Association Between Diabetes and Hippocampal Atrophy in Elderly Japanese: The Hisayama Study

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OBJECTIVE

To investigate the association between diabetes and brain or hippocampal atrophy in an elderly population.

RESEARCH DESIGN AND METHODS

A total of 1,238 community-dwelling Japanese subjects aged ≥65 years underwent brain MRI scans and a comprehensive health examination in 2012. Total brain volume (TBV), intracranial volume (ICV), and hippocampal volume (HV) were measured using MRI scans for each subject. We examined the associations between diabetes-related parameters and the ratios of TBV to ICV (an indicator of global brain atrophy), HV to ICV (an indicator of hippocampal atrophy), and HV to TBV (an indicator of hippocampal atrophy beyond global brain atrophy) after adjustment for other potential confounders.

RESULTS

The multivariable-adjusted mean values of the TBV-to-ICV, HV-to-ICV, and HV-to-TBV ratios were significantly lower in the subjects with diabetes compared with those without diabetes (77.6% vs. 78.2% for the TBV-to-ICV ratio, 0.513% vs. 0.529% for the HV-to-ICV ratio, and 0.660% vs. 0.676% for the HV-to-TBV ratio; all $P < 0.01$). These three ratios decreased significantly with elevated 2-h postload glucose (PG) levels (all P for trend <0.05) but not fasting plasma glucose levels. Longer duration of diabetes was significantly associated with lower TBV-to-ICV, HV-to-ICV, and HV-to-TBV ratios. The subjects with diabetes diagnosed in midlife had significantly lower HV-to-ICV and HV-to-TBV ratios than those without and those diagnosed in late life.

CONCLUSIONS

Our data suggest that a longer duration of diabetes and elevated 2-h PG levels, a marker of postprandial hyperglycemia, are risk factors for brain atrophy, particularly hippocampal atrophy.

The increasing burden of dementia is a serious social, medical, and economic problem worldwide. The prevalence of Alzheimer disease, the most major subtype of dementia, has rapidly increased in elderly Japanese during the past three decades (1). However, the pathological mechanisms of Alzheimer disease have not been fully elucidated, and a curative treatment has not been established. There is thus an urgent need to identify risk factors and protective factors for the development of Alzheimer disease and to prevent the disease.

Several population-based prospective studies have reported that diabetes is associated with an increased risk of Alzheimer disease (2). Since brain atrophy, particularly hippocampal atrophy, is one of the morphological features of Alzheimer

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disease, patients with diabetes may have hippocampal atrophy compared with individuals without diabetes. However, previous cross-sectional studies conducted in Western countries showed conflicting results regarding the association between diabetes and hippocampal atrophy (3–7), and there are no population-based studies examining this issue in Asian populations.

The Hisayama Study is a population-based prospective study of cerebro- and cardiovascular diseases and dementia in a general Japanese population. Using the data from the Hisayama Study, we previously observed that diabetes and elevated 2-h postload glucose (PG) concentrations were significantly associated with the development of Alzheimer disease (8) and neuritic plaque formation (9). The current study was conducted to investigate the association between diabetes-related parameters and brain and hippocampal atrophy, using MRI scans in elderly residents of Hisayama, Japan.

RESEARCH DESIGN AND METHODS

Study Population

The Hisayama Study was established in 1961 in the town of Hisayama, a suburb of the Fukuoka metropolitan area of Kyushu Island in Japan. In this town, comprehensive screening surveys of cognitive function and activities of daily living for elderly residents have been repeated every 6–7 years since 1985 (1,8). In 2012, a total of 1,906 residents aged ≥65 years (93.6% of the town's total population in this age-group) participated in the screening survey, and 1,342 (70.4%) underwent brain MRI scans. After the exclusion of 1 subject who refused to participate in the study, 41 subjects who did not participate in a comprehensive health examination performed in the same year, 6 with no plasma glucose data, and 56 with any errors in the MRI scans (26 without T1-weighted 3-dimensional images, 4 with metal artifacts, 7 with excessive motion artifacts, and 19 for whom hippocampal volume [HV] could not be measured appropriately due to segmentation errors), the remaining 1,238 subjects (540 men and 698 women) were enrolled in the current study.

