Original Contribution Kitasato Med J 2012; 42: 83-90

Relationship among white matter hyperintensity, arterial stiffness, associated diseases, and lifestyle in late-onset Alzheimer's disease patients

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Objective: White matter hyperintensity (WMH) is related to cerebrovascular disease, which deteriorates the cognitive function in Alzheimer's disease (AD) patients. In this study, we examined the association between WMH in AD patients and various vascular factors.
Methods: A total of 107 patients with mild to moderate AD aged 65 years or older were recruited. Comparisons were made between the high- and low-WMH groups, using the Fazekas classification system, in terms of cognitive function, arterial stiffness, vascular risk factors, and lifestyle-related risk factors.
Results: High-WMH were observed in approximately 60% of the AD patients in this study. The high-WMH patients were significantly older than the low-WMH patients. The mean brachial-ankle pulse wave velocity was higher in the high-WMH group than that in the low-WMH group. After correction for age and gender, the diastolic blood pressure (DBP) was significantly higher in the high-WMH group than that in the low-WMH group. The percentage of patients showing white matter lesions significantly increased in correlation with the number of lifestyle-related risk factors as well as in correlation with frequencies of both exercise and fruit consumption.
Conclusions: In the AD patients in the present study, WMH is associated with cognitive impairment, age, arterial stiffness, diastolic blood pressure, and lifestyle-related vascular risk factors.

Key words: Alzheimer's disease, cerebrovascular disease, white matter hyperintensity, arterial stiffness, lifestyle

Introduction

Arterial stiffness can be assessed by a relatively simple method. The severity of arterial stiffness is related to cerebrovascular disease (CVD) and white matter lesions and affects the cognitive functions of the patients.[1-3] However, to the best of our knowledge, there are only two reports on arterial stiffness in patients with Alzheimer's disease (AD). One is on the correlation between the morbidity of AD and the severity of arterial stiffness,[4] and the other showed that the arterial stiffness in AD patients tended to be milder than that in patients with vascular dementia.[5]

When AD is complicated by ischemic brain lesions, the cognitive function of AD patients further declines.[6] The risk factors for CVD including ischemic lesions have been pointed out to be related to the pathogenesis and prognosis of AD as well as vascular dementia.[4,7] Although CVD does not directly cause AD, AD patients tend to be secondarily complicated with CVD because AD and CVD have common risk factors (e.g., hypertension, hyperlipidemia, and diabetes mellitus).[8] Because the complication and exacerbation of CVD increase the burden of nursing care, preventive and control methods for CVD are necessary for AD patients as well.

White matter lesions pathologically represent small brain infarctions, myelin degeneration, and expansion of perivascular space.[9] Recently, many studies have revealed the association between white matter hyperintensity (WMH) and cognitive decline.[10,11] Some reports suggest

Received 21 December 2011, accepted 11 January 2012
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an association between WMH and vascular risk factors.[12,13] It is well known that lifestyle affects vascular disease. However, much remains unclear about the associations among WMH, arterial stiffness, vascular risk factors, and the lifestyles of AD patients. Therefore, we carried out a cross-sectional study to examine the relationships among WMH, risk factors for arterial stiffness, CVD, and the lifestyles of AD patients.

Materials and Methods

Subjects

From the medical-record database of 349 patients who attended the dementia diagnosis course at Kitasato University East Hospital from April 2004 to May 2010, records of 319 patients, who agreed to participate in this study, were obtained. Alzheimer's Criteria[14] were extracted from these records of 109 patients aged 65 years or older, who were diagnosed as having AD in accordance with the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). The records of two patients were excluded because of insufficient data. As a result, the records of a total of 107 patients were used in this study. The patients were diagnosed as having mild or moderate dementia using the Clinical Dementia Rating (CDR).[15]

