structure can be divided into the area just beneath the neocortex and the area surrounding the ventricles. The periventricular region contains many long association fibers that connect the cerebral cortex with subcortical nuclei such as found in the striatum and with more distant cortical areas. On the other hand, the subcortical region close to the neocortex features a high density of short looped U-fibers connecting adjacent cortical areas (39). Periventricular WMHs damage the long-tract white matter pathways connecting many cortical areas, which might explain their effects on multiple domains of cognition.

Impaired cognitive function in elderly diabetics was correlated with subcortical WMHs in parietal lobe as well as hyperintensities in the thalamus in this study. Thalamus is recognized to be associated with cognitive function such as learning, memory and executive function (32, 40). Parietal lobe constitutes association areas that are the site of cortical integration for all behaviour such as vision, body awareness and spatial orientation and for abstract and complex cognitive functions. Recent neuroradiological studies have demonstrated reduced regional cerebral blood flow and metabolism in Alzheimer's diseases especially in the parieto-temporal cortical areas and correlated with the distribution of Alzheimer pathological features, while the primary sensori-motor and visual cortical areas were relatively preserved (41, 42). Symptoms of early stage Alzheimer's disease originate from the impaired temporal and parietal lobe functions. Incidental onset of Alzheimer's disease in elderly diabetics can be expected to exacerbate the functional loss and clinical symptoms related to temporal and parietal lobes, as also observed in the case of diabetic cognitive dysfunction.

The pathophysiological origins of WMHs are still unclear, with vascular and nonvascular contributions likely to be causative factors. Subcortical WMHs on T2-weighted MR imaging correlate with several pathological changes such as myelin pallor, dilatation of the perivascular space, myelin or axonal loss, scattered cystic infarcts and angionecrosis. Periventricular hyperintensities on MR scans are associated with partial break down of the ependymal cell lining and subependymal gliosis in addition to the pathological changes of subcortical WMHs (43, 44). Although characteristic pathological features of the diabetic brain have yet not been identified, vascular compromise is common in the elderly and is accompanied by damage to white matter pathways (12, 45). Age and hypertension have been the most consistent predictors of WMHs (32, 33, 46, 47), while some other studies have indicated that diabetes increases the risk of WMHs (13, 36, 48). The increased WMHs in elderly diabetics, presumably accompanied by as yet unidentified clinical variables, may account, at least in part, for diabetic cognitive dysfunction.

To reduce the rate of dementia in elderly diabetics, it is crucial to identify the factors responsible for the progression towards severe cognitive decline. Degenerative changes in cerebral small vessels may affect diabetic cognitive dysfunction, while it seems likely that it is also influenced by diabetic metabolic abnormalities and complications with or without unidentified genetic susceptibility. However, the results of our study do not support the notion of any relationship between cognitive dysfunction and diabetic clinical characteristics. Whether variations in glucose homeostasis influence cognitive function remains controversial (49-51), although it has been found that the cognitive function of

diabetic and nondiabetic subjects fluctuates in accordance with the serum glucose levels (50, 51). At the same time, increased insulin resistance is associated with atrophy of medial temporal lobe structures in elderly diabetics (52). For these reasons, new surrogate markers that reflect chronic hyperglycemia in the diabetic brain are needed. Hyperglycemia causes oxidative stress via the polyol pathway, enhances advanced glycation end-products (AGE), and increases lipid peroxidation and imbalances in the generation of reactive oxygen species and their scavengers (53, 54). N^{ε}-Carboxymethyllysine (CML), the most prominent AGE product, is crucially involved in the development of diabetic microangiopathy (55), and the level of CML expression is high in the blood vessels and brain of diabetics, but low in aging controls (56). Oxidative stress has also been implicated in the pathophysiology of Alzheimer's disease and hypoxic brain insults (57-59). Progression of diabetic retinopathy strongly correlates with the total sum of blood glucose control, and may constitute a predictor for cerebral small vessel disease (60, 61).