MRI Analysis

In the MRI examination, T1-weighted three-dimensional magnetization-prepared rapid gradient echo images, conventional T1- and T2-weighted images, fluid-attenuated inversion recovery images, T2*-weighted images, and magnetic resonance angiography of the brain were examined using a 1.5-Tesla MRI scanner (Intera Pulsar; Philips Medical Systems, Best, the Netherlands) with a multichannel head coil. T1-weighted three-dimensional images acquired in the sagittal plane with the following parameters were used to determine brain and hippocampal atrophy: repetition time 8.5 ms, echo time 4.0 ms, inversion time 1,000 ms, flip angle 8°, field of view 240 mm, acquisition matrix 192 × 192, slice thickness 1.2 mm, and number of excitations 1.

The segmentation and volume measurements of the hippocampus and other subcortical brain structures were performed automatically using the software FMRIB's Integrated Registration and Segmentation Tool (FIRST) implemented in FSL, version 5.0.6 (Oxford University, Oxford, U.K.) (10). HV was calculated by summing the left and right HVs. All processed images were visually checked for errors in segmentation. The gray matter volume, white matter volume, and cerebrospinal fluid volume of the brain were measured using VBM8 Toolbox, version 435 (University of Jena, Jena, Germany [http://dbm.neuro.uni-jena.de/vbm/]) in SPM8 (Wellcome Department of Imaging Neuroscience, University College London, London, U.K. [http://www.fil.ion.ucl.ac.uk/spm/]) running in MATLAB (MathWorks, Natick, MA). The default settings were used except that affine regularization was performed with the International Consortium for Brain Mapping template for East Asian brains.

The total brain volume (TBV) was calculated as the sum of the gray and white matter volumes. The intracranial volume (ICV) was calculated as the sum of the TBV and the cerebrospinal fluid volume. In the current study, three parameters for brain atrophy were defined: *1*) the TBV-to-ICV ratio (%) as an indicator of global brain atrophy, *2*) the HV-to-ICV ratio (%) as an indicator of hippocampal atrophy, and *3*) the HV-to-TBV ratio (%) as an indicator of hippocampal atrophy beyond global brain atrophy, which assesses whether hippocampal atrophy is more predominant than global brain atrophy.

Cerebrovascular lesions were defined as brain infarction or hemorrhage on MRI regardless of the presence or absence of neurological symptoms. Brain infarction included lesions of ≥3 mm in diameter visible on both the T1-weighted image (as a hypointense lesion) and the T2-weighted image (as a hyperintense lesion) with a surrounding hyperintense rim on the fluid-attenuated inversion recovery image. Brain hemorrhage was defined as any hemorrhagic lesions, including cerebral microbleeds, visible on the T2*-weighted image (as a hypointense lesion). Each scan was read by two trained stroke neurologists who were blinded to the clinical information (interrater agreement ratio: 74.7% for the brain infarctions, 83.6% for the brain hemorrhages). In case of conflicting interpretations, a third stroke neurologist read the scan and made a final decision.

Definition of Diabetes

In the comprehensive health examination, all subjects aged 40–79 years except for the subjects with severe diabetes or insulin treatment were encouraged to undergo a 75-g oral glucose tolerance test (75g-OGTT). For the subjects aged ≥80 years, a 75g-OGTT was conducted for those who preferred to have the test. Consequently, among a total of 1,238 eligible subjects, 914 (73.8%) underwent the 75g-OGTT, and the remaining 324 (26.2%) had a single measurement of fasting or postprandial plasma glucose concentrations. Plasma glucose levels were determined by the hexokinase method. Diabetes was defined as fasting plasma glucose (FPG) concentrations of ≥7.0 mmol/L, postprandial or 2-h PG concentrations of ≥11.1 mmol/L, or current use of any antidiabetes medication (oral hypoglycemic agents, injectable glucagon-like peptide analogs, or insulin).