Factors analyzed

The factors analyzed included age, gender, height, body weight, number of complications, the mini-mental state examination (MMSE) score,[16] education (period of study), pulse wave velocity (PWV) test results, lifestyle-related factors determined by a questionnaire survey, and magnetic resonance (MR) imaging findings. Regarding complications, the presence or absence of hypertension, diabetes mellitus, hyperlipidemia, renal disease, arrhythmia, and ischemic heart disease was examined, and the total number of complications was counted. We selected these complications for which previous studies showed associations to cerebrovascular disorder.[12,17-19] For CVD-related factors, body mass index (BMI) (=body weight (kg)/[height (m)]^2), systolic blood pressure (SBP) and diastolic blood pressure (DBP) of the upper arm obtained in the PWV test, mean ankle-brachial pressure index (mABI) (mean of the left and right mABIs), and mean brachial-ankle pulse wave velocity (mbaPWV) were extracted from the medical-record database. Blood pressure and PWV was measured using a waveform analyzer (PWV/ABI; Colin, Komaki, Japan) after a 5-min rest at dorsal position. Because we did not find more than 10% difference between right and left ABI or PWV values, we used the mean value for comparisons as in previous studies.[20,21] For lifestyle-related risk factors, the following eight items were surveyed using a questionnaire completed by the family members of the patients: number of meals; frequencies of eating fish, vegetables, and fruit (meal-related habits); drinking, smoking, and exercise habits; and quality of sleep. These eight factors, namely, (1) irregular meals, (2) eating fish once a week or less often, (3) eating vegetables once a week or less often, (4) eating fruit once a week or less often, (5) habitual drinking once a week or less often, (6) habitual smoking, (7) no habit of exercising, and (8) lack of sleep, were regarded as the lifestyle-related risk factors in the present study. The total number of these lifestyle-related risk factors that applied to each patient was counted, and, thus, ranged from 0 to 8.

Evaluation of WMH

All MRI studies were performed using a 1.0- or 1.5-tesla scanner. The lesions that appear as WMH areas were

Table 1. Demographic data of the high- and low-WMH groups

Characteristics	High-WMH n = 64	Low-WMH n = 43	P
Age (y)	77.5 ± 5.0	74.4 ± 6.3	0.006*
Female n (%)	24 (37.5)	12 (27.9)	0.303
Education (y)	10.7 ± 2.9	10.9 ± 3.1	0.746
MMSE	19.3 ± 4.4	21.3 ± 3.3	0.013*
Total number of complications	1.2 ± 1.0	0.9 ± 1.0	0.181

*P < 0.05

WMH, white matter hyperintensity; MMSE, mini-mental state examination

Data are shown as mean ± SD.

P values were calculated using the *t*-test or the chi-square test.

graded visually (the WMH grade) from fluid-attenuated inversion recovery (FLAIR) MR images of the head using the Fazekas classification system.[22] The grades were determined by at least three psychiatrists. The patients were classified into two groups: patients with a WMH grade ≧2 (the high-WMH group, $n = 64$) and those with a WMH grade of 0 or 1 (the low-WMH group, $n = 43$). WMH grade 1 is defined as an aging related change,[22] so we classified WMH grade 0 and 1 as the low-WMH group. The clinical background characteristics of these patients are summarized in Table 1.

Ethical consideration

This study was carried out with the approval of the Ethics Committee of Kitasato University.

Statistical analyses

The *t*-test and chi-square test were performed to compare the results between the two groups. The factors related to arterial stiffness were compared, e.g., BMI, blood pressure, mABI, mbaPWV, and the total number of lifestyle-related risk factors. To obtain an estimated mean value corrected for age and gender, a generalized estimation equation (GEE) approach[23,24] was used because the GEE is applicable for obtaining an estimated mean value of a group in the event that there are some missing data. In addition, the number and percentage of patients who were judged to be at risk were determined for each lifestyle-related risk factor, and logistic regression analysis was performed to obtain the relative risk (relative odds ratio) of each factor by correcting the obtained data for age and gender. P values of <0.05 were considered to

Table 2. Comparison of complications between the high- and low-WMH groups

Disease	High-WMH n = 60	Low-WMH n = 43	P[a]	Relative odds ratio[b]	(95% CI)	P
Hypertension	34 (53.1)	15 (34.9)	0.063	1.81	(0.79, 4.13)	0.161
Diabetes mellitus	15 (23.4)	5 (11.6)	0.139	2.10	(0.68, 6.52)	0.198
Hyperlipidemia	4 (6.3)	7 (16.3)	0.113	0.38	(0.10, 1.42)	0.149
Renal disease	4 (6.3)	2 (4.7)	1.000	1.53	(0.24, 9.89)	0.658
Arrythmia	8 (12.5)	5 (11.6)	1.000	0.86	(0.25, 2.98)	0.815
Ischemic heart disease	10 (15.6)	5 (11.6)	0.777	0.77	(0.24, 2.50)	0.662

*P < 0.05

WMH, white matter hyperintensity

Data are shown in (%).