Certain limitations of our study need to be considered. The first limitation is that this analysis was a cross-sectional study. The second is the possibility that participants with some other cognitive dysfunction could be involved in this study. The mean MMSE score of our diabetic patients was 26.2 ± 0.3, which means that most of the subjects did not attain the full MMSE score. In particular, we could not completely exclude the patients with mild cognitive impairment. The third limitation is the method for measuring brain atrophy. We used linear measurements to evaluate subcortical atrophy adjacent to the lateral ventricles,

and this procedure is outdated and less accurate than the recently developed volumetric analysis of MR images (62). However, volumetric MR analyses of a number of diabetic patients from the different institutes and hospitals could not be performed. Finally, we did not estimate the effects of treatment per se for diabetes, hypertension, and lipid abnormalities on diabetic cognitive domains. The Rotterdam study has suggested that use of oral medication and insulin treatment for diabetes increases the association with dementia. While MR imaging has demonstrated that hypertension is associated with cognitive dysfunction and WMHs (63, 64). Recent prospective intervention studies have indicated that appropriate blood pressure control delays the progression of cognitive decline (65). Furthermore, there are indications that impaired cholesterol transport may have a pathophysiological roles in Alzheimer's disease and that HMG-CoA reductase inhibitors (statin) may have a protective effects on cognitive dysfunction in the elderly (66-68). Most of the diabetic subjects enrolled in this study were successfully treated for their blood pressure and lipid abnormalities, which could diminish the impacts of hypertension and lipid abnormalities on diabetic cognitive impairment and brain structural changes. The effects of these limitations of our study will be analyzed in the prospective intervention J-EDIT study.

In summary, WMHs and subcortical brain atrophy observed on MRI scans of elderly diabetics without symptomatic brain infarctions were found to be associated with impaired speed of mental processes and memory, while WMHs are thought to be responsible for degenerative changes of cerebral small vessels and to be implicated in the pathogenesis of cognitive impairment. These

findings suggest that hyperintensities in the parietal lobe and thalamus and subcortical atrophy in particular constitute predictors of the rate of cognitive dysfunction in elderly diabetics and may underlie procession towards severe cognitive impairment. Our prospective J-EDIT study should help to determine the factors that can prevent cognitive dysfunction in elderly diabetics.

Acknowledgements

This work was supporeted by a Research Grant for Longevity Sciences from the Ministry of Health, Labour and Welfare,Japan, and a grant from the Novartis Foundation for Gerontological Research (T.S.).

References

1. Kawamori R. Diabetes trends in Japan. *Diabetes Metab Res Rev.* 2002; 18: S9-S13

2. Davidson JA. Treatment of the patient with diabetes: importance of maintaining target HbA(1c). *Curr Med Res Opin.* 2004; 20: 1919-1927

3. Miles WR, Root HF. Psychologic tests applied to diabetic patients. *Arch Intern Med.* 1922; 30: 767-777

4. Strachen MW, Ewing FM, Deary IJ, et al. Is type 2 diabetes associated with an increased risk of cognitive dysfunction? A critical review of published studies. *Diabetes Care* 1997; 20: 438-445

5. Ott A, Stolk RP, van Harskamp F, *et al.* Diabetes mellitus and the risk of dementia: the Rotterdam Study. *Neurology* 1999; 53: 1937 1942

6. Luchsinger JA, Tang MX, Stern Y, *et al.* Diabetes mellitus and risk of Alzheimer's disease and dementia with stroke in a multiethnic cohort. *Am J Epidemiol.* 2001; 154: 635-641

7. Peila R, Rodriguez BL, Launer LJ. Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: the Honolulu-Asia Aging Study. *Diabetes* 2002; 51: 1256 1262

8. MacKnight C, Rockwood K, Awalt E, *et al.* Diabetes mellitus and the risk of dementia, Alzheimer's disease and vascular cognitive impairment in the Canadian study of health and aging. *Dement Geriatr Cogn Disord.* 2002; 14: 77-83

