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NUTRITION AND VASCULAR DEMENTIA

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Abstract: *Objective:* The objective of this review was to elucidate the relationship between VaD and various nutritional factors based on epidemiological studies. *Background:* Vascular dementia (VaD) is the second most common type of dementia. The prevalence of VaD continues to increase as the US population continues to grow and age. Currently, control of potential risk factors is believed to be the most effective means of preventing VaD. Thus, identification of modifiable risk factors for VaD is crucial for development of effective treatment modalities. Nutrition is one of the main modifiable variables that may influence the development of VaD. *Methods:* A systematic review of literature was conducted using the PubMed, Web of Science, and CINAHL Plus databases with search parameters inclusive of vascular dementia, nutrition, and vascular cognitive impairment (VCI). *Results:* Fourteen articles were found that proposed a potential role of specific nutritional components in VaD. These components included antioxidants, lipids, homocysteine, folate, vitamin B12, and fish consumption. Antioxidants, specifically Vitamin E and C, and fatty fish intake were found to be protective against VaD risk. Fried fish, elevated homocysteine, and lower levels of folate and vitamin B12 were associated with increased VaD. Evidence for dietary lipids was inconsistent, although elevated midlife serum cholesterol may increase risk, while late-life elevated serum cholesterol may be associated with decreased risk of VaD. *Conclusion:* Currently, the most convincing evidence as to the relationship between VaD and nutrition exists for micronutrients, particularly Vitamin E and C. Exploration of nutrition at the macronutrient level and additional long term prospective cohort studies are warranted to better understand the role of nutrition in VaD disease development and progression. At present, challenges in this research include limitations in sample size, which was commonly cited. Also, a variety of diagnostic criteria for VaD were employed in the studies reviewed, indicating the need for constructing a correct nosological definition of VaD for consistency and conformity in future studies and accurate clinical diagnosis of VaD.

Key words: Vascular dementia, nutrition, diet.

Introduction

In the United States, the proportion of people over the age of 65 is projected to increase from 35 million in the year 2000 to 71 million in the year 2030 (1). This aging of the population will have important public health implications as there will be a greater need for geriatric care, and an anticipated rise in the incidence of chronic degenerative diseases. One area that has received special attention over the last few years has been dementia, and more recently vascular dementia (VaD).

Despite multiple attempts over the past 80 years, there is a lack of universal neuropathologic diagnostic criteria for VaD (2). It is generally described as cognitive decline caused by vascular brain lesions and disorders of cerebral vessels (3, 4). The diagnosis is usually based on a temporal relation between occurrence of vascular lesions and dementia, in the absence of other degenerative disease (5, 6). Currently, VaD is considered the second most common type of dementia, yet may also be the most under-diagnosed type of dementia (7). The Aging, Demographics, and Memory Study (ADAMS) estimates the prevalence of VaD in the US for those aged 71 and older to be approximately 594,000; however, this might be understated as the prevalence may actually be as high as 1 million (7, 8). Another unique aspect of this disease is that survival is lower following disease onset when compared to Alzheimer's disease (AD) (9). Healthcare utilization costs are also higher for VaD care than AD, other dementias, or cerebrovascular disease without dementia (10).

Currently, control of VaD risk factors is believed to be the most effective way to prevent onset or delay progression of the disease (11). Such risk factors include atherosclerosis, lipoproteins, diabetes mellitus, stroke, hypertension, obesity, and smoking (12-18). Diet is an important modifiable factor that has been shown to have direct and indirect influence on the development of these vascular risk factors, which may lead to vascular cognitive impairment (VCI), and ultimately VaD. Therefore, dietary interventions are believed to be effective and fundamental in treatment modalities for abatement of disease onset and progression.

Although it is posited that the nutritional risk factors for VaD are similar to those for stroke, different mechanisms may be implicated, through which diet may impact cerebrovascular physiology and the different pathways that lead to VaD. Further, though there is significant literature associating nutrition and AD (19, 20), reviews relating VaD and nutrition are lacking in the literature. Hence, the purpose of this review is to better elucidate the relationship between nutritional factors and VaD.

Methods

A systematic literature review was conducted using the PubMed, CINAHL, and Web of Science databases with search

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parameters inclusive of vascular dementia, vascular cognitive impairment, nutrition, and diet. Studies not available in English were excluded. Our initial search included studies on humans only and studies in which VaD was the primary disease of interest. However, we were unable to identify any articles within these search criteria. We then expanded the inclusion criteria to studies with VaD as one of the diseases of interest. From this search we were able to identify specific nutrients (antioxidants, dietary lipids, B vitamins, monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA)), foods (fatty fish), and plasma lipids (total cholesterol, high-density lipoprotein (HDL), low-density lipoproteins (LDL), and triglycerides) that may be associated with VaD. The references of the selected studies were also reviewed to ensure all pertinent and relevant articles were included.

Results

In our search, fourteen articles were found that met the inclusion criteria, of which 5 were cross-sectional, 7 prospective, and 2 retrospective longitudinal studies (Table 1).

