calcium (mg) was not significantly associated with LogLesion ($\beta = -0.000035$, SE = 0.00015, $F_{1,139} = 0.06$, $p = 0.81$), nor was duration of supplement use significantly associated with LogLesion ($\beta = -0.040$, SE = 0.043, $F_{1,134} = -0.93$, $p = 0.35$). It should be noted that duration data were available for only N = 106 of 149, and no sex differences were found for duration of supplement use.

Secondary Analyses

Male-Female Differences—A sex*supplement use interaction term was added to the main model, described previously, in order to examine potential for sex differences in the relationship between calcium and LogLesion. This interaction term was not significant ($\beta = 0.27$, SE = 0.20, $F_{1,216} = 1.80$, $p = 0.18$).

Vitamin D Intake—When total vitamin D intake was added to the main model, calcium supplement use remained significantly associated with LogLesion (Calcium supplement use: $\beta = 0.27$, SE = 0.13, $F_{1,216} = 4.29$, $p = 0.040$). Vitamin D intake was not significantly associated with LogLesion in this model ($\beta = 0.0092$, SE = 0.011, $F_{1,216} = 0.71$, $p = 0.40$).

Discussion

The main finding of this study is that older adults who used calcium-containing dietary supplements had higher brain lesion volumes than non-users. This association was significant even after controlling for dietary calcium intake (from foods and beverages), as well as age, sex, race, education, energy intake, depression, and hypertension. Given that dietary calcium intake was included in the main model and was found to be non-significant, supplemental calcium per se may be an important risk factor. This study did not identify sex differences in this relationship, nor a significant influence of vitamin D on the calcium-lesion relationship. Surprisingly, duration of supplement use was not significantly associated with lesions, although duration data were available for only 71% of users. It is possible that duration was confounded with comorbid illness, a factor associated with lesion etiology. Supplemental calcium amount also was not related to lesion volume, among users of supplements, indicating that use of any calcium-containing dietary supplement, regardless of dose, may confer risk.

Use of calcium-containing dietary supplements has not been examined previously in relationship to brain lesions. However, several randomized controlled trials (RCTs) have examined the role of calcium supplements for stroke risk, which may be relevant to the current findings given that lesions and stroke often have a shared etiology. A recent meta-analysis examined data from 28,072 RCT participants, of whom 768 individuals suffered an incident stroke, and showed a trend for an increased risk of stroke among those assigned to receive a calcium supplement (Relative Risk: 1.15; Confidence Interval: 1.00 to 1.32; p = 0.06)([17]). A re-analysis of the Women's Health Initiative Calcium-Vitamin D RCT revealed that calcium supplementation conferred an increased cardiovascular risk only upon those participants who were not taking personal calcium supplementation at the time of randomization, and also showed that the dose of calcium supplement was not related to risk([17]). The researchers suggested that these findings indicate a lack of dose-response relationship for calcium and vascular risk, and that even low-dose supplementation may confer risk. This notion is consistent with the present study, for which supplement use was defined as use of any calcium-containing supplement, including multivitamin/mineral supplements, which generally have much smaller doses of calcium (e.g., 100–200 mg per pill) than calcium-only or calcium plus vitamin D preparations. Among supplement users, the total amount of supplemental calcium was not related to lesion volumes, consistent with the Bolland analysis([17]). It is possible that even small dose supplements may be harmful, perhaps by stressing the calcium homeostatic mechanism. Alternatively, the use of calcium-containing supplements may be associated with another factor that relates to brain lesions.

Large quantities of calcium found in a single dose of a supplement, often referred to as loading, have been found to cause a substantial and rapid increase in serum calcium concentrations, proportional to calcium supplement load([20]), which in turn may promote the development of calcium deposits in the vasculature (i.e., arterial calcification), primarily at sites of atheromas (fatty deposits). This calcification, in turn, may lead downstream to ischemia and the development of brain lesions([34, 35]). In addition to a vascular mechanism, excess calcium may have direct effects upon brain health([36]), especially if there is damage to the blood brain barrier, such as occurs with advancing age or neurodegenerative conditions.

The primary modifiable risk factor that has been previously established for lesions is hypertension([37, 38]). New data from the current study suggest that calcium supplements have a similar magnitude of effect upon lesions as hypertension (see Table 3). If this finding is confirmed in longitudinal studies, it could have important health implications – because it is obviously much easier to *cease calcium supplement use* than to *medically manage hypertension*. Age and depression were also significantly associated with lesions, consistent with prior reports([39, 40]), while sex, race, education, energy intake, and BMI were not significant for lesions. The role of vitamin D in the development of brain lesions remains unclear. In our prior study, higher vitamin D intake was significantly related to higher lesion volumes([12]). However, a study that examined serum concentrations of vitamin D found that vitamin D insufficiency, not supplementation nor excess, was related to greater lesions([41]). It is possible that both excess intake and vitamin D insufficiency may promote lesions. Secondary analyses for this project showed that the inclusion of total vitamin D in the main

model did not eliminate the significant association between calcium supplement use and lesions, nor was vitamin D significant in the model. Interpretation of these results is complicated given the generally high correlation between calcium supplement use and total vitamin D intake, lack of information on sun exposure, and the fact that many calcium supplements contain vitamin D. Also, it is unclear if vitamin D would have a significant impact upon a calcium pathology, given that the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (the active hormone) might be limited at the medium-to-high calcium intakes reported by both groups in this study (700 mg and above).