[a]Calculated using the chi-square test

[b]CVD, cerebrovascular disease positivity relative odds ratio of risk-factor-positive group corrected for age and gender

Table 3. Comparison of factors related to arterial lesions between the high- and low-WMH groups

Variables	High-WMH (n = 64)		Low-WMH (n = 43)		P	High-WMH (n = 64)		Low-WMH (n = 43)		P
	Mean	(95% CI)	Mean	(95% CI)		Estimated mean[a]	(95% CI)	Estimated mean[a]	(95% CI)	
BMI	22.2	(21.4, 23.0)	21.8	(20.6, 23.0)	0.517	22.2	(21.5, 23.0)	21.8	(20.7, 22.9)	0.547
SBP (mmHg)	143.3	(138.1, 148.5)	136.4	(130.7, 142.1)	0.079	142.2	(137.3, 147.0)	136.1	(130.3, 141.9)	0.122
DBP (mmHg)	78.2	(75.5, 80.9)	75.1	(72.4, 77.8)	0.125	78.8	(76.2, 81.3)	74.8	(72.1, 77.4)	0.031*
mABI	1.13	(1.10, 1.16)	1.12	(1.10, 1.14)	0.777	1.14	(1.11, 1.16)	1.13	(1.11, 1.15)	0.851
mbaPWV (cm/s)	1869.1	(1783.1, 1955.1)	1709.5	(1602.8, 1816.2)	0.021*	1849.9	(1766.6, 1933.1)	1761.2	(1652.1, 1870.2)	0.172
No. of lifestyle-related risk factors	1.6	(1.3, 1.9)	1.1	(0.8, 1.4)	0.026*	1.6	(1.3, 1.9)	1.1	(0.8, 1.4)	0.009*

*P < 0.05

WMH, white matter hyperintensity; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; mABI, mean ankle-brachial pressure index; mbaPWV, mean brachial-ankle pulse wave velocity

[a]Estimated mean calculated using a general equal estimation corrected for age and gender

indicate statistically significant differences. The correction for multiple comparisons was not done in the present study because the number of subjects was small, and because it was an exploratory study. The SPSS version 17.0 was used for statistical analyses.

Results

Comparison of clinical background characteristics between the high- and low-WMH groups

High-WMH were observed in approximately 60% of the patients aged 65 years or older who attended the dementia diagnosis course and who were diagnosed as having AD (Table 1). The clinical background characteristics of the high- and low-WMH groups are summarized in Table 1. The mean age of the high-WMH group was significantly higher than that of the low-WMH group. The score of the mini-mental state examination (MMSE) of the high-WMH group was lower than that of the low-WMH group. There were no significant differences in the number of years of education, number of complications, or gender between the two groups.

Comparison of CVD-related complications between the high- and low-WMH groups

Table 2 shows a summary of the number of patients and prevalences of diseases that were reported to be related to CVD in the high- and low-WMH groups. The prevalences of hypertension and diabetes mellitus were higher in the high-WMH group than those in the low-WMH group; however, these differences were not statistically significant. The relative odds ratios for each disease were calculated using data corrected for age and gender. The relative odds ratios for hypertension and diabetes mellitus were approximately 2.0 but not statistically significant.

Comparison of factors related to arterial lesions between the high- and low-WMH groups

The factors related to arterial lesions, BMI, SBP, DBP, mABI, mbaPWV, and the number of lifestyle-related risk factors were compared between the two groups (Table 3). Before correction, mbaPWV and the number of lifestyle-related risk factors of the high-WMH group were higher than those of the low-WMH group. After correction for age and gender, DBP and the number of lifestyle-related risk factors of the high-WMH group were significantly higher than those of the low-WMH group. BMI and mABI were similar between the two groups.

Comparison of lifestyle-related risk factors between the high- and low-WMH groups

Table 4 shows a summary of the number and percentage of patients who were determined at risk of CVD on the basis of the presence of the eight lifestyle-related risk factors in the two groups. The percentage of patients who do not have a habit of exercising was significantly high in the high-WMH group compared with that in the low-WMH group. After correction for age and gender, the relative odds ratios for the low frequency of fruit consumption and not having a habit of exercising increased to approximately 5 and 2.5, respectively.