Antioxidants: Four articles were identified that studied the association of VaD with serum levels of α-tocopherol (vitamin E) and vitamin C. Prospective studies have demonstrated a protective effect of antioxidants obtained from supplements on VaD risk. In a 13-year prospective follow-up study among Japanese-American men living in Oahu, Hawaii, Masaki et al. (21) observed an 88% reduced risk of developing VaD among subjects who used both Vitamin C and E supplements together (Adjusted odds ratio (ORadj) = 0.12, confidence interval (CI): 0.02-0.88, $p < 0.05$), but not when using vitamin C alone (ORadj = 0.83, CI: 0.27-2.57) or vitamin E alone (ORadj =

Table 1
Summary findings of the relationship between nutritional risk factors and VaD*

Study	Study Design and follow-up	Sample size	Factors studied	VaD diagnostic criteria	Outcome
Masaki et al. (14) (2000)	Prospective Cohort, 13 years	3,734, age 71-93y/o (47 AD, 35 VaD, 50 other)	Vitamin C and E supplement use	ADDTC[1]	Vitamin C and E combined ↓ risk of VaD.
Maxwell et al. (15) (2005)	Prospective longitudinal, 5 years	894, 65+y/o (107 AD, 230 other)	Vitamin antioxidant supplement use	ICD-10[9]	Antioxidants assoc. w/ ↓ risk of incident VCI.
Laurin et al. (16) (2004)	Prospective cohort, 30.2 years	2459 (102 AD, 38 AD with contrib. CVD, 44 VaD, 51 other)	Dietary energy, β-carotene, flavonoids, vitamin A and C	CADDTC[16]	No assoc. of antioxidants and risk of VaD.
Ryglewicz et al. (17) (2002)	Cross-sectional	114 (26 AD, 42 VaD, 46 age-matched controls)	Plasma α-tocopherol, LDL[6]	NINDS-AIREN[4], MRI[2]/ CT[5] Hachinski Ischemic scale	↓ α-tocopherol, LDL[6], TG[7] ($p<0.05$) in VaD.
Koseoglu & Karaman (18) (2007)	Cross-sectional	168 , >65y/o (51 AD, 67 VaD, 40 controls)	Plasma HCY[3], folate, vitamin B12	NINDS-AIREN[4], MRI[2]/CT[5]	↑ HCY[3], ↓folate and B12 in VaD and AD, diff. greater in VaD.
Quadri et al. (19) (2004)	Cross-sectional	228, 60+y/o (74 AD, 18 VaD, 81 MCI, 55 controls)	Plasma HCY[3], folate, vitamin B12	CERAD[13], Hachinski Ischemic Score	↑ HCY[3] among VaD subjects
Malaguarnera et al. (20) (2004)	Cross-sectional	68, 62-60y/o (22 VaD, 22 AD, 24 controls)	Plasma HCY[3], vitamin B12, folate, PLP[14], cholesterol, HDL[15], LDL[6], TG[7]	MRI[2]/CT[5], NINDS-AIREN	↑ HCY[3], ↓folate, ↑ TG[7] and LDL[6] in VaD only.
Kalmijn et al. (21) (1997)	Prospective cohort, 2.1 years	5,386, >55y/o (42 AD, 7 VaD, 9 other)	Dietary total fat, SFA[10], cholesterol, PUFA[11]	NINDS-AIREN[4] (some underwent MRI[2])	VaD assoc. w/ ↑total and SFA[10].
Engelhart et al. (22) (2002)	Prospective cohort, 6 years	5,395, 60-73y/o (146 AD, 29 VaD, 22 other)	Dietary total fat, SFA10, cholesterol, trans fat, MUFA[12] and PUFA[11]	NINDS-AIREN[4] (some underwent MRI[2])	Dietary fats not associated w/ ↑ risk of dementia
Otsuka et al. (23) (2002)	Case control, retrospective	91, (27 AD, 15 VaD, 49 age-matched controls)	Dietary SFA[12], PUFA[11], MUFA[12], vitamin B, C, antioxidants, and macronutrients	NINDS-AIREN[10], MRI[2]	↑energy, ↓antioxidant, ↑n-6 and ↓n-3 intake among VaD.
Huang et al. (24) (2005)	Prospective Cohort, 5.4 years	2,233 Medicare participants >65y/o (245 AD, 62 VaD, 151 mixed, 557 MCI, 227 other)	Dietary lean and fatty fish	ADDTC1, MRI[2]	Low intake of fried lean fish assoc. w/ ↑ risk, fatty fish assoc. ↓ risk (insignif) of VaD.
Reitz et al. (25) 2004	Cross-sectional	4316, ≥65y/o (244 AD, 119 VaD, 231stroke w/out dementia, 2224 controls	Plasma LDL[6], HDL[15], total cholesterol	standard research criteria, diagnosis by physicians, neurologists and history or clinical evidence of stoke	↑ non-HDL and LDL[6], and ↓ HDL[15] weakly assoc. w/ ↑ VaD risk
Soloman et al. (26) (2009)	Retrospective cohort	9844, 66-72y/o (496 AD, 127 VaD, 9248 controls)	Plasma midlife serum cholesterol	ICD-9 CM[17] 331.0 and 290.4	↑ midlife cholesterol assoc. w/ ↑ risk of VaD
Mielke et al. (27) (2005)	Prospective longitudinal, 18 years	382, 79-88y/o (19 AD, 23 VaD, 3 other)	Plasma total cholesterol and TG[7]	Case records, DSM-IIIR[8], NINDS-AIREN[4], CT[5]	↑ cholesterol in late life assoc. w/ ↓ risk in AD and VaD.