This study has a number of strengths, including the use of a highly-reliable method for quantifying lesion volumes from MRI([32]), use of blinded imaging analysts, and the relatively substantial sample size *for an MRI study*. Assessment of calcium intake using the validated Block FFQ is a further strength of this project. In addition, the models incorporated an extensive list of potential confounders, including hypertension and depression. Limitations of the study include its cross sectional nature, which precludes the establishment of a causal relationship between calcium supplement use and lesion development, potential for residual confounding, and the lack of measures of serum calcium, arterial calcification, or other potential mediator. Objective measures of cardiometabolic risk, including glycemic control and blood pressure, were unavailable. In addition, the Block 1998 assessment does not distinguish between calcium-only and combined calcium/vitamin D supplements, nor were calcium-containing antacids specifically queried. Generalizability to older population groups may be limited given that study sample was from a clinical psychiatric study of older adults.

As this study is the first to detect a positive relationship between use of supplemental calcium and MRI-defined brain lesions, many questions remain to be answered. This potentially important finding needs to be replicated in samples of older adults which are more representative of the general population than this clinical psychiatric sample. In addition, temporality needs to be determined before causality between supplemental calcium and brain lesions may be established. Lastly, if supplemental calcium is determined to be causal for brain lesions, biochemical mechanisms need to be identified.

Conclusion

Use of calcium-containing dietary supplements by older adults was found to be associated with greater brain lesion volumes, even after controlling for usual amount of dietary calcium intake. Interestingly neither the amount nor duration of supplemental calcium was related to lesion volumes. These findings may indicate that adverse biochemical effects of supplemental calcium exist in older adults, regardless of dosage. These results should be considered preliminary given the cross sectional design, potential for residual confounding, and specialized study population. Evaluation of randomised, controlled trials is warranted in order to examine the potential for an etiological relationship between calcium supplement use and lesion development.

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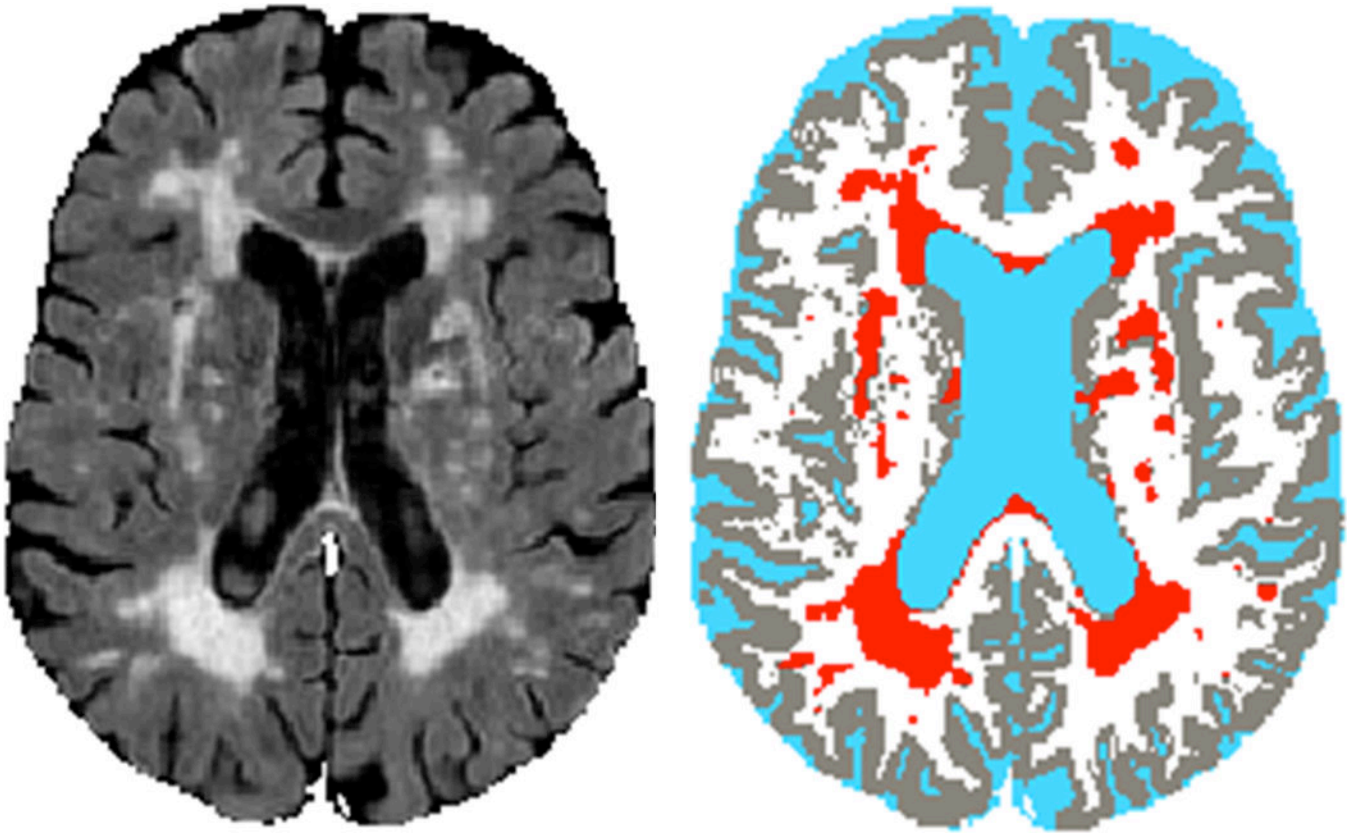

