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Diet and Neuroimaging Markers of Cerebrovascular Disease

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Abstract

Stroke is one of the leading causes of long-term disability and mortality. Mounting evidence from observational studies suggests that among lifestyle factors, diet may be playing an important role for the prevention of stroke. Neuroimaging markers, particularly white matter hyperintensity (WMH) volume and brain infarcts (BI) are more sensitive measurements of cerebrovascular disease than clinical assessments. We reviewed published observational and clinical studies that evaluate the association between dietary factors and WMH and BI. The few existing studies examined only a handful individual nutrients or foods (dietary intake of alcohol, B vitamins, fish, choline, serum markers of antioxidants, and a few food groups, Mediterranean-style diet, and nutrient biomarker patterns. Findings from these studies are inconclusive either due to conflicting results from different studies or due to lack of replication. Further studies are necessary to replicate the existing findings. Many other foods or nutrients or dietary patterns may worth of investigation and longitudinal studies are needed.

Keywords

Diet; nutrition; nutrients; foods; Mediterranean diet; white matter hyperintensity; stroke; infarct

Introduction

Stroke is one of the leading causes of serious, long-term disability and mortality in the United States.[1] Mounting evidence from observational studies suggests diet is one of the important lifestyle factors for the prevention of stroke.[2] However, the mechanisms for the relationship between diet and stroke have not been fully explored in the past, partly due to the limited availability of methods that allow a sensitive and accurate measurement of cerebrovascular disease.

Recent advances in magnetic resonance imaging (MRI) techniques have made it possible to visualize and to quantify the structural changes of the brain.[3] Neuroimaging markers are extremely sensitive measurements of changes occurring in the aging brain. Therefore, using these neuroimaging markers could help uncover associations between diet and

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cerebrovascular disease –related brain dysfunctions which might not be detectable using rough clinical stroke outcomes. For example, a population-based, longitudinal study demonstrated that 18% of the elderly study participants developed incident brain infarct on follow-up MRI scan 5 years later, while nearly 90% of those cases had no documented transient ischemic attack or clinical stroke between the scans[4]. Another population-based study reported low specificity (79%) and sensitivity (32%) of self-reported stroke using brain MRI as the standard.[5]

Two major neuroimaging markers of cerebrovascular disease, i.e. white matter hyperintensity (WMH)[6, 7] and brain infarcts (BI),[8–12] are very tightly related to risk of clinical stroke. However, there has been relatively little work on association of diet with these MRI markers. In this review, published observational studies and clinical trials that evaluated the association between dietary factors and MRI-assessed cerebrovascular disease (WMH and BI) are summarized (Table 1) and future directions of research are suggested.

MRI-assessed cerebrovascular diseases

BIs appear as punctate or circumscribed hypointense lesions on T1-weighted scans (and hyperintense in T2 and FLAIR sequences). Evidence from observational investigations suggest that increasing age, hypertension, and other cardiovascular risk factors are strongly associated with BI. Most of BI are lacunar infarcts and small-vessel disease seems to play a crucial role in their pathogenesis.[13] Nevertheless, BIs larger than lacunes may also be noted.

WMH, or leukoaraiosis, consists of bilateral patchy or diffuse areas of hyperintensity of the cerebral white matter on T2-weighted MRI images, including FLAIR sequences. There are several reports suggesting that the severity of WMH increases with age.[14] Although their pathogenesis is uncertain, WMH is traditionally thought to be a surrogate marker of small vessel vascular disease[15] resulting from ischemic damage due to chronic systemic hypoperfusion.[16]

BI and WMH are highly related to each other[14] and they seem to represent two different manifestations of cerebral small-vessel disease [16] (although BI can be a manifestation of large vessel disease too). Overall, they are both associated with traditional vascular risk factors,[6, 17, 18] and are often associated with higher risk of subsequent clinical stroke.[19, 20] Thus, modifying risk factors that contribute to the development of these brain changes seen in MRI may help ultimate goal of preventing stroke.

Epidemiological evidence on diet and cerebrovascular diseases

Alcohol

Moderate drinking (1–2 drinks, or 10–30 g alcohol, per day) may be protective while heavy drinking may be harmful for clinically diagnosed ischemic stroke (compared to nondrinking or to drinking very small quantities)[21] To date, several studies have examined the association between alcohol consumption and brain MRI markers among non-alcohol-dependent populations. [22–27] Three studies suggested a beneficial role of alcohol consumption on cerebrovascular diseases. In a cross-sectional study of 994 Korean symptom-free adults, history of mild alcohol consumption was associated with a low risk for silent cerebral infarction.[28] In 1992–1994, the association between alcohol use and subclinical brain findings was investigated among 3660 participants of Cardiovascular Health Study (CHS) who completed cranial MRI examination. The study found light to moderate alcohol drink in older adults was inversely associated with the presence MRI infarction and WMH compared to non-drinkers or heavy drinkers.[22] In the Rotterdam

Scan Study, an inverse U-shaped association between WMH, but not infarcts, and alcohol consumption was found among 1074 non-demented older persons.[23] In contrast, a Japanese study of 385 adults found light and moderate alcohol drinkers had larger WMH volume and higher odds of having BI than non-drink adults.[24]

There are also a few studies that did not find any association between alcohol and MRI-assessed cerebrovascular diseases.[25–27] The associations of alcohol use with WMH and BI were examined in the Atherosclerosis Risk in Communities (ARIC) study, in which 1920 adults aged 55–72 years underwent MRI. The study found that current drinking was not statistically associated with WMH or BI overall.[25] However, this study found current drinking was associated with greater WMH among African Americans, but not among European Americans, suggesting a potential interaction between alcohol drinking and race. [25] Alcohol consumption was not associated with WMH among 385 elderly participants of the Australia PATH Through Life Project.[26] Similarly, no significant association between alcohol consumption and WMH was found among 1839 subjects from the Framingham Offspring Study.[27] BI was not evaluated in the latter two studies.[26, 27]

In summary, the evidence on the relationship between alcohol consumption on markers of cerebrovascular disease is inconsistent.