9. Arvanitakis Z, Wilson RS, Bienias JL, *et al.* Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. *Arch Neurol.* 2004; 61: 661-666

10. Gispen WH, Biessels GJ. Cognition and synaptic plasticity in diabetes mellitus. *Trends Neurosci.* 2000; 23: 542-549

11. Watson GS, Craft S. Modulation of memory by insulin and glucose: neuropsychological observation in Alzheimer's disease. *Eur J Phamacol.* 2004; 490: 97-113

12. Buckner RL. Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. *Neuron.* 2004; 44: 195-208

13. Lazarus R, Prettyman R, Cherryman G. White matter lesions on magnetic resonance imaging and their relationship with vascular risk factors in memory clinic attenders. *Int J Geriatr Psychiatry.* 2005; 20: 274-279

14. The expert committee on the diagnosis and classification of diabetes mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 2003; 26: suppl. 1. 5-20

15. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th edition. Washington, DC: American Psychiatric Association, 1994

16. Amiel SA. Iatrogenic hypoglycemia, Kahn CR, Weir GC, King GL, Jacobson AM, Moses AC, Smith RJ. (Eds) Lippincott Williams & Wilkins: Boston MA, 2005; 671-686

17. Piguet O, Ridley LJ, Grayson DA, *et al.* Comparison white matter lesions on T2 and FLAIR MRI in the Sydney Older Persons Study. *Eur J Neurol.* 2005; 12: 399-402

18. de Groot JC, de Leeuw F-E, Oudkerk M, *et al.* Cerebral white matter lesions and cognitive function: the Rotterdam Scan Study. *Ann Neurol.* 2000; 47: 145-151

19. Erkinjuntti T, Inzitari D, Pantoni L, *et al.* Research criteria for subcortical vascular dementia in clinical trials. *J Neural Transm Suppl.* 2000; 59: 23-30

20. Evans WA. An encephalographic ratio for estimating ventricular enlargement and cerebral atrophy. *Arch Neurol Pyschiat.* 1942; 47: 931

21. Haug G. Age and sex dependence of the size of normal ventricles on computed tomography. *Neuroradiology* 1977; 14: 201

22. Sawai F. Computed tomographical diagnosis of brain atrophy by aging. *J Nara Med Assoc* 1987; 38: 974-979

23. Ushida C, Umegaki H, Hattori A, *et al.* Assessment of brain atrophy in elderly subjects with diabetes mellitus by computed tomography. *Geriatr Gerontol Int.* 2001; 1: 33 37

24. Stroop JR. Studies of interference in serial verbal reactions. *Journal of Experimental Psychology.* 1935; 18: 643-662

25. Wechsler D. Manual for the Wechsler Adult Intelligence Scale-Revised. *New York, Psychological Corporation* 1981

26. Mohs RC, Rosen WG, Davis KL. The Alzheimer's Disease Assessment Scale; an instrument for assessing treatment efficacy. *Psychophamacol Bull* 1983; 19: 448-450

27. Ueda M. Takayama Y, Sasanuma S. Memory disorders in the elderly stage of dementia of the Alzheimer type: preliminary findings. *Japanese Journal of Neuropsychology* 1996; 12: 178-186

28. Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state.' A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975; 12: 189-198

29. Johnson RA, Wichern DW. Applied Multivariate Statistical Analysis, 5th ed London. Prentice Hall. 2002

30. Razavi AR, Gill H, Stal O *et al,* Exploring cancer register data to find risk factors for recurrence of breast cancer—application of canonical correlation analysis. *BMC Med Inform Decis Mak.* 2005; 22: 5-29

31. Sherry A, Henson RK. Conducting and interpreting canonical correlation analysis in personality research: a user-friendly primer. *J Pers Assess.* 2005; 84: 37-48

32. O' Brien JT, Wiseman R, Burton EJ, *et al.* Cognitive associations of subcortical white matter lesions in older people. *Ann. N.Y. Acad. Sci.* 2002; 977: 436-444