Table 4. Comparison of lifestyle-related risk factors between the high- and low-WMH groups

Risk factors	High-WMH n = 60	Low-WMH n = 43	P[a]	Relative Odds ratio[b]	(95% CI)	P
Number of meals	3 (5.0)	1 (2.3)	0.638	5.04	(0.39, 64.0)	0.214
Fish consumption	14 (23.3)	6 (14.0)	0.235	1.75	(0.59, 5.24)	0.317
Vegetable consumption	0 (0.0)	0 (0.0)	1	1		
Fruit consumption	10 (16.7)	3 (7.0)	0.229	4.77	(1.09, 20.86)	0.038*
Drinking	16 (29.1)	15 (34.9)	0.541	0.82	(0.32, 2.08)	0.669
Smoking	2 (3.4)	3 (7.0)	0.648	0.43	(0.06, 2.94)	0.387
Exercise	29 (47.5)	11 (25.6)	0.023*	2.52	(1.03, 6.15)	0.042*
Sleep	21 (35.6)	11 (26.2)	0.317	1.67	(0.66, 4.20)	0.278

*P < 0.05

WMH, white matter hyperintensity

Data are shown as number (%).

[a]Calculated using the chi-square test

[b]CVD, cerebrovascular disease positivity relative odds ratio of risk-factor-positive group corrected for age and gender

Discussion

In this study, moderate or severe white matter lesions were observed in approximately 60% of AD patients aged 65 years or older. Kuo et al.[13] reported that about 20% of elderly patients without dementia showed moderate to severe WMH. Fazekas et al.[22] reported that 4 of 12 AD patients and 3 of 9 subjects in the control group had ischemic lesions. Compared with these figures, the prevalence of moderate or severe white matter lesions obtained in the present study was high. Our finding is in agreement with previous findings that the percentage of patients having white matter lesions is higher in AD patients than in control subjects.[25,26] According to Krishnan et al.,[27] moderate subcortical ischemic lesions were observed in the MR images of 54% of the patients with depression aged 60 years or older-a prevalence similar to that observed in the present study. It is very interesting that the prevalence of CVD, as indicated by the presence of white matter lesions, in the patients with depression, is equivalent to that in the AD patients, considering that depression is a risk factor for dementia.[28,29]

It has also been reported that WMH is a risk or an exacerbation factor for AD[30,31] and that the severity of WMH is a significant predictor of lesion progression in AD patients.[25] Therefore, the prevention and control of the progression of WMH are particularly important to suppress cognitive function decline in patients. In the present study, similarly, the MMSE score of the high-WMH group was significantly lower than that of the low-WMH group, suggesting a relationship between WMH and cognitive function decline. Recently, a relationship between white matter lesions and brain atrophy has been pointed out[32]; therefore, psychiatrists should pay especial attention to white matter lesions, particularly in AD patients.

Age is an important factor for the onset of white matter lesions.[20,33] In the present study, the mean age of the patients in the high-WMH group was significantly higher than that in the low-WMH group. Moreover, the effects of hypertension, diabetes mellitus, cardiac disorder, metabolic syndrome, and deterioration in renal function on white matter lesions have been reported.[12,17-19] In the present study, we expected the number of complications in the high-WMH group would be higher than that in the low-WMH group, and detected the tendency of such, but without statistical significance. In this study, although we were unable to clarify any relationships between white matter lesions and any particular diseases, the presence of hypertension and diabetes mellitus tended to increase the risk of having high WMHs. Regarding the relationship between high WMHs and other diseases, the number of patients was small so that the reliability of these results was considered to be too low to determine any definitive relationships.

Blood pressure, arterial stiffness, and high BMI are reported to be factors related to CVD.[18,21,34,35] Results of this study showed that both SBP and DBP tended to be higher in the high-WMH group than those in the low-WMH group; however, these differences were not statistically significant. When the obtained results were corrected for age and gender, DBP in the high-WMH group was significantly higher than that in the low-WMH group. Brickman et al.[36] reported that wide fluctuations of blood pressure affect the progression of WMH in elderly patients, and suppression of fluctuations of blood pressure is also important to inhibit the progression of WMH. Hirono et al.[37] showed that WMH volume is associated with hypertension in AD patients. These results indicate that appropriate control of blood pressure is important for AD patients.