B vitamins

Several large studies have found that intake of folate was associated with a significantly lower risk of clinical ischemic[29–31] or hemorrhagic stroke.[32] The Health Professionals Follow-Up Study found intake of vitamin B12 was marginally inversely associated with risk of ischemic stroke.[29] Furthermore, data from randomized trials suggested that folic acid supplementation with or without a combination with other B vitamins could reduce the risk of stroke.[33] Thus, it would be interesting to investigate whether B vitamins are also associated with MRI-assessed WMH or BI.

B vitamins (folic acid, vitamin B12, and B6) have been mainly related to cerebrovascular disease by their effect on lowering serum homocysteine (Hcy) levels, which is a strong risk factor for cardiovascular disease.[34] Several cross-sectional studies reported a direct association between elevated blood concentrations of total Hcy and greater burden of WMH volume or more BI.[35–38] In a recent longitudinal study of 121 community-dwelling participants of the Chicago Health and Aging Project (CHAP), the associations between serum markers of vitamin B12 status (including vitamin B12, Hcy, methylmalonic acid, cystathionine, and 2-methylcitric acid) and brain MRI measures were examined.[39] The study found that Hcy concentration was the only vitamin B12 indicator that was associated with WMH volume[39] but none of the vitamin B12 indicators was associated with cerebral infarcts.[39] In another study of 124 patients who had their first lacunar stroke, lower vitamin B12 level was significantly associated with more severe periventricular WMH, but not with deep WMH.[40]

However, data on the association between dietary intake or intake of supplements of B vitamins and WMH volume or BI were rare. Only two clinical trials examined the effect of supplements of B vitamins on MRI measured cerebrovascular lesions. In a sub-study of the VITamins TO Prevent Stroke (VITATOPS) trial, a prospective, randomized, double-blind, placebo-controlled clinical trial, researchers assessed whether the once-daily supplements of B vitamins would reduce the progression of cerebrovascular brain lesions on MRI.[41] A total of 174 patients, who had a stroke (ischemic or hemorrhagic) or a transient ischemic attack in the past 7 months, were randomly assigned to receive either B vitamins or placebo. After 2 years of treatment, progression of WMH and frequency of incident lacunes were not significantly different between the two groups. However, in a post hoc subset analysis of

100 patients with MRI evidence of severe cerebrovascular lesions, B-vitamin supplementation was associated with a significant reduction in WMH volume change.[41] In another clinical trial using supplements of B vitamins in 158 healthy siblings of patients with premature atherosclerotic disease, B vitamins treatment, as compared to placebo, was non-significantly associated less white matter damage.[42] To date, no observational study has investigated whether B vitamin intake is associated with lower risk of developing cerebrovascular lesions among general populations.

In summary, several observational studies on serum markers of vitamin B12 have suggested a potential beneficial role of B vitamins in MRI-assessed cerebrovascular disease among healthy elderly populations. The two clinical trials that showed some preliminary benefits of B vitamins supplementation in reducing the cerebrovascular lesion burden were among populations who had higher risk of stroke or among stroke patients. Nevertheless, whether such effect of supplementation of B vitamins can also be seen among healthy populations, or whether dietary intake of B vitamins have similar effect on MRI-detected cerebrovascular disease has yet to be determined.

Fish and Fatty Acids

Many previous studies on fish consumption in relation to clinical stroke in general indicated that fish or unsaturated fatty acids consumption was inversely associated with risk of stroke, [43–45] but negative studies also exist.[46–52] Whether fish consumption affects the risk of WMH, BI, or other MRI-measured cerebrovascular diseases is largely unknown and has only been explored in one population-based study.

Researchers of the CHS investigated the cross-sectional associations of fish and dietary eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) consumption with MRI-defined subclinical brain abnormalities including infarcts WMH. They also explored longitudinal associations between fish and EPA+DHA consumption and subclinical BI. In the cross-sectional analysis that included more than 4000 subjects, higher consuming tuna/other fish was associated with reduced risk of having subclinical BI or better white matter grade scores; in contrast, fried fish consumption was associated with non-significant trends toward higher prevalence of subclinical infarct. In the longitudinal analyses of a subgroup of 1124 subjects, tuna/other fish consumption again tended to be associated with lower incidence of subclinical BI, while fried fish was not associated with risk of incident subclinical BI. Findings for estimated consumption of dietary EPA and DHA in this study were generally similar to those for consumption of tuna/other fish.[53]

Choline

Choline is an essential nutrient that is a precursor of acetylcholine. It also serves as the precursor of sphingomyelin and phosphatidylcholine-structural components of cell membranes.[54] Main food sources of choline are red meat, poultry, milk, eggs, fish, and some beverages (coffee or beer) and fruit (orange) or vegetables (potatoes, broccoli)[55]. A recent study examined whether choline intake from foods was related with WMH level in a dementia-free cohort of 1391 subjects from the Framingham Heart Study Offspring Study. The study found although concurrent dietary intake of choline was not associated with WMH volume, choline intake in the past (approximately 7 years prior to the MRI measurement) was inversely related to log-transformed WMH volume or presence of large WMH.[56]