1ADDTC, Alzheimer's Disease Diagnostic and Treatment Centers; 2MRI, Magnetic Resonance Imaging; 3HCY, Homocysteine; 4NINDS-AIREN, National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences; 5CT, Computed Tomography; 6LDL, low-density lipoprotein; 7TG, Triglycerides; 8DSM-IIIR, Diagnostic and Statistical Manual of Mental Disorders-III-R; 9ICD-10, International Classification of Disease-10; 10SFA, Saturated fatty acids; 11PUFA, polyunsaturated fatty acid;12MUFA, monounsaturated fatty acid; 13CERAD, Consortium to Establish a Registry for Alhzheimer's Disease; 14PLP, Pyridoxal phosphate; 15HDL, high-density lipoprotein; 16CADDTC, California Alzheimer's Disease Diagnostic and Treatment Centers;17ICD-9 CM, International Classification of Disease-9 Clinical Modification;

1.28, CI: 0.35-4.69) as compared to non-demented subjects. A minimally protect effect was also observed for mixed/other dementia subtypes, which included all dementias other than pure VaD and pure AD, when vitamins E and C were consumed together (ORadj = 0.31, CI: 0.11-0.89). However, no protective effect was found for AD with any combination of vitamin use. In the same study, the long-term effect of supplement use was assessed among subjects that were not diagnosed with dementia at follow-up. Compared to non-users, long-term combined use of both vitamins E and C was associated with significantly better cognitive function (OR: 1.74, 95% CI: 1.26-2.39) while more recent use was not associated with better cognition (21). In the same study, the long-term effect of supplement use was assessed among subjects that were not diagnosed with dementia at follow-up. Compared to non-users, long-term combined use of both vitamins E and C was associated with significantly better cognitive function (OR: 1.74, 95% CI: 1.26-2.39) while more recent use was not associated with better cognition (21).

In a similar study, Maxwell et al. (22) prospectively examined the effects of antioxidant supplementation on the risk of VCI and cognitive decline based on Mini Mental State Examination (3MS) scores over a 5-year period. VCI included participants with VaD, possible AD with vascular components, and VCI without dementia. After five years follow-up, and adjustment for age, gender, baseline 3MS score, history of stroke and arterial hypertension, a statistically significant risk reduction of VCI was observed among consumers of any vitamins(e.g. vitamin C, E, or multivitamin) (ORadj = 0.34, CI: 0.13-0.89) but not with vitamin E and C or multivitamin use (vitamin E and C with or without multivitamins, vitamin E and multivitamins, vitamin C and multivitamins, and multivitamins alone, ORadj = 0.39, CI: 0.14-1.14), vitamin C alone (ORadj = 0.31, CI: 0.04-2.74), or vitamin E alone (data not shown) as compared to non-users. Participants consuming any vitamins (ORadj = 0.57, CI: 0.43-0.93) or vitamin C and E supplements and multivitamins (ORadj = 0.51, CI: 0.29-0.90) were also less likely to have decreased cognitive decline at follow-up. In patients with probable AD and incident dementia, no association was noted with any combinations of vitamins (ORadj = 1.00, CI: 0.53-1.87 and ORadj = 0.79, CI: 0.48-1.32, respectively) (22).

On the other hand, when antioxidant intake was measured from a 24-hour dietary recall, Laurin et al. (23) did not find a statistically significant relationship between beta carotene, vitamin C or flavonoid intake in midlife, and risk of developing late life incident dementia, AD, Alzheimer's with and without cerebrovascular disease, and VaD. Participants' use of nutrients were divided into quartiles based on the distribution of intake within the sample, with the first quartile (the reference group) having the lowest intake and the fourth having the highest intake. A slight increase in risk of dementia (Relative Risk (RR): 1.47, CI: 1.01-2.14) and AD (RR: 1.84, CI: 1.04-3.25) was observed in the second quartile of energy-adjusted intake of vitamin E, but not in third or fourth quartiles. Risk of AD with and without CVD also showed significance for the second (RR: 1.92, CI: 1.16-3.18) and fourth (RR: 1.78, CI: 1.06-2.98) quartiles. The energy-adjusted intake of vitamin E was not related to the incidence of VaD. All relative risks were adjusted for age, education, smoking status, alcohol intake, BMI, physical activity, blood pressure, year of birth, total energy intake, cholesterol, CVD, supplemental vitamin intake, and Apolipoprotein (APOE) ε4 (23).