Ochi et al.[21] reported that the blood pressure and mbaPWV of the patients with a small asymptomatic brain infarction were significantly higher than those of the control group. Hatanaka et al.[35] reported that the prevalence of WMH tended to increase with increasing mbaPWV. In the present study, mbaPWV, an index of arterial stiffness, was significantly higher in the high-WMH group than that in the low-WMH group; after data correction for age and gender, no significant differences were observed. Age is considered to be the predominant factor for the development of arterial stiffness. It has been reported that arterial stiffness is affected by aging[20] and blood pressure and is related to WMH,[35,38] which is in agreement with our results. In the present study, we used mbaPWV as an index of arterial stiffness. Kearney-Schwartz et al.[3] obtained similar results using carotid-femoral PWV as an index. In this study, we were unable to show that a high PWV is a risk factor for white matter lesions from the results corrected for age and gender. Chalmers et al.[39] showed that frontal white matter damage in AD patients is closely related to parenchymal beta-amyloid load, but they found no associations between white matter damage and atherosclerosis or arteriosclerosis using a neuropathological technique. Thus, the possibility of amyloid deposits and arterial stiffness exacerbating WMH with age should be taken into account in AD patients.

The high-WMH group had more lifestyle-related habits that were risk factors for vascular disease in this study. Eating fruit, vegetables, fish, and low-fat foods is

considered to decrease the risk of CVD.[40,41] In the present study, the patients in the low-WMH group ate fruit more frequently than did those in the high-WMH group. Fung et al.[42] reported that fruit consumption is effective for controlling the blood pressure of patients with hypertension. It is also reported that fruit consumption can decrease the risk of CVD.[43,44] Exercise is also reported to be related to the prevention of cognitive function decline,[20] and exercise reduces the risk of cerebrovascular cognitive impairment and cerebrovascular dementia.[45,46] In the present study, the patients who did not exercise regularly had a high risk of having high WMHs. Our findings suggest that lifestyle-related vascular risk factors may contribute to WMHs in AD patients. In future studies, investigation is warranted to clarify the relationships among these factors.

The limitations of this study were: 1. the number of patients was small and, therefore, the statistical results were not highly reliable, 2. the subjects were limited to AD patients, and the patients with mixed dementia having more severe CVD were excluded, 3. blood test data and medication influence were not evaluated, 4. severity of physical complications was not accounted for, and 5. carotid artery evaluation was not performed. The study subjects were patients who attended the dementia diagnosis course to detect dementia at an early stage. Therefore, it is possible that they were keenly interested in their own health, so they maintained a healthy lifestyle, which may have led to the findings of a large number of lifestyle-related risk factors showing no significant differences between the low- and high-WMH groups. In the present study, we focused on WMH from the viewpoint of care for elderly AD patients. This was a cross-sectional study; therefore, we could not determine how, or whether or not, the risk factors affect WMH progression. In the future, we would like to clarify the factors associated with WMH progression by performing a large-scale longitudinal study.

Acknowledgments

This study was partially supported by the Ministry of Health, Labour and Welfare. The authors thank Dr. Katsutoshi Tanaka, of Kitasato University Graduate School of Medical Science, for his valuable advice.