Antioxidants

There has been only one study examining the relationship between antioxidants blood level and cerebrovascular lesion. In the Austrian Stroke Prevention Study plasma concentrations

of 10 natural antioxidants, including zeaxanthin, cryptoxanthin, canthaxanthin, lycopene, alpha- and beta-carotene, retinol, gamma- and alpha-tocopherol (vitamin E), as well as ascorbate, were measured for 355 clinically healthy elderly participants.[57] The study found lower plasma alpha-tocopherol and lycopene were found to be correlated with a higher extent of MRI white matter abnormalities.[57] These findings were in line with the evidence that showed high serum alpha-tocopherol was associated with decreased the risk of clinical cerebral infarction.[58] Nevertheless, to our knowledge, no study has investigated directly the dietary intake of antioxidants and risk of cerebrovascular lesions using MRI. This may not be surprising, however, as previous investigations from large observational studies have yielded conflicting results with regard to whether dietary intakes of antioxidants may reduce the risk of clinical stroke.[59–62] Furthermore, clinical trials generally found that supplementation of these antioxidants did not prevent stroke.[63]

Food groups

The relationship between food groups and brain lesions has been examined in a study including 54 elderly vascular depression subjects (vascular depression defined by presence of WMH on brain MRI). Consumption of six food groups (fruits, vegetables and whole grains, high and low-fat dairy products meats) were calculated from the Block Food Frequency Questionnaire, and brain lesion (periventricular and deep WMH, and subcortical gray matter) volumes were calculated from MRI. This study found that intakes of high-fat dairy and whole grains were positively associated with brain lesion volume among individuals with current or prior vascular depression, while there were no significant associations for vegetables, fruits, meats, and low-fat dairy products.[64] Saturated fat, a prominent component of fatty dairy foods, is known to be a cardiovascular risk factor. Thus, the findings regarding high-fat dairy products are consistent with the literature, given the ischemic nature of brain lesions seen in late-life depression. However, it is unknown why the whole grains were associated with higher burden of brain hyperintensive lesions, as one would expect a protective effect of whole grains for ischemic brain lesions given the beneficial effects of whole grains on cardiovascular events.[65] It should be noted though that the study was small in terms of sample size, the study subjects were vascular depression patients rather than general population, and brain lesion included both grey and white matter hyperintensity. Further larger studies are needed.

Dietary patterns

In addition to individual nutrients or food items, dietary patterns are continuously receiving attention, probably due to the ability of dietary patterns to represent complicated interactions and cumulative effects of nutrients or food items in a diet.[66, 67]

Mediterranean-style diet—One of the dietary patterns that have been extensively studied is the Mediterranean-style diet (MeDi). The MeDi, representing the typical dietary habits of the populations bordering the Mediterranean Sea, is a diet high in plant foods (such as fruits, nuts, legumes, and cereals) and fish, with olive oil as the primary source of monounsaturated fat (MUFA) and low to moderate intake of wine, as well as low intake of red meat and poultry.[68] The MeDi has been associated with a number of healthful outcomes including reduced risk of cardiovascular disease, cancer, and mortality.[69, 70] In a recent randomized trial of MeDi for the primary prevention of cardiovascular events in Spain, 7447 participants who were at high cardiovascular risk, but with no cardiovascular disease at enrollment, were randomly assigned to one of three diets: a MeDi supplemented with extra-virgin olive oil, a MeDi supplemented with mixed nuts, or a low-fat diet. After a median follow-up of 4.8 years, a MeDi supplemented with extra-virgin olive oil or nuts reduced the incidence of stroke and other major cardiovascular events.[71]

The relationship between MeDi and WMHV or BI has been explored in two community-based cohorts, both with participants residing in uptown New York. In the first study, BI and WMH were assessed using high-resolution structural MRI on 707 elderly participants of the Washington Heights/Hamilton Heights Columbia Aging Project (WHICAP) imaging substudy. The dietary assessments were administered an average of 5.8 years before the MRI. The study found that compared to the low (the lowest tertile of MeDi), those in the moderate (the middle tertile) and high (the highest tertile) MeDi adherence groups had significantly reduced odds of MRI-assessed infarcts. No significant association between MeDi and WMH was found in this subgroup of WHICAP population.[8] Nevertheless, higher adherence to MeDi was associated with a lower WMH burden in another population, the Northern Manhattan Study. In this study of 966 participants, each 1-point increase in MeDi score was associated with a significantly lower ($\beta = -0.04$, $p = 0.01$) value of log WMH volume.[72] In summary, both of these two studies suggested a possible protective association between increased adherence to a MeDi and MRI-assessed cerebrovascular diseases.