Finally, in a cross-sectional analysis, Ryglewicz et al. (24) found that serum levels of α-tocopherol were lower among VaD patients (mean 9.9 ± 3.48 μg/ml, $p < 0.05$) as compared to AD patients (mean 12.8 ± 3.42 μg/ml, $p < 0.05$).

B-Vitamins: Evidence as to the relationship between B-vitamins and VaD comes from cross-sectional studies. Koseoglu et al. (25) found serum homocysteine (HCY) to be negatively correlated with serum vitamin B12 and folate levels in VaD patients ($p<0.05$), but not in AD patients or controls subjects. Significantly higher HCY (mean 18.6 ± 4.15 μmol/L, $p < 0.001$), lower folate (mean 8.8 ± 1.59 ng/mL, $p < 0.05$) and lower vitamin B12 levels (mean 230.17 ± 7.26 pg/mL, $p < 0.001$) were observed among VaD subjects as compared to AD patients and controls. Significantly higher HCY (mean: 14.2 ± 2.97 μmol/L, $p<0.001$, and lower Vitamin B12: (mean: 280.6 ± 20.86 pg/mL, $p<0.001$, and folate: (mean: 9.45 ± 1.94 ng/mL, $p<0.001$) was also observed for AD subjects as compared to controls. (25). Similarly, Quadri et al. (26) found low serum folate levels to be significantly associated with mild cognitive impairment (MCI) and high HCY levels with dementia. The highest HCY concentrations were observed amongst the VaD participants.

Malaguarnera et al. (27) compared VaD patients with AD patients and healthy controls and reported increased serum HCY levels in VaD patients (mean 26 ± 6.58 μmol/l, $p<0.00001$) as compared to controls (10.7±2.81 nmol/l) and AD patients (22.3±4.51 μmol/l, $p<0.001$). Significantly reduced serum folate was observed in both VaD (mean 10.8±2.81 l μmol/l) and AD patients (mean 10.0±2.72 nmol/l, $p<0.001$) compared to controls. Reduced serum vitamin B12 levels were only statistically significant for AD (mean 392.1 ± 65.32 pmol/l for AD, $p<0.045$) as compared to controls.

Dietary lipids: Three articles that implicated dietary lipids in VaD were reviewed. Within the large prospective Rotterdam study, contradictory findings were reported when the study was carried out with two different follow up periods (28, 29). Kalmijn et al. (28) first investigated the relationship between total fat, saturated fat, trans fats, cholesterol, MUFA, and n-3 and n-6 PUFA in total dementia, AD without cerebrovascular disease, and dementia with a vascular component (VaD and AD with cerebrovascular disease). 5,386 non-demented participants were followed for 2.1 years, at which point 58 subjects were diagnosed with dementia (37 AD, 5 AD with cerebrovascular disease, 7 VaD, and 9 other types of dementia). Intakes were categorized into tertiles, the lowest intake being

the first tertile as the referent category, and the highest being the third tertile. Individuals in the third tertile, who consumed the highest amount of total fat, had significantly higher risk of acquiring total dementia (RR: 2.4, CI: 1.1-5.2, p trend: 0.02), compared to the referent group. Intakes of saturated fat and cholesterol in the third tertile were associated with increased risk of total dementia, however these trends were not significant (RR: 1.9, CI: 0.9-4.0, p trend: 0.12; RR: 1.7, CI: 0.9-3.2, p trend: 0.11, respectively) after adjusting for age, sex, education, and total energy intake. The second and third tertiles of total fat intake increased risk of dementia with a vascular component although not significant (RR: 1.7, CI: 0.3-10.3; RR: 3.0, CI: 0.6-14.7, respectively). The third tertile of saturated fat intake was also associated with increased risk of dementia with a vascular component (RR: 2.9, CI: 0.6-13.8, p trend: 0.01). In contrast, the highest tertile of cholesterol intake was not associated with dementia with a vascular component (RR: 0.9, CI: 0.2-3.7, p: 0.80) (28). However, a subsequent Rotterdam study followed 5,395 participants for 6 years, during which 197 subjects developed dementia, including 146 AD, 29 VaD, and 22 other types of dementia. Here, higher intake of total fat, saturated fat, trans fat, cholesterol and low intake of MUFA, n-6 PUFA, and n-3 PUFA were not associated with risk of dementia or subtypes after adjusting for age, sex, education, total energy intake, vitamin E, energy-adjusted fatty acids, and cholesterol (29).

Differences in overall dietary intake between VaD and AD patients have also been examined. Otsuka et al. (30) compared dietary patterns between AD patients and VaD patients against age-matched male controls in a cross-sectional study. N-6 PUFA consumption and n-6 to n-3 ratios were both found to be significantly higher in VaD ($p<0.05$) and AD ($p<0.001$) subjects as compared to controls. Both groups had similar nutritional status, including antioxidant deficiencies and overall higher energy intake (30).