33. de Leeuw FE, de Groot JC, Oudkerk M, *et al.* Hypertension and cerebral white matter lesions in prospective cohort study. *Brain.* 2002; 125: 765-772

34. Ylikoski R, Ylikoski A, Erkinjuntti T, *et al.* White matter changes in healthy elderly persons correlates with attention and speed of mental processing. *Arch Neurol.* 1993; 50: 818-824

35. Schmidt R, Fazekas F, Offenbacher H, *et al.* Neuropsychologic correlates of MRI white matter hyperintensities: a study of 150 normal volunteers. *Neurology* 1993; 43: 2490 2494

36. Ylikoski R, Erkinjuntti T, Raininko R, *et al.* White matter hyperintensities on MRI in the neurological nondiseased elderly. Analysis of cohorts of consecutive subjects aged 55 to 85 years living at home. *Stroke.* 1995; 26: 1171-1177

37. Gunning-Dixon FM, Raz N. The cognitive correlates of white matter abnormalities in normal aging: A quantitative review. *Neuropsychology.* 2000; 14: 224-232

38. de Groot JC, de Leeuw FE, Oudkerk M, *et al.* Periventricular cerebral white matter lesions predict rate of cognitive decline. *Ann Neurol.* 2002; 52: 335-341

39. Filley CM. The behavioral neurology of cerebral white matter. *Neurology* 1998; 50: 1535-1540

40. Schmahmann JD. Vascular syndromes of the thalamus. Stroke. 2003; 34 2264-2278

41. Rapoport SI. Integrated phylogeny of the primate brain, with special reference to humans and their disease. *Brain Res Brain Res Rev.* 1990; 15: 267-294

42. Salmon E, Sadzot B, Maquet P, *et al.* Differential diagnosis of Alzheimer's disease with PET. *J Nucl Med.* 1994; 35: 391-398

43. Fazekas F, Kleinert R, Offenbacher H, *et al.* Pathologic correlates of incidental MRI white matter signal hyperintensities. *Neurology* 1993; 43: 1683-1689

44. Udaka F, Sawada H, Kameyama M. White matter lesions and dementia MRI-pathological correlation. *Ann. N.Y. Acad. Sci.*2002; 977: 411 -415

45. Pugh KG, Lipsitz LA. The microvascular frontal-subcortical syndrome of aging. *Neurobiol Aging.* 2002; 23: 421-431

46. Longstreth WT, Manolio Ta, Arnold A, *et al.* Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. *Stroke.* 1996; 27: 1274 1282

47. Raz N, Rodrigue KM, Acker JD. Hypertension and the brain: vulnerability of the prefrontal regions and executive functions. *Behav Neurosci.* 2003; 117: 1169-1180

48. Taylor WD, MacFall JR, Provenzale JM, *et al.* Serial MR imaging of volumes of hyperintense white matter lesions in elderly patients: correlation with vascular risk factors. *AJR Am J Roentgenol.* 2003; 181: 571-576

49. Cosway R, Strachan MWJ, Dougall A, *et al.* Cognitive function and information processing in Type 2 diabetes. *Diabet Med.* 2001; 18: 803-810

50. Mogi N, Umegaki H, Hattori A, *et al.* Cognitive function in Japanese elderly with type 2 diabetes mellitus. *J Diabetes Complications.* 2004; 18: 42-46

51. Cox DJ, Kovatchev BP, Gonder-Frederick LA, *et al.* Relationships between hyperglycemia and cognitive performance among adults with type 1 and type 2 diabetes. *Diabetes Care.* 2005; 28: 71-77

52. den Heijer T, Vermeer SE, van Dijk, *et al.* Type 2 diabetes and atrophy of medial temporal lobe structures on brain MRI. *Diabetologia* 2003; 46: 1604-1610

53. Ceriello A, Quatraro A, Guigliano D. Diabetes mellitus and hypertension: the possible role of hyperglycemia through oxidative stress. *Diabetologia* 1993; 36: 265-266