Nutrient biomarkers—In a recent study, nutrient biomarker patterns were constructed to represent the combined effect of nutrients.[73] In this study, a total of 30 plasma nutrient biomarkers were assayed in 104 participants of the Oregon Brain Aging Study cohort. Principal component analysis was used to construct nutrient biomarker patterns. The study found that subjects with higher marine ω -3 pattern scores had less WMH volume, although the association was attenuated and no longer significant after adjustment for depression and hypertension.[73] These findings are consistent with the CHS study findings of a beneficial role of fish and EPA + DHA on CSVD.[53]

Conclusions

In summary, research on the associations between diet and neuroimaging markers of cerebrovascular lesions has been relatively sparse. The few existing studies examined only a handful individual nutrients or foods (dietary intake of alcohol,[22–27] B vitamins,[41, 42] fish,[53] choline,[56] serum markers of antioxidants[57]), and a few food groups [65], dietary patterns[8, 72] and nutrient biomarker patterns [74]. For most of these dietary factors, findings can be considered as inconclusive either due to conflicting results from different studies or due to lack of replication. Alcohol is the food item studied relatively commonly but results are quite mixed with protective, [22, 23] detrimental, [24] or no effect[25–27] of alcohol intake on cerebrovascular lesions all being reported. Available evidence for B vitamins, fish, choline, and antioxidants usually come from one or two studies. Results from dietary pattern analysis tended to suggest a potential protective role of MeDi or a dietary pattern high in marine ω -3 consumption, but more studies are needed to confirm these findings. Therefore, for most of the dietary factors that have been examined, further study is necessary to replicate the existing findings, and to determine the role these foods may play on the preservation of brain health.

Future studies may also need to consider many other foods or nutrients in light of their association with clinical stroke. For example, long-term coffee drinking [75, 76], tea consumption,[77] dairy consumption [78–83] have all been associated with reduced risk of stroke, but no studies have examined how consumption of these foods may impact the MRI-measured BI or WMH. Besides MeDi, there are many ways to extract dietary patterns that could best represent the eating habits in a population. Available dietary pattern analysis methods, such as reduced rank regression analysis,[84] and cluster analysis,[85] have yet to be applied in this area.

In terms of study design, most of the past observational studies had a cross-sectional design, which limits assumptions of an etiological effect of diet on brain lesions. The effect of diet on longitudinal changes in imaging markers over time has been rarely studied. Some intervention studies are exceptions to this but they are quite few.

In summary, current evidence regarding the role of dietary factors on MRI-assessed cerebrovascular lesions is limited. Future studies are needed to confirm the previous findings, explore new dietary factors, and apply longitudinal study design.

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Reference

1. Feigin VL, et al. Stroke epidemiology: A review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. *Lancet Neurology*. 2003; 2(1):43–53. [PubMed: 12849300]
2. Kokubo Y. Traditional risk factor management for stroke: A never-ending challenge for health behaviors of diet and physical activity. *Current Opinion in Neurology*. 2012; 25(1):11–17. [PubMed: 22157106]
3. Hampel H, et al. Core candidate neurochemical and imaging biomarkers of Alzheimer's disease. *Alzheimer's and Dementia*. 2008; 4(1):38–48. This paper was presented in part by the 1st author at the 10th International Conference of Alzheimer's Disease and Related Disorders (ICAD), Madrid, Spain, July 2006, as an invited plenary lecture.
4. Longstreth WT Jr, et al. Incidence, manifestations, and predictors of brain infarcts defined by serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. *Stroke*. 2002; 33(10):2376–2382. [PubMed: 12364724]
5. Reitz C, et al. Validity of self-reported stroke in elderly African Americans, Caribbean Hispanics, and Whites. *Archives of Neurology*. 2009; 66(7):834–840. [PubMed: 19433651]
6. Longstreth WT Jr, et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people: The cardiovascular health study. *Stroke*. 1996; 27(8):1274–1282. [PubMed: 8711786]
7. Brickman AM, et al. Measuring cerebral atrophy and white matter hyperintensity burden to predict the rate of cognitive decline in Alzheimer disease. *Archives of Neurology*. 2008; 65(9):1202–1208. [PubMed: 18779424]
8. Scarmeas N, et al. Mediterranean diet and magnetic resonance imaging-assessed cerebrovascular disease. *Annals of Neurology*. 2011; 69(2):257–268. [PubMed: 21387371]
9. Price TR, et al. Silent brain infarction on magnetic resonance imaging and neurological abnormalities in community-dwelling older adults. The Cardiovascular Health Study. CHS Collaborative Research Group. *Stroke*. 1997; 28(6):1158–1164. [PubMed: 9183343]
10. Lopez OL, et al. Risk factors for mild cognitive impairment in the cardiovascular health study cognition study. *Archives of Neurology*. 2003; 60(10):1394–1399. [PubMed: 14568809]
11. Vermeer SE, et al. Silent brain infarcts and the risk of dementia and cognitive decline. *New England Journal of Medicine*. 2003; 348(13):1215–1222. [PubMed: 12660385]
12. Luchsinger JA, et al. Subclinical cerebrovascular disease in mild cognitive impairment. *Neurology*. 2009; 73(6):450–456. [PubMed: 19667320]
13. Vermeer SE, Longstreth WT Jr, Koudstaal PJ. Silent brain infarcts: a systematic review. *Lancet Neurol*. 2007; 6(7):611–619. [PubMed: 17582361]
14. DeCarli C, et al. Measures of brain morphology and infarction in the framingham heart study: establishing what is normal. *Neurobiol Aging*. 2005; 26(4):491–510. [PubMed: 15653178]
15. Pantoni L, Poggesi A, Inzitari D. The relation between white-matter lesions and cognition. *Curr Opin Neurol*. 2007; 20(4):390–397. [PubMed: 17620872]