References

1. Tsuchikura S, Shoji T, Kimoto E, et al. Central versus peripheral arterial stiffness in association with coronary, cerebral and peripheral arterial disease. *Atherosclerosis* 2010; 211: 280-5.
2. Kim YS, Kim DH, Choi BH, et al. Relationship between brachial-ankle pulse wave velocity and cognitive function in an elderly community-dwelling population with metabolic syndrome. *Arch Gerontol Geriat* 2009; 49: 176-9.
3. Kearney-Schwartz A, Rossignol P, Bracard S, et al. Vascular structure and function is correlated to cognitive performance and white matter hyperintensities in older hypertensive patients with subjective memory complaints. *Stroke* 2009; 40: 1229-36.
4. Hofman A, Ott A, Breteler MM, et al. Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. *Lancet* 1997; 349: 151-4.
5. Dhoat S, Ali K, Bulpitt CJ, et al. Vascular compliance is reduced in vascular dementia and not in Alzheimer's disease. *Age Ageing* 2008; 37: 653-9.
6. Snowdon DA, Greiner LH, Mortimer JA, et al. Brain infarction and the clinical expression of Alzheimer's disease; the Nun Study. *JAMA* 1997; 277: 813-7.
7. Honig LS, Tang MX, Albert S, et al. Stroke and the risk of Alzheimer disease. *Arch Neurol* 2003; 60: 1707-12.
8. Waragai M, Furukawa K, Arai H. Cerebrovascular disease as an exacerbating factor for Alzheimer's dementia. *Cardioangiology* 2008; 64: 572-7 (in Japanese).
9. Matsusue E, Sugihara S, Fujii S, et al. White matter changes in elderly people: MR-pathologic correlations. *Magn Reson Med Sci* 2006; 5: 99-104.
10. de Groot JC, de Leeuw FE, Oudkerk M, et al. Cerebral white matter lesions and cognitive function: the Rotterdam Scan Study. *Ann Neurol* 2000; 47: 145-51.
11. van Dijik EJ, Prins ND, Vrooman HA, et al. Progression of cerebral small vessel disease in relation to risk factors and cognitive consequences: Rotterdam Scan study. *Stroke* 2008; 39: 2712-9.
12. Otani H, Kikuya M, Hara A, et al. Association of kidney dysfunction with silent lacunar infarcts and white matter hyperintensity in the general population: the Ohasama study. *Cerebrovasc Dis* 2010; 30: 43-50.
13. Kuo HK, Chen CY, Liu HM, et al. Metabolic risks, white matter hyperintensities, and arterial stiffness in high-functioning healthy adults. *Int J Cardiol* 2010; 143: 184-91.

14. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's disease. AD diagnosis standard. *Neurology* 1984; 34: 939-44.
15. Hughes CP, Berg L, Danziger WL, et al. A new clinical scale for the staging of dementia. *Br J Pscyhiatry* 1982; 140: 566-72.
16. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State." A practical method for grading the cognitive state of patients for the clinician. *J Psychiat Res* 1975; 12: 189-98.
17. Fazekas F, Niederkor K, Schmidt R, et al. White matter signal abnormality in normal individuals: Correlation with carotid ultrasonography, cerebral blood flow measurements, and cerebrovascular risk factors. *Stroke* 1988; 19: 1285-8.
18. Bokura H, Yamaguchi S, Iijima K, et al. Metabolic syndrome is associated with silent ischemic brain lesions. *Stroke* 2008; 39: 1607-9.
19. Khatri M, Wright CB, Nickolas TL, et al. Chronic kidney disease is associated with white matter hyperintensity volume. The Northern Manhattan study (NOMAS). *Stroke* 2007; 38: 3121-6.
20. Ohmori K, Emura S, Takashima T. Risk factors of atherosclerosis and aortic pulse wave velocity. *Angiology* 2000; 51: 53-60.
21. Ochi N, Kohara K, Tabara Y, et al. Association of central systolic blood pressure with intracerebral small vessel disease in Japanese. *Am J Hypertens* 2010; 23: 889-94.
22. Fazekas F, Chawluk JB, Alavi A, et al. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJNR Am J Roentgenol* 1987; 149: 351-6.
23. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986; 42: 121-30.
24. Zeger SL, Liang KY, Albert PS. Models for longitudinal data: a gereralized estimating equation approach. Biometrics 1988; 44: 1049-60. *Erratum* in *Biometrics* 1989; 45: 347.
25. Burton EJ, McKeith IG, Burn DJ, et al. Progression of white matter hyperintensities in Alzheimer disease, dementia with lewy bodies, and Parkinson disease dementia: a comparison with normal aging. *Am J Geriatr Psychiatry* 2006; 14: 842-9.
26. He J, Iosif AM, Lee DY, et al. Brain structure and cerebrovascular risk in cognitively impaired patients: Shanghai Community Brain Health Initiative-pilot phase. *Arch Neurol* 2010; 67: 1231-7.
27. Krishnan KR, Taylor WD, McQuoid DR, et al. Clinical characteristics of magnetic resonance imaging-defined subcortical ischemic depression. *Biol Psychiatry* 2004; 55: 390-7.
28. Steffens DC, Potter GG, McQuoid DR, et al. Longitudinal magnetic resonance imaging vascular changes, apolipoprotein E genotype, and development of dementia in the neurocognitive outcomes of depression in the elderly. *Am J Geriatr Psychiatry* 2007; 15: 839-49.
29. Middleton LE, Yaffe K. Promising strategies for the prevention of dementia. *Arch Neurol* 2009; 66: 1210-5.
30. Carmichael O, Schwarz C, Drucker D, et al. Longitudinal changes in white matter disease and cognition in the first year of the Alzheimer disease neuroimaging initiative. *Arch Neurol* 2010; 67: 1370-8.
31. Brickman AM, Honig LS, Scarmeas N, et al. Measuring cerebral atrophy and white matter hyperintensity burden to predict the rate of cognitive decline in Alzheimer disease. *Arch Neurol* 2008; 65: 1202-8.
32. Appel J, Potter E, Bhatia N, et al. Association of white matter hyperintensity measurements on brain MR imaging with cognitive status, medial temporal atrophy, and cardiovascular risk factors. *AJNR Am J Neuroradiol* 2009; 30: 1870-6.
33. Gunning-Dixon FM, Brickman AM, Cheng JC, et al. Aging of cerebral white matter: a review of MRI findings. *Int J Geriatr Psychiatry* 2009; 24: 109-17.
34. Gottesman RF, Coresh J, Catellier DJ, et al. Blood pressure and white-matter disease progression in a biethnic cohort: Atherosclerosis Risk in Communities (ARIC) study. *Stroke* 2010; 41: 3-8.
35. Hatanaka R, Obara T, Watabe D, et al. Association of arterial stiffness with silent cerebrovascular lesions: the Ohasama study. *Cerebrovasc Dis* 2011; 31: 329-37.
36. Brickman AM, Reitz C, Luchsinger JA, et al. Long-term blood pressure fluctuation and cerebrovascular disease in an elderly cohort. *Arch Neurol* 2010; 67: 564-9.
37. Hirono N, Kitagaki H, Kazui H, et al. Impact of white matter changes on clinical manifestation of Alzheimer's disease: A quantitative study. *Stroke* 2000; 31: 2182-8.
38. Liu XN, Gao HQ, Li BY, et al. Pulse wave velocity as a marker of arteriosclerosis and its comorbidities in Chinese patients. *Hypertens Res* 2007; 30: 237-42.
39. Chalmers K, Wilcock G, Love S. Contributors to white matter damage in the frontal lobe in Alzheimer's disease. *Neuropathol Appl Neurobiol* 2005; 31: 623-31.
40. Galimanis A, Mono ML, Arnold M, et al. Lifestyle and stroke risk: a review. *Curr Opin Neurol* 2009; 22: 60-8.

41. European Stroke Organization Executive Committee, ESO Writing Committee. Guidelines for management of ischemic stroke and transient ischemic attack 2008. *Cerebrovasc Dis* 2008; 25: 457-507.
42. Fung TT, Chiuve SE, McCullough ML, et al. Adherence to a DASH-style diet and risk of coronary heart disease and stroke in women. *Arch Intern Med* 2008; 168: 713-20.
43. Mizrahi A, Knekt P, Montonen J, et al. Plant foods and the risk of cerebrovascular diseases: a potential protection of fruit consumption. *Br J Nutr* 2009; 102: 1075-83.
44. Dauchet L, Amouyel P, Dallongeville J. Fruit and vegetable consumption and risk of stroke: a meta-analysis of cohort studies. *Neurology* 2005; 65: 1193-7.
45. Liu-Ambrose T, Eng JJ, Boyd LA, et al. Promotion of the mind through exercise (PROMoTE): a proof-of-concept randomized controlled trial of aerobic exercise training in older adults with vascular cognitive impairment. *BMC Neurology* 2010; 10: 14. Available at: http://www.biomeducentral.com/1471-2377/10/14/. Accessed Feb 25, 2011.
46. Aarsland D, Sardahaee FS, Anderssen S, et al. Alzheimer's society systematic review group. Is physical activity a potential preventive factor for vascular dementia? A systematic review. *Aging Ment Health* 2010; 14: 386-95.