Figure 1.
Brain lesions shown on MRI: Fluid-attenuated inversion recovery image (left), tissue classification image (right; lesions in red).

Table 1

Participant characteristics: Sociodemographics, comorbidity, lesions, and diet.

	Total (n=227)		Calcium supplement users (n=149)		Non-users (n=78)		p value*
	Mean or #	SE or %	Mean or #	SE or %	Mean or #	SE or %	
Age in years	70.9	0.4	71.2	0.5	70.3	0.7	0.3
Sex (female)	148	65%	110	74%	38	49%	0.0002
Race							0.02
White	193	85%	133	89%	60	77%	
African American	22	10%	8	5%	14	18%	
Asian	5	2%	4	3%	1	1%	
Multiracial	7	3%	4	3%	3	4%	
Education in years	14.8	0.2	15.1	0.2	14.1	0.3	0.003
Hypertension (yes)	80	35%	50	34%	30	38%	0.5
Depression (yes)	96	42%	56	38%	40	51%	0.05
Calcium (mg/d)							
Food	797.0	27.0	848.8	34.4	698.0	40.7	0.008
Supplemental	488.5	33.3	744.2	36.0	0	n/a	n/a
Total	1285.5	46.4	1593.0	51.9	698.0	40.7	<0.0001
Vitamin D (mcg/d)†	8.6	0.4	11.3	0.4	3.5	0.4	<0.0001
Energy (kJ/d)	7227.1	189.6	7197.8	258.0	7283.1	250.3	0.8
Body mass index (kg/m^2)	26.2	0.3	25.9	0.4	26.7	0.5	0.2
Lesion Volume (ml)	6.2	0.5	7.2	0.8	4.1	0.4	0.0004
LogLesion‡	1.4	0.05	1.5	0.07	1.2	0.07	0.0005
Geometric Mean (ml)§	4.1	1.1	4.6	1.1	3.3	1.1	n/a

*p value for difference between groups (chi-squared test used to compare proportions; t-test used to compare means).

†Total intake (food + supplemental).

‡Natural logarithm of lesion volume.

§Geometric mean = e(mean of LogLesion).

Table 2

The influence of supplemental calcium use on lesion volumes (a multivariable model with 8 covariates)

	Estimate	SE	F value*	p value
Supplemental calcium (yes/no)†	0.34	0.10	10.98	0.0011
Food calcium (mg/d)	0.00020	0.00014	2.02	0.16
Age (years)	0.061	0.0076	65.04	<0.0001
Sex (female/male)	0.052	0.10	0.27	0.61
Race (White/non-White)	0.067	0.13	0.26	0.61
Education (years)	0.0057	0.021	0.07	0.79
Hypertension (yes/no)‡	0.27	0.099	7.62	0.0063
Depression (yes/no)§	0.28	0.096	8.75	0.0034
Energy (kJ/d)	0.000010	0.000020	0.26	0.61

*Analysis of Covariance (ANCOVA), degrees of freedom $F_{1,217}$ for all variables.

†Yes if supplemental calcium intake greater than zero milligrams per day.

‡Determined from closest annual self-report within the NIMH Diagnostic Interview Schedule portion of the Duke Depression Evaluation Schedule (DDES)(33).

§Yes if met diagnostic criteria for major depressive disorder according to DSM-IV at study baseline(27).

Table 3

Geometric means of lesion volume by calcium supplement use, depression and hypertension*

Predictor condition	Yes	No	Ratio of geometric means of lesion volume (yes:no)†	Confidence interval
Calcium supplement use	5.07 ml	3.63 ml	1.40	(1.15, 1.71)
Depression	4.94 ml	3.72 ml	1.32	(1.10, 1.61)
Hypertension	4.92 ml	3.74 ml	1.31	(1.08, 1.60)

*Geometric means comparison for the significant categorical predictor variables (difference between having or not having the identified predictor condition).

†Ratio = $e^{(\beta * Yes)}/e^{(\beta * No)}$ where β=parameter estimate from full model for that categorical predictor variable.