16. Pantoni L, Garcia JH. Pathogenesis of leukoaraiosis: a review. *Stroke*. 1997; 28(3):652–659. [PubMed: 9056627]
17. DeCarli C, et al. Cerebrovascular and brain morphologic correlates of mild cognitive impairment in the National Heart, Lung, and Blood Institute Twin Study. *Arch Neurol*. 2001; 58(4):643–647. [PubMed: 11295996]
18. Inzitari D, et al. Vascular risk factors and leuko-araiosis. *Arch Neurol*. 1987; 44(1):42–47. [PubMed: 3800721]
19. Vermeer SE, et al. Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. *Stroke*. 2003; 34(5):1126–1129. [PubMed: 12690219]
20. DeBette S, et al. Association of MRI markers of vascular brain injury with incident stroke, mild cognitive impairment, dementia, and mortality: the Framingham Offspring Study. *Stroke*. 2010; 41(4):600–606. [PubMed: 20167919]
21. Patra J, et al. Alcohol consumption and the risk of morbidity and mortality for different stroke types—a systematic review and meta-analysis. *BMC Public Health*. 2010; 10:258. [PubMed: 20482788]
22. Mukamal KJ, et al. Alcohol consumption and subclinical findings on magnetic resonance imaging of the brain in older adults: the cardiovascular health study. *Stroke*. 2001; 32(9):1939–1946. [PubMed: 11546878]
23. den Heijer T, et al. Alcohol intake in relation to brain magnetic resonance imaging findings in older persons without dementia. *Am J Clin Nutr*. 2004; 80(4):992–997. [PubMed: 15447910]
24. Fukuda K, et al. Alcohol intake and quantitative MRI findings among community dwelling Japanese subjects. *Journal of the Neurological Sciences*. 2009; 278(1–2):30–34. [PubMed: 19059611]
25. Ding J, et al. Alcohol intake and cerebral abnormalities on magnetic resonance imaging in a community-based population of middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) study. *Stroke*. 2004; 35(1):16–21. [PubMed: 14657449]
26. Anstey KJ, et al. Weekly alcohol consumption, brain atrophy, and white matter hyperintensities in a community-based sample aged 60 to 64 years. *Psychosomatic Medicine*. 2006; 68(5):778–785. [PubMed: 17012533]
27. Paul CA, et al. Association of alcohol consumption with brain volume in the Framingham study. *Arch Neurol*. 2008; 65(10):1363–1367. [PubMed: 18852353]
28. Lee SC, et al. Prevalence and risk factors of silent cerebral infarction in apparently normal adults. *Hypertension*. 2000; 36(1):73–77. [PubMed: 10904015]
29. He K, et al. Folate, vitamin B6, and B12 intakes in relation to risk of stroke among men. *Stroke*. 2004; 35(1):169–174. [PubMed: 14671243]
30. Larsson SC, et al. Folate, vitamin B6, vitamin B12, and methionine intakes and risk of stroke subtypes in male smokers. *Am J Epidemiol*. 2008; 167(8):954–961. [PubMed: 18270369]
31. Weng LC, et al. Is ischemic stroke risk related to folate status or other nutrients correlated with folate intake? *Stroke*. 2008; 39(12):3152–3158. [PubMed: 18988909]
32. Van Guelpen B, et al. Folate, vitamin B12, and risk of ischemic and hemorrhagic stroke: a prospective, nested case-referent study of plasma concentrations and dietary intake. *Stroke*. 2005; 36(7):1426–1431. [PubMed: 15933256]
33. Huang T, et al. Meta-analysis of B vitamin supplementation on plasma homocysteine, cardiovascular and all-cause mortality. *Clin Nutr*. 2012; 31(4):448–454. [PubMed: 22652362]
34. Refsum H, et al. Homocysteine and cardiovascular disease. *Annu Rev Med*. 1998; 49:31–62. [PubMed: 9509248]
35. Hassan A, et al. Homocysteine is a risk factor for cerebral small vessel disease, acting via endothelial dysfunction. *Brain*. 2004; 127(Pt 1):212–219. [PubMed: 14607791]
36. Vermeer SE, et al. Homocysteine, silent brain infarcts, and white matter lesions: The Rotterdam Scan Study. *Ann Neurol*. 2002; 51(3):285–289. [PubMed: 11891822]
37. Wright CB, et al. Total homocysteine is associated with white matter hyperintensity volume: the Northern Manhattan Study. *Stroke*. 2005; 36(6):1207–1211. [PubMed: 15879345]