Fatty Fish: The relationship between fish consumption and VaD was investigated in one prospective study among 2,233 participants, of which 50 developed pure VaD and 190 developed AD. As compared to intake of <0.25 servings per week, intake of 0.25-2 servings of fried fish per week was associated with a higher risk of VaD (Hazard ratio (HR): 2.6, CI: 1.39-4.96), but not when consumption was increased to 2-4 servings per week (HR: 1.68, CI: 0.74-3.84). Intake of fatty fish was categorized into four levels of intake, with <0.25 servings per week as the lowest (referent) group, and the highest being ≥4 servings per week. As compared to the lowest consumers, increasing consumption of fatty fish was associated with lower risk of developing dementia (HR: 0.65, CI: 0.43-0.98 for the highest level), but results were attenuated when controlling for education and income (HR: 0.79, CI: 0.53-1.20); a similar dose response relationship was observed for AD (HR: 0.54, CI: 0.31-0.95 for highest quartile) with attenuation after controlling for education and income (HR: 0.69, CI: 0.91-1.22). Finally, the protective effect of fatty fish on dementia was found to occur with the absence of the APOE ε4 allele, (HR: 0.54, CI: 0.36-0.95 for the highest level), although the results were attenuated when education and income were considered (31).

Plasma lipids: Five articles were found that made observations between plasma lipids and VaD. In a cross-sectional analysis of 2820 subjects, Reitz et al. (32) observed a significant decrease in the prevalence of VaD among subjects in the second and fourth (highest) quartiles of plasma HDL (OR: 0.46, CI: 0.27-0.79, OR: 0.47, CI: 0.27-0.83, respectively) and a non-significant increased risk with higher non-HDL (OR: 1.60, CI: 0.92-2.79) as compared to the lowest quartile. In the same study, prospective analysis of 1168 subjects with a mean follow-up of 4.8 ± 2.9 years, indicated significant increased risk of VaD with increasing quartile of non-HDL (HR: 2.38, 95% CI: 1.05-5.37, in the highest (fourth) quartile)) and LDL (HR: 2.45 95% CI: 1.05-5.70, in the highest (fourth quartile)) (32).

A recent retrospective cohort study assessed midlife (40-45 years old) serum cholesterol levels and risk of future AD and VaD. At 30 years follow-up, 127 VaD and 469 AD cases were identified. After adjustment for age, sex, race/ethnic group, midlife BMI, diabetes, and hypertension, high serum cholesterol (≥ 240 mg/dL) at midlife was associated with increased risk of AD only (HR: 1.57, C.I: 1.23-2.01), whereas borderline (200-239 mg/dL) midlife cholesterol levels were associated with risk of VaD only (HR-1.5, 95% CI: 1.01-2.23), with desirable levels (<200 mg/dL) as the referent category (33). On the other hand, in an 18 year follow-up longitudinal study, Mielke et al. (34) found that high levels of total plasma cholesterol in late life was associated with a reduced risk of incident dementia, which included AD, VaD, and other dementias. Increased total plasma cholesterol was associated with reduced risk of incident dementia when cholesterol was measured at age 70 (HR: 0.77; C.I: 0.61-0.96), 75 (HR: 0.70; C.I: 0.52-0.93) and 79 (HR: 0.73; C.I: 0.55-0.98), after adjustment for body mass index (BMI), diastolic blood pressure, sex, education, and smoking. The reduced risk was observed only in the highest quartiles of cholesterol level at age 70 (HR: 0.31; C.I: 0.11-0.85), age 75 (HR: 0.20, C.I: 0.05-0.75), and age 79 (HR: 0.45, C.I: 0.17-1.24). No statistically significant relationship between triglyceride levels and dementia in any age group were observed (34).

Malaguarnera et al. (27) described increased levels of triglycerides and LDL only in VaD patients and not AD patients; hypertension, coronary heart disease, and diabetes were more common among VaD subjects than AD subjects. On the contrary, Ryglewicz et al. (24) found levels of triglycerides and LDL to be significantly lower in VaD patients as compared to AD patients. Although susceptibility of LDL to oxidation was slightly higher for VaD in comparison to AD patients, these results were not statistically significant.

Discussion

Our review uncovered some associations between various nutritional factors and VaD. While antioxidant supplementation, specifically vitamins C and E, appears to be protective against VaD and VCI, this relationship is not evident

for dietary antioxidants (21-23). Cross sectional studies demonstrated higher HCY, and lower folate and Vitamin B12 levels among individuals with AD, yet this was more pronounced in VaD (25-27). Although it appears that elevated midlife serum cholesterol may increase risk (33) and late-life elevated serum cholesterol may decrease risk of VaD (34), evidence regarding the relation between dietary lipid levels and VaD is less clear (28, 29). One study reported a non-significant beneficial association of fatty fish consumption and VaD, whereas lean fried fish was associated with increased risk, but the latter conclusion was only observed for the lowest intake group (31).