54. Lipinski B. Pathophysiology of oxidative stress in diabetes mellitus. *J Diabetes its Complicat.* 2001; 15: 203-210

55. Lander HM, Tauras JM, Ogiste JS, *et al.* Activation of the receptor for advanced glycation end products triggers a p21(ras)-dependent mitogen-activated protein kinase pathway regulated by oxidant stress. *J Biol Chem.* 1997; 272: 17810-17814

56. Girones X, Guimera A, Cruz-Sanchez CZ, *et al.* N epsilon-carboxymethyllysine in brain aging, diabetes mellitus, and Alzheimer's disease. *Free Radic Biol Med.* 2004; 36: 1241-1247

57. Yan SD, Chen X, Fu J, *et al.* RAGE and amyloid-beta peptide neurotoxicity in Alzheimer's disease. *Nature* 1996; 382: 685-691

58. Thomas T, Thomas G, McLendon C, *et al.* β -Amyloid-mediated vasoactivity and vascular endothelial damage. *Nature* 1996; 380: 168 171

59. Sastre J, Pallardo FV, Vina J. Mitochondrial oxidative stress plays a key role in aging and apoptosis. *IUBMB Life* 2000; 49: 427-435

60. Petitti DB, Bhatt H. Retinopathy as a risk factor for nonembolic stroke in diabetic subjects. *Stroke.* 1995;26: 593 -596

61. Inoue T, Fushimi H, Yamada Y, *et al.* Asymptomatic multiple lacunae in diabetics and non-diabetics detected by brain magnetic resonance imaging. *Diabetes Res Clin Pract.* 1996; 31: 81-86

62. Frisoni GB, Scheltens PH, Galluzzi S *et al.* Neuroimaging tools to rate regional atrophy, subcortical cerebrovascular disease, and regional cerebral blood flow and metabolism: consensus paper of the EADC. *J Neurol Neurosurg Psychiatry* 2003; 74: 1371 1381

63. Insel KC, Palmer RF, Stroup-Benham CA *et al.* Association between change in systolic blood pressure and cognitive decline among elderly Mexican Americans: data from the Hispanic established population for epidemiology study of the elderly. *Exp Aging Res.* 2005; 31: 35-54

64. den Heijer T, Launer LJ, Prins ND, *et al.* Association between blood pressure, white matter lesions, and atrophy of the medial temporal lobe. *Neurology* 2005; 64: 263-267

65. Forette F, Seux ML, Staessen JA, *et al.* Prevention of dementia in randomized double-blind placebo-controlled systolic hypertension in Europe (Syst-Eur) trial. *Lancet.* 1998; 352: 1347-1351

66. Jick H, Zornberg GL, Jick SS, *et al.* Statins and the risk of dementia. *Lancet.* 2000; 356: 1627-1631

67. Kristine Y, Elizabeth BC, Feng L, *et al.* Serum lipoprotein levels, stain use, and cognitive function in older women. *Ach Neurol.* 2002; 59: 378-384

68. Shepherd J. A prospective study of pravastatin in the elderly at risk: New hope for older persons. *Am J Geriatr Cardiol.* 2004; 13: 17-24