38. Dufouil C, et al. Homocysteine, white matter hyperintensities, and cognition in healthy elderly people. *Ann Neurol.* 2003; 53(2):214–221. [PubMed: 12557288]
39. Tangney CC, et al. Vitamin B12, cognition, and brain MRI measures: a cross-sectional examination. *Neurology.* 2011; 77(13):1276–1282. [PubMed: 21947532]
40. Pieters B, et al. Periventricular white matter lucencies relate to low vitamin B12 levels in patients with small vessel stroke. *Stroke.* 2009; 40(5):1623–1626. [PubMed: 19286604]
41. Cavalieri M, et al. B vitamins and magnetic resonance imaging-detected ischemic brain lesions in patients with recent transient ischemic attack or stroke: the VITAMINS TO Prevent Stroke (VITATOPS) MRI-substudy. *Stroke.* 2012; 43(12):3266–3270. [PubMed: 23093615]
42. Vermeulen EG, et al. Effect of homocysteine-lowering treatment with folic acid plus vitamin B on cerebrovascular atherosclerosis and white matter abnormalities as determined by MRA and MRI: a placebo-controlled, randomized trial. *Eur J Clin Invest.* 2004; 34(4):256–261. [PubMed: 15086356]
43. He K. Dietary fat and stroke: a different story from coronary heart disease. *Ital Heart J.* 2003; 4(12):821–823. [PubMed: 14976844]
44. Mozaffarian D, et al. Fish consumption and stroke risk in elderly individuals: the cardiovascular health study. *Arch Intern Med.* 2005; 165(2):200–206. [PubMed: 15668367]
45. Laaksonen DE, et al. Prediction of cardiovascular mortality in middle-aged men by dietary and serum linoleic and polyunsaturated fatty acids. *Arch Intern Med.* 2005; 165(2):193–199. [PubMed: 15668366]
46. Orenca AJ, et al. Fish consumption and stroke in men. 30-year findings of the Chicago Western Electric Study. *Stroke.* 1996; 27(2):204–209. [PubMed: 8571410]
47. Keli SO, Feskens EJ, Kromhout D. Fish consumption and risk of stroke. The Zutphen Study. *Stroke.* 1994; 25(2):328–332. [PubMed: 8303739]
48. Yuan JM, et al. Fish and shellfish consumption in relation to death from myocardial infarction among men in Shanghai, China. *Am J Epidemiol.* 2001; 154(9):809–816. [PubMed: 11682363]
49. Folsom AR, Demissie Z. Fish intake, marine omega-3 fatty acids, and mortality in a cohort of postmenopausal women. *Am J Epidemiol.* 2004; 160(10):1005–1010. [PubMed: 15522857]
50. Morris MC, et al. Fish consumption and cardiovascular disease in the physicians' health study: a prospective study. *Am J Epidemiol.* 1995; 142(2):166–175. [PubMed: 7598116]
51. Montonen J, et al. Fish consumption and the incidence of cerebrovascular disease. *Br J Nutr.* 2009; 102(5):750–756. [PubMed: 19356270]
52. Bravata DM, et al. Dietary fish or seafood consumption is not related to cerebrovascular disease risk in twin veterans. *Neuroepidemiology.* 2007; 28(3):186–190. [PubMed: 17703102]
53. Virtanen JK, et al. Fish consumption and risk of subclinical brain abnormalities on MRI in older adults. *Neurology.* 2008; 71(6):439–446. [PubMed: 18678827]
54. Zeisel SH, da Costa KA. Choline: an essential nutrient for public health. *Nutr Rev.* 2009; 67(11):615–623. [PubMed: 19906248]
55. Cho E, et al. Dietary choline and betaine assessed by food-frequency questionnaire in relation to plasma total homocysteine concentration in the Framingham Offspring Study. *Am J Clin Nutr.* 2006; 83(4):905–911. [PubMed: 16600945]
56. Poly C, et al. The relation of dietary choline to cognitive performance and white-matter hyperintensity in the Framingham Offspring Cohort. *Am J Clin Nutr.* 2011; 94(6):1584–1591. [PubMed: 22071706]
57. Schmidt R, Fau - Hayn M, et al. Magnetic resonance imaging white matter hyperintensities in clinically normal elderly individuals. Correlations with plasma concentrations of naturally occurring antioxidants. 1996 (0039-2499 (Print)).
58. Leppala JM, et al. Different risk factors for different stroke subtypes: association of blood pressure, cholesterol, and antioxidants. *Stroke.* 1999; 30(12):2535–2540. [PubMed: 10582974]
59. Ascherio A, et al. Relation of consumption of vitamin E, vitamin C, and carotenoids to risk for stroke among men in the United States. *Ann Intern Med.* 1999; 130(12):963–970. [PubMed: 10383366]