Evidence for the biological role of particular nutrients in the etiology of VaD supports both direct mechanisms, or neurodegeneration, and indirect pathways that may influence vascular risk factors, which are, for the greater part, related to oxidation-reduction pathways (35). Reduced levels of docosahexaenoic acid (DHA), a PUFA that is highly concentrated in the brain and predominantly found in fatty fish, is associated with cognitive decline (36). DHA plays a role in physiological pathways that not only modulate vascular risk factors, but also reduces neuroinflammation and oxidative damage that may lead to neuronal dysfunction. It is thought that the aforementioned mechanisms may be effective in VaD prevention and treatment (37). However, to date, only one study which was limited by the paucity of VaD subjects, has examined this relationship, and further investigation is warranted (31). For antioxidants, the most popular explanation for their salutary effect in VaD is thought to be through prevention of stroke; however, an alternative hypothesis may suggest a straightforward protective effect on VaD. In the study conducted by Masaki et al. (21) the prevalence of stroke was highest among the VaD subjects, yet no association was detected between antioxidant use and stroke. Further, controlling for stroke did not impact the observed protective effect of antioxidants on VaD. Therefore it is possible that, as opposed to decreasing the frequency of strokes, antioxidant vitamins may protect against VaD by reducing the post-stroke sequelae and ischemia related neuronal injury (36, 37).

Current evidence suggests HCY may be an appropriate marker for prediction and prognosis of neurodegenerative diseases (38, 39). It is thought to potentiate oxidative injury and accelerate neurodegenerative processes (40). Hyperhomocysteinemia can cause small vessel injury secondary to oxidative stress and subsequent accumulation of neurotoxic byproducts, and is thought to be the mechanism shared between dementia and stroke (39). Therefore, decreasing HCY may reduce risk of vascular lesions and impede the progression of dementia. HCY metabolism is also dependent on antioxidants modulating specific biochemical pathways, such as folate, vitamins B12 and B6 (25, 27). In the present review, the relationship between elevated HCY and low folate and vitamin B12 was more pronounced in VaD as compared to AD subjects. Koseoglu et al. (25) also found that the relationship between high HCY and low folate and vitamin B12 only occurred in VaD subjects, not in AD or controls, and this may suggest that the pathogenesis of elevated HCY may be different in AD as compared to VaD. Suffice it to say, research is needed to further elucidate the specific mechanisms.

The link between cholesterol and VaD is less clear. Solomon et al. (33) attributed the conflicting evidence to a number of mechanisms. First, although the association of low HDL and high LDL with CHD and atherosclerosis is well documented the relationship between cholesterol and stroke is less clear. Secondly, not all individuals with stroke subsequently end up with VaD. Moreover, the relationship between VaD and cholesterol could vary depending on the type of vascular lesion contributing to VaD, which could have different risk factor profiles and may lead to different types of VaD. However, these VaD subtypes have not been well defined within current diagnostic criteria (33).

Examining the relationship between nutritional factors and VaD is fraught with challenges, which were consistently observed in this review. The limited number of existing studies on this subject matter is a limitation in itself. The paucity of VaD cases was also cited in several studies as a potential methodological issue, making it difficult to statistically evaluate the relationship between nutritional factors and VaD risk (28, 29, 31, 34). Huang et al. (31) cited insufficient power to assess VaD risk and fish consumption through further stratification of the APOE ε4 allele, a recognized genetic risk factor for AD. Likewise, the second Rotterdam study failed to confirm an association between dietary lipids and risk of VaD due to limited number of cases (29). An additional challenge in identifying VaD cases in the clinical and research setting is that, at present, there are eight unique sets of diagnostic criteria used for VaD (41). It is not surprising that variations in the use of diagnostic criteria were encountered in the studies reviewed. VaD represents a large group of heterogeneous lesions which have multifactorial pathogeneses. Cognitive decline, in VaD, has been attributed to different mechanisms such as multiple cortical infarcts, strategic infarct in the thalamus and striatum, and sub-cortical small vessel disease. Others have further subdivided VaD based on etiology, size of infarct, and location. That is why VaD is not a single disease entity, but rather a spectrum of diseases. In two separate cross-sectional investigations of HCY, folate, and vitamin B12, Quadri et al. (26) used Consortium to Establish A Registry for Alzheimer's Disease (CERAD), while Koseoglu et al. (25) used NINDS-AIREN. NINDS-AIREN was the most commonly used criteria. It requires focal neurological deficits for diagnosis of VaD, and is thus the most exclusive criteria. Although the use of NINDS-AIREN criteria exclusively may decrease the sensitivity and increase the specificity, thereby limiting the chances of including false positives in the study, it may also exclude subjects that have VaD without prominent imaging and focal findings. The challenges of diagnosing VaD in epidemiological studies have been cited elsewhere, and it has been shown that the use of different diagnostic criteria may result in the identification of unique cohorts of disease cases

(42). This is believed to be partly attributed to the low concordance between clinical diagnostic criteria such as NINDS-AIREN and DSM-IV, shown to be as low as 40% (43). Therefore, a more cohesive and integrated diagnostic definition of VaD would be helpful in future studies in order to accurately assess the risk factors, incidence, and prevalence of VaD.