Table 1 Clinical Characteristics of elderly patients with diabetes mellitus

	N	Mean±SEM
Clinical character		
Age (years)	95	72.8±0.5
Male: Female	38 : 57	
Education (years)	77	10.7±0.3
Duration of diabetes mellitus (years)	92	18.4±1.2
Body mass index (kg/m^2)	92	23.2±0.4
Waist/hip ratio	92	0.92±0.0
Systolic blood pressure (mmHg)	95	135.4±1.2
Diastolic blood pressure (mmHg)	95	75.5±0.9
Cardiovascular complication	95	0.16±0.0
Retinopathy	88	0.70±0.1
Nephropathy	87	0.59±0.1
Neuropathy	87	0.66±0.1
Fasting blood glucose (mg/dl)	82	164.2±5.1
HbA1c (%)	95	7.9±0.1
Insulin	77	9.3±1.3
Total cholesterol (mg/dl)	95	203.4±3.2
Triglyceride (mg/dl)	95	150.1±12.8
HDL cholesterol (mg/dl)	94	65.0±2.7
Cognitive function		
Mini-mental state examination	80	26.2±0.3
Immediate word-list recall	81	8.2±0.2
Delayed word-list recall	80	6.8±0.3
Immediate paragraph recall	80	7.5±0.3
Delayed paragraph recall	80	5.8±0.3
Stroop test (B)	80	40.2±1.6
Digit symbol substitution test	77	35.8±1.2
MRI		
White matter hyperintensities (WMHs)		
Frontal lobe (ml)	95	1.8±0.2
Parietal lobe (ml)	95	1.0±0.1
Temporal lobe (ml)	95	0.8±0.1
Occipital lobe (ml)	95	0.3±0.1
Thalamus (ml)	95	0.1±0.0
Basal ganglia (ml)	95	0.3±0.0
Total (ml)	95	4.3±0.4
Periventricular hyperintensity	86	9.7±0.31
Evans ratio	95	26.0±0.34
Caudate head index	95	13.5±0.25
inverse Cella media index	95	26.3±0.40
Basal cistern index	95	19.6±0.27

Table 2 Canonical correlation between cognitive function and WMHs

Canonical correlation coefficient; 0.64			P=0.004
Immediate word-list recall	0.33	WMHs of frontal lobe	-0.07
Delayed word-list recall	0.47	WMHs of parietal lobe	-0.33
Immediate paragraph recall	0.14	WMHs of temporal lobe	-0.31
Delayed paragraph recall	0.29	WMHs of occipital lobe	0.33
MMSE	0.65	Thalamus	-0.39
Stroop test (B)	-0.41	Basal ganglia	-0.23
Digit symbol substitution test	0.76	Total WMHs	-0.34
		Periventricular hyperintensity	-0.45

Each value represents correlation of canonical valuables.

Table 3 Canonical correlation between cognitive function and subcortical brain atrophy

Canonical correlation coefficient; 0.61			p=0.004
Immediate word-list recall	-0.79	Evans ratio	0.83
Delayed word-list recall	-0.61	Caudate head index	0.79
Immediate paragraph recall	-0.28	inverse Cella media index	0.92
Delayed paragraph recall	-0.55	Basal cistern index	0.35
MMSE	-0.32		
Stroop test (B)	0.30		
Digit symbol substitution test	-0.71		

Each value represents correlation of canonical valuables.

Table 4 Multivariate regression analysis for subcortical WMHs with adjustment for age, education, and blood pressure

Digit symbol substitution test	P value	95% CI
WMHs of frontal lobe	0.13	-0.0004— 0.0033
WMHs of parietal lobe	<.05	-0.0057—-0.0002
WMHs of temporal lobe	0.99	-0.0039— 0.0038
WMHs of occipital lobe	0.56	-0.0048— 0.0087
Thalamus	0.34	-0.0187— 0.0065
Basal ganglia	0.31	-0.0092— 0.0030
Periventricular hyperintensity	0.54	-1.34— 0.70

MMSE	P value	95% CI
WMHs of frontal lobe	0.85	-0.0004— 0.0005
WMHs of parietal lobe	0.10	-0.0012— 0.0001
WMHs of temporal lobe	0.47	-0.0006— 0.0012
WMHs of occipital lobe	0.18	-0.0005— 0.0027
Thalamus	<.05	-0.0062—-0.0002
Basal ganglia	0.57	-0.0018— 0.0010
Periventricular hyperintensity	0.93	-0.23— 0.25