60. Hirvonen T, et al. Intake of flavonoids, carotenoids, vitamins C and E, and risk of stroke in male smokers. *Stroke*. 2000; 31(10):2301–2306. [PubMed: 11022054]
61. Yochum L, et al. Dietary flavonoid intake and risk of cardiovascular disease in postmenopausal women. *Am J Epidemiol*. 1999; 149(10):943–949. [PubMed: 10342803]
62. Voko Z, et al. Dietary antioxidants and the risk of ischemic stroke: the Rotterdam Study. *Neurology*. 2003; 61(9):1273–1275. [PubMed: 14610137]
63. Hankey GJ. Nutrition and the risk of stroke. *Lancet Neurology*. 2012; 11(1):66–81. [PubMed: 22172622]
64. Payne ME, et al. Food group intake and brain lesions in late-life vascular depression. *International Psychogeriatrics*. 2007; 19(2):295–305. [PubMed: 17054820]
65. Jacobs, Dr, Jr; Fau - Meyer, KA., et al. Whole-grain intake may reduce the risk of ischemic heart disease death in postmenopausal women: the Iowa Women's Health Study. (0002-9165 (Print)).
66. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. *Curr Opin Lipidol*. 2002; 13(1):3–9. [PubMed: 11790957]
67. Gu Y, Scarmeas N. Dietary Patterns in Alzheimer's Disease and Cognitive Aging. *Curr Alzheimer Res*. 2011
68. Roman B, et al. Effectiveness of the Mediterranean diet in the elderly. *Clin Interv Aging*. 2008; 3(1):97–109. [PubMed: 18494169]
69. Babio N, Bullo M, Salas-Salvado J. Mediterranean diet and metabolic syndrome: the evidence. *Public Health Nutr*. 2009; 12(9A):1607–1617. [PubMed: 19689829]
70. Sofi F, et al. Adherence to Mediterranean diet and health status: meta-analysis. *BMJ*. 2008; 337:a1344. [PubMed: 18786971]
71. Estruch R, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet. *N Engl J Med*. 2013
72. Gardener H, et al. Mediterranean diet and white matter hyperintensity volume in the Northern Manhattan Study. *Arch Neurol*. 2012; 69(2):251–256. [PubMed: 22332193]
73. Bowman GL, et al. Nutrient biomarker patterns, cognitive function, and MRI measures of brain aging. *Neurology*. 2012; 78(4):241–249. [PubMed: 22205763]
74. Witte AV, et al. Caloric restriction improves memory in elderly humans. *Proceedings of the National Academy of Sciences of the United States of America*. 2009; 106(4):1255–1260. [PubMed: 19171901]
75. Lopez-Garcia E, et al. Coffee consumption and risk of stroke in women. *Circulation*. 2009; 119(8):1116–1123. [PubMed: 19221216]
76. Larsson SC, et al. Coffee and tea consumption and risk of stroke subtypes in male smokers. *Stroke*. 2008; 39(6):1681–1687. [PubMed: 18369170]
77. Arab L, Liu W, Elashoff D. Green and black tea consumption and risk of stroke: a meta-analysis. *Stroke*. 2009; 40(5):1786–1792. [PubMed: 19228856]
78. Warensjo E, et al. Stroke and plasma markers of milk fat intake--a prospective nested case-control study. *Nutr J*. 2009; 8:21. [PubMed: 19457271]
79. Iso H, et al. Prospective study of calcium, potassium, and magnesium intake and risk of stroke in women. *Stroke*. 1999; 30(9):1772–1779. [PubMed: 10471422]
80. Abbott RD, et al. Effect of dietary calcium and milk consumption on risk of thromboembolic stroke in older middle-aged men. The Honolulu Heart Program. *Stroke*. 1996; 27(5):813–818. [PubMed: 8623098]
81. Kinjo Y, et al. Possible protective effect of milk, meat and fish for cerebrovascular disease mortality in Japan. *J Epidemiol*. 1999; 9(4):268–274. [PubMed: 10510585]
82. Umetsawa M, et al. Dietary intake of calcium in relation to mortality from cardiovascular disease: the JACC Study. *Stroke*. 2006; 37(1):20–26. [PubMed: 16339476]
83. Umetsawa M, et al. Dietary calcium intake and risks of stroke, its subtypes, and coronary heart disease in Japanese: the JPHC Study Cohort I. *Stroke*. 2008; 39(9):2449–2456. [PubMed: 18635855]
84. Gu Y, et al. Food combination and Alzheimer's disease risk: a protective diet. *Archives of Neurology*. 2010; 67(6):699–706. [PubMed: 20385883]

85. Samieri C, et al. Dietary patterns derived by hybrid clustering method in older people: association with cognition, mood, and self-rated health. *J Am Diet Assoc.* 2008; 108(9):1461–1471. [PubMed: 18755318]

Table 1
Studies on the association between dietary factors and MRI-measured white matter hyperintensity or brain infarcts.

Publication	Population	Study design	Dietary factor	MRI outcome: WMH	MRI outcome: SBI
Alcohol					
Lee 2000	Korean, 994 aged 20–79 healthy subjects	Cross-sectional	nondrinker, mild drinker (1–2 times/week), or frequent drinker (>=3 times/week)	N/A	Mild alcohol intake associated with less brain infarcts compared to nondrinkers; no association among aged >=50
Mukamal 2001	Cardiovascular Health Study (CHS), 3660 adults 65 years, mean 75 yrs,	Cross-sectional	none, former, <1, 1–7, 7–15, and 15 drink/week.	Moderate associated with less WM grade compared to non-drinkers.	Alcohol intake inversely associated with infarcts.
Ding 2004	Atherosclerosis Risk in Communities (ARIC) Study; 1909 middle-aged adults (40% men and 49% blacks)	Cross-sectional	never, former, <1, 1–7, and 7 drinks/week. (>=14 in the moderate group)	No linear association	No association after adjustment
den Heijer 2004	Rotterdam Scan Study, 1074 persons aged 60–90 without dementia	Cross-sectional	Lifetime abstinence, former, <1, 1–7, 7–28, and 28 drinks/week	Moderate associated with less WM grade compared to non-drinkers.	No association after adjustment
Anstey 2006	Australia 385 PATH Through Life Project participants aged 60–64	Cross-sectional	Amount of alcohol intake	No association.	N/A
Paul 2008	Framingham Offspring Study; 1839 (861M); 60 yrs (range 33–88)	Cross-sectional	abstainers, former, 1–7, 8–14, and 14 drink/week (55% m)	No association.	N/A
Fukuda 2009	385 Japan >or= 40 years, mean 67.2	Cross-sectional	non-drinkers <7, and moderate drinkers (7 drinks/week)	Moderate associated with increased WMH volume compared to non-drinkers.	Moderate associated with increased BI compared to non-drinkers.
Fish, EPA+DHA					
Virtanen 2008	Cardiovascular Health Study (CHS), 3660 adults 65 years, mean 75 yrs. Participants with known cerebrovascular disease were excluded from the analyses.	Cross-sectional and Longitudinal	Dietary fish consumption, and dietary intake of EPA+DHA	N/A	Higher consumption of tuna/other fish or EPA+DHA associated with lower risk of prevalent and incidence of subclinical BI.
B vitamins-related factors					
Hassan 2004	142 Caucasian patients with an average age 67 with cerebrovascular brain	Cross-sectional	serum Hcy concentration	Hcy levels were higher amongst patients with ischaemic leukoaraiosis	Hcy levels were higher amongst patients with isolated lacunar