Conclusion

Thus far, the most convincing evidence as to the relationship between VaD and nutrition exists for micronutrients, particularly antioxidants including Vitamin C and E, which demonstrate a beneficial effect on cognitive performance, and reducing the risk of CVD and VaD It has been suggested that supplementation may influence the onset and progression of the disease (21, 24). With a great deal of evidence supporting the role of nutrition in cognitive health and aging, the prospect of other nutritional parameters having a role in VaD should be explored in order to formulate appropriate nutritional recommendations for prevention and clinical management of VaD. Studying well defined long-term prospective cohorts can help elucidate beneficial effects of nutritional factors that can be instituted early in life, and allow clinically effective prevention measures. In addition, exploring the relationship between nutrition and VaD at the macronutrient and food group level may also allow greater insight into the disease and provide feasible and implementable prevention programs at the individual and community level. Finally, establishing a unified diagnostic criteria for VaD is crucial for the sake of accurate clinical diagnosis and consistency across studies.

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References

1. U.S Census Bureau. International Database. Table 094. Midyear population, by age and sex. http://www.census.gov/population/www/projections/natdet-D1A.html. Accessed 22 August 2010
2. Meyer A (1937) The histological criteria of vascular disturbances in the brain. J Ment Sci. 83:509
3. Jellinger KA, Attems J (2005) Prevalence and pathogenic role of cerebrovascular lesions in Alzheimer disease. J Neurol Sci 229-230: 37-41
4. Esiri MM, Nagy Z, Smith MZ, Barnetson L, Smith AD (1999) Cerebrovascular disease and threshold for dementia in the early stages of Alzheimer's disease. Lancet 354(9182): 919-920
5. Cairns NJ, Bigio EH, Mackenzie IR, et al. (2007) Neuropathologic diagnostic and nosologic criteria for frontotemporal lobar degeneration: consensus of the consortium for frontotemporal lobar degeneration. Acta Neuropathol 114(1): 5-22
6. Pantoni L, Sarti C, Alafuzoff I, Jellinger K, Munoz DG, Ogata J, Palumbo V (2006) Postmortem examination of vascular lesions in cognitive impairment: a survey among neuropathological services. Stroke 37(4): 1005-1009
7. Román GC (2002) Vascular dementia may be the most common form of dementia in the elderly. J Neurol Sci 203-204: 7-10.
8. Plassman BL, Langa KM, Fisher GG, et al. (2007) Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology 29: 125-32
9. Fitzpatrick AL, Kuller LH, Lopez OL, Kawas CH, Jagust W (2005) Survival following dementia onset: Alzheimer's disease and vascular dementia. J Neurol Sci 229-230: 43-49
10. Hill J, Fillit H, Shah SN, del Valle MC, Futterman R (2005) Patterns of healthcare utilization and costs for vascular dementia in a community-dwelling population. J Alzheimers Dis 8(1): 43-50
11. Kirshner HS (2009) Vascular dementia: a review of recent evidence for prevention and treatment. Curr Neurol Neurosci Rep 9(6): 437-442
12. Lin JC, Hsu HP, Fung HC, Chen ST (2007) Risk factors for vascular dementia: a hospital-based study in Taiwan. Acta Neurol Taiwan 16: 22-26
13. Watanabe T, Koba S, Kawamura M, Itokawa M, Idei T, Nakagawa Y, Iguchi T, Katagiri T (2004) Small dense low-density lipoprotein and carotid atherosclerosis in relation to vascular dementia. Metabolism. 53(4): 476-82
14. Watanabe T, Miyazaki A, Katagiri I, Yamamoto H, Idei T, Iguchi T (2005) Relationship between serum insulin-like growth factor-1 levels and Alzheimer's disease and vascular dementia. J Am Geriatr Soc 53: 1748-1753
15. Hayden KM, Zandi PP, Lyketsos CG, Khachaturian AS, Bastian LA, Charoonruk G, et al (2006) Vascular risk factors for incident Alzheimer disease and vascular dementia: the Cache County study. Alzheimer Dis Assoc Disord 22: 93-100
16. Anstey KJ, von Sanden C, Salim A, O'Kearney R (2007) Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. Am J Epidemiol 166: 367-78
17. Whitmer RA, Gunderson EP, Quesenberry CP, Zhou J, Yaffe K (2007) Body mass index in midlife and risk of Alzheimer disease and vascular dementia. Curr Alzheimer Res 4:103-9
18. Chiang CJ, Yip PK, Wu SC, Lu CS, Liou CW, Liu HC, et al. (2007) Midlife risk factors for subtypes of dementia: a nested case-control study in Taiwan. Am J Geriatr Psychiatry 15(9):762-71
19. Van Dyk K, Sano M (2007) The impact of nutrition on cognition in the elderly. Neurochem Res 32(4-5): 893-904