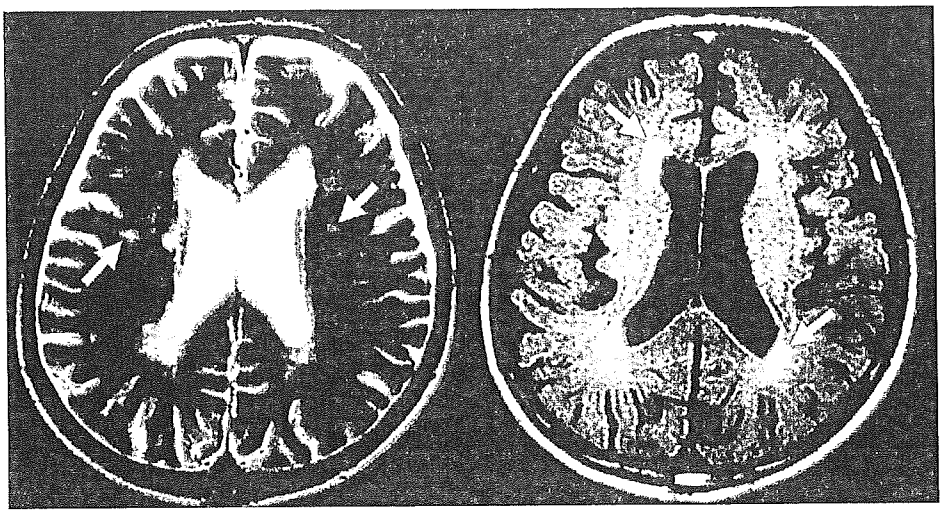
Each variable is adjusted for age, education, and systolic blood pressure
CI; confidence intervals

Table 5 Multivariate regression analysis for subcortical atrophy with adjustment for age, education, and blood pressure

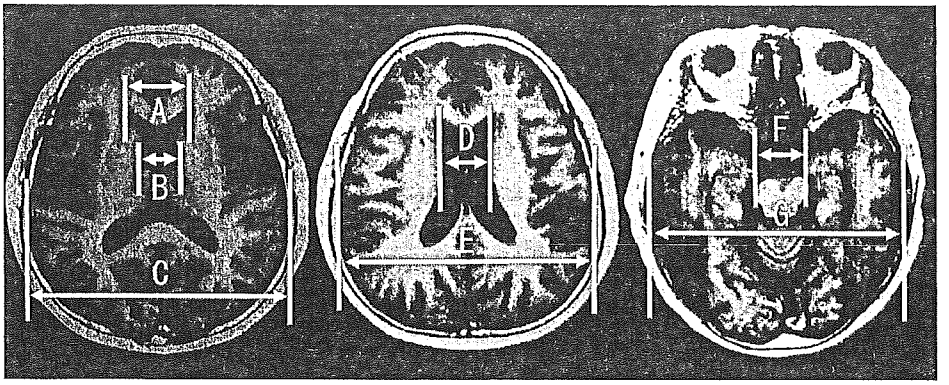
Immediate word-list recall	P value	95% CI
Evans ratio	0.50	-0.24— 0.12
Caudate head index	<.05	-0.33—-0.02
inverse Cella media index	0.28	-0.22— 0.07
Basal cistern index	0.77	-0.14— 0.11

Digit symbol substitution test	P value	95% CI
Evans ratio	0.87	-1.15— 1.35
Caudate head index	1.00	-1.07— 1.08
inverse Cella media index	<.05	-2.07—-0.08
Basal cistern index	0.13	-1.54— 0.20

Each variable is adjusted for age, education, and systolic blood pressure
CI; confidence intervals



An example of subcortical (left) and periventricular (right) white matter hyperintensities on brain MR imaging.



Measured portions on MR imaging. A, the maximum distance between the tips of the anterior horns; B the width between the bilateral heads of the caudate nuclei; C, the maximum transverse inner diameter of the cranial space at the same MR section (left); D, the maximum width of the cella mediae; E, the maximum transverse inner diameter at the same section (center); F, the internal width between the bilateral temporal lobe at the level of basal cistern; G, the maximum transverse inner diameter at the same level (right). Evans ratio= A/C, Caudate Head Index=B/C, inverse Cella Media Index= D/E, Basal Cistern Index= F/G.