Publication	Population	Study design	Dietary factor	MRI outcome:WMH	MRI outcome: SBI
Vermeer 2002	lesions and 172 community controls of similar age and sex. 1077 participants aged 60 to 90 years from the Rotterdam Scan Study	Cross-sectional	Total plasma Hcy Level	compared with both controls and those with isolated lacunar infarction. The severity of periventricular WMH and extent of subcortical WMH were significantly associated with total Hcy levels.	infarction compared with controls. The risk of silent brain infarcts increased with increasing total Hcy levels.
Wright 2005	259 stroke-free participants (with mean age of 65) of the Northern Manhattan Study (NOMAS)	Cross-sectional	Serum tHcy and MMA levels, Vitamin B12 deficiency was defined as an MMA level >271 nm/L.	Higher levels of tHcy were associated with WMHV adjusting for sociodemographics and vascular risk factors.	N/A
Dufouil 2002	841 subjects of the Epidemiology of Vascular Ageing (EVA) study	Cross-sectional	Plasma Hcy, folates, and B12 vitamin concentrations	Frequency of moderate or severe WMH increased slightly by level of Hcy, but the linear trend did not reach significance ($p = 0.09$).	N/A
Tangney 2011	121 community-dwelling participants of the Chicago Health and Aging Project (CHAP),	Cross-sectional	Serum markers of vitamin B12 status (including vitamin B12, homocysteine, methylmalonic acid, cystathionine, and 2-methylcitric acid)	Hcy concentration was associated with WMH volume; vitamin B12, methylmalonic acid, cystathionine, and 2-methylcitric acid were not associated with WMH volume.	N/A
Pieters 2009	124 Dutch patients with first lacunar stroke	Cross-sectional	serum vitamin B12	vitamin B12 level showed a statistically significant association with periventricular WMH, but not with deep WMH.	N/A
Vermeulen 2004	158 healthy siblings (mean age 46 years) of patients with premature atherosclerotic disease, followed up for 2 years.	randomized, placebo-controlled trial	5 mg of folic acid plus 250 mg of vitamin B6 daily (n = 78) or placebo medication (n = 80).	Vitamin treatment, as compared with placebo, was associated with nonsignificantly less severe WMH.	N/A
Cavallieri 2012	174 patients, who had a stroke or a transient ischemic attack in the past 7 months, from the VITamins TO Prevent Stroke (VITATOPS) trial, followed up for 2 years.	Randomized, placebo-controlled trial using	B vitamins (2mg folic acid, 25mg vitamin b6, and 0.5mg vitamin b12) or placebo.	Treatment with B vitamins or placebo did not differ in progression of WMH and frequency of incident lacunes	N/A
Choline					
Poly 2011	1391 subjects aged 36–83 years from the Framingham Heart Study Offspring Study	Cross-sectional	dietary choline intake	Remote choline intake was inversely related to log-transformed WMHV	N/A

Publication	Population	Study design	Dietary factor	MRI outcome:WMH	MRI outcome: SBI
Antioxidants					
Schmidt 1996	355 clinically normal participants aged 45 to 75 years from the Austrian Stroke Prevention Study	Cross-sectional	plasma concentrations of antioxidants including zeaxanthin, cryptoxanthin, canthaxanthin, lycopene, alpha- and beta-carotene, retinol, gamma- and alpha-tocopherol (vitamin E), as well as ascorbate	Serum vitamin E (or tocopherol) and lycopene were found to be inversely correlated with WMH.	N/A
Food groups					
Payne 2007	54 vascular depression (vascular depression defined by presence of WMH on brain MRI) subjects aged 60 or older from North Carolina.	Cross-sectional	Consumption of six food groups (fruits, vegetables and whole grains, high and low-fat dairy products) calculated from the Block Food Frequency Questionnaire.	high-fat dairy and whole grains were positively associated with brain lesion (white matter hyperintensity plus subcortical gray matter lesions) volume among individuals with current or prior vascular depression	N/A
Dietary patterns					
<i>Mediterranean-style diet</i>					
Scarmeas 2011	707 elderly participants of the Washington Heights/Hamilton Heights Columbia Aging Project (WHICAP)	Cross-sectional	MeDi score calculated from Food Frequency Questionnaire.	Not associated.	Compared to the low (the lowest tertile of MeDi) adherence group, those in the moderate (the middle tertile) and high (the highest tertile) MeDi adherence group had a 22% and 36% reduced odds (p for trend = 0.04), respectively.
Gardener 2012	966 participants of the Northern Manhattan Study	Cross-sectional	MeDi score calculated from Food Frequency Questionnaire.	Each 1-point increase in MeDi score was associated with a significantly lower (=-0.04, p=0.01) value of log WMH volume.	N/A
<i>Nutrient biomarker patterns</i>					
Bowman 2012	a total of 30 plasma nutrient biomarkers were assayed in 104 participants of the Oregon Brain Aging Study cohort.	Cross-sectional	Eight nutrient biomarker patterns derived from Principal component analysis of 30 plasma nutrient biomarkers.	Subjects with higher marine -3 pattern scores had less WMH volume	N/A