20. Van der Beek EM, Kamphius PJ (2008) The potential role of nutritional components in the management of Alzheimer's Disease. Eur J Pharmacol 585(1): 197-207
21. Masaki KH, Losonczy KG, Izmirlian G, Foley DJ, Ross GW, Petrovitch H, Havlik R, White LR (2000) Association of vitamin E and C supplement use with cognitive function in elderly men. Neurology 54:1265-1272
22. Maxwell CJ, Hicks MS, Hogan DB, Basran J, Ebly EM (2005) Supplemental use of antioxidant vitamins and subsequent risk of cognitive decline and dementia. Dement Geriatr Cogn Disord 20: 45-51
23. Laurin D, Masaki KH, Foley DJ, White LR, Launer LJ (2004) Midlife dietary intake of antioxidants and risk of late-life incident dementia: the Honolulu-Asia Aging Study. Am J Epidemiol 159: 959-967
24. Ryglewicz D, Rodo M, Kunicki PK, Bednarska-Makaruk M, Graban A, Lojkowska W, Wehr H (2002) Plasma antioxidant activity and vascular dementia. J Neurol Sci 203-204:195-197
25. Koseoglu E, Karaman Y (2007) Relations between homocysteine, folate and vitamin B12 in vascular dementia and in Alzheimer disease. Clin Biochem 40: 859-863
26. Quadri P, Fragiacomo C, Pezzati R, Zanda E, Forloni G, Tettamanti M, Lucca U (2004) Homocysteine, folate, and vitamin B-12 in mild cognitive impairment, Alzheimer disease, and vascular dementia. Am J Clin Nutr 80:114-122
27. Malaguarnera M, Ferri R, Bella R, Alagona G, Carnemolla A, Pennisi G (2004) Homocysteine, vitamin B12 and folate in vascular dementia and Alzheimer disease. Clin Chem Lab Med 42:1032-1035
28. Kalmijn S, Launer LJ, Ott A, Witteman JC, Hofman A, Breteler MM (1997) Dietary fat intake and the risk of incident dementia in the Rotterdam Study. Ann Neurol 42: 776-782
29. Engelhart MJ, Geerlings MI, Ruitenberg A, Van Swieten JC, Hofman A, Witteman JC, Breteler MM (2002) Diet and risk of dementia: Does fat matter?: The Rotterdam Study. Neurology 59:1915-1921
30. Otsuka, M, Yamaguchi K, Ueki (2002) Similarities and differences between Alzheimer's disease and vascular dementia from the viewpoint of nutrition. Ann N Y Acad Sci. 977:155-261
31. Huang TL, Zandi PP, Tucker KL, Fitzpatrick AL, Kuller LH, Fried LP, Burke GL, Carlson ML (2005) Benefits of fatty fish on dementia risk are stronger for those without APOE epsilon4. Neurology. 65:1409-1414
32. Reitz C, Tang MX, Luchsinger J, Mayeux R (2004) Relation of plasma lipids to Alzheimer disease and vascular dementia. Arch Neurol 61: 705-714
33. Solomon A, Kivipelto M, Wolozin B, Zhou J, Whitmer RA (2009) Midlife serum cholesterol and increased risk of Alzheimer's and vascular dementia three decades later. Dement Geriatr Cogn Disord 28: 75-80.
34. Mielke MM, Zandi PP, Sjogren M, Gustafson D, Ostling S, Steen B, Skoog I (2005) High total cholesterol levels in late life associated with a reduced risk of dementia. Neurology 64:1689-1695.
35. Deschamps V, Barberger-Gateau P, Peuchant E, Orgogozo JM (2001) Nutritional factors in cerebral aging and dementia: epidemiological arguments for a role of oxidative stress. Neuroepidemiology 20(1): 7-15
36. Beydoun MA, Kaufman JS, Satia JA, Rosamond W, Folsom AR (2007) Plasma n-3 fatty acids and the risk of cognitive decline in older adults: the Atherosclerosis Risk in Communities Study. Am J Clin Nutr 85(4): 1103-11
37. Cole GM, Frautschy (2010) DHA May Prevent Age-Related Dementia. J. Nutr 140(4): 869-874
38. Herrmann W, Lorenzl S, Obeid R (2007) Review of the role of hyperhomocysteinemia and B-vitamin deficiency in neurological and psychiatric disorders- current evidence and preliminary recommendations. Fortschr Neurol Psychiatr 75(9): 515-527
39. Herrmann W, Obeid R (2011) Homocysteine: a biomarker for neurodegenerative diseases. Clin Chem Lab Med 49(3): 435-41
40. Mattson MP, Shea TB (2003) Folate and homocysteine metabolism in neural plasticity and neurodegenerative disorders. Trends Neurosci 26(3): 137-146
41. Wiederkehr S, Simard M, Fortin C, van Reekum R (2008) Validity of clinical diagnostic criteria for vascular dementia: a critical review. Part II. J Neuropsychiatry Clin Neurosci 20: 162-177
42. Lopez OL, Kuller LH, Becker JT, Jagust WJ, DeKosky ST, Fitzpatrick A, Breitner J, Lyketsos C, Kawas C, Carlson M (2005) Classification of vascular dementia in the Cardiovascular Health Study Cognition Study. Neurology 64: 1539-1547
43. Tang WK, Chan SS, Chiu HF, Ungvari GS, Wong KS, Kwok TC, Mok V, Wong KT, Richards PS, Ahuja AT (2004) Impact of applying NINDS-AIREN criteria of probable vascular dementia to clinical and radiological characteristics of a stroke cohort with dementia. Cerebrovasc Dis 18: 98-103