Diabetes was also classified as newly diagnosed or known diabetes by a self-administered questionnaire. Newly diagnosed diabetes was defined as when the subject reported having no history of diabetes and was newly diagnosed as having diabetes in the health examination. Known diabetes was defined as when the subject reported having diabetes diagnosed before the examination. The subjects with known diabetes were further subclassified into tertiles according to the duration of diabetes (≤9, 10–16, and ≥17 years).

Glucose Tolerance Status and Plasma Glucose Levels

Among a total of 1,238 subjects, 936 (423 men and 513 women) who underwent the 75g-OGTT (914 subjects) or were treated with insulin (22 subjects) were included in a subanalysis for our investigation of the associations of glucose tolerance status, FPG levels, and 2-h PG levels with brain atrophy. Glucose tolerance status was defined according to the 1998 World Health Organization criteria (11): normal glucose tolerance, FPG <6.1 mmol/L and 2-h PG <7.8 mmol/L; impaired fasting glycemia (IFG), FPG 6.1–6.9 mmol/L and 2-h PG <7.8 mmol/L; impaired glucose tolerance (IGT), FPG <7.0 mmol/L and 2-h PG 7.8–11.0 mmol/L; and diabetes, FPG ≥7.0 mmol/L and 2-h PG ≥11.1 mmol/L. The subjects who were being treated with antidiabetes medications were included in the diabetes group irrespective of their glucose levels. The FPG and 2-h PG levels were each divided into three categories as follows: FPG, <6.1, 6.1–6.9, and ≥7.0 mmol/L; 2-h PG, <7.8, 7.8–11.0, and ≥11.1 mmol/L.

Midlife and Late-Life Diabetes

Among the total of 1,201 participants who were aged 65–88 years in 2012, 849 (347 men and 502 women) who had participated in the health examination in 1988, i.e., 24 years earlier during their midlife (aged 41–64 years), were included in another subanalysis investigating the influence of diabetes diagnosed in midlife on brain and hippocampal atrophy in late life. The subjects were classified into three categories: *1*) the subjects without diabetes in both the 1988 and 2012 health examinations (no diabetes), *2*) the subjects who had not been diagnosed as having diabetes in 1988 but were diagnosed as having diabetes in 2012 (late-life diabetes), and *3*) the subjects who had already been diagnosed as having diabetes in 1988 (midlife diabetes).

Other Risk Factor Measurements

In the 2012 health examination, each subject completed a self-administered questionnaire covering educational status, medical history (including the time of disease diagnoses) and treatment (antihypertension, antidiabetes, and lipid-lowering medications), smoking habits, alcohol consumption, and physical activity. Low education levels were defined as ≤9 years of formal education. Smoking habits and alcohol intake were categorized as current use or no current use. Regular exercise was defined as engaging in sports three or more times a week during leisure time.

Blood pressure was measured three times using an automated sphygmomanometer (BP-203 RVIIIB; Omron Healthcare, Kyoto, Japan) with the subject in the sitting position after resting for ≥5 min. The mean of the three measurements was used for the analysis. Hypertension was defined as blood pressure levels ≥140/90 mmHg or current treatment with antihypertension agents. Serum total cholesterol levels were measured enzymatically. Hypercholesterolemia was defined as serum total cholesterol levels ≥5.69 mmol/L or current use of lipid-lowering medication. Body height and weight were measured with the subject in light clothing without shoes, and the BMI was calculated.

Dementia was ascertained using the criteria of the DSM-III (12) through the screening survey using the Hasegawa Dementia Scale-Revised (13) and the Mini-Mental State Examination (14) and secondary comprehensive investigations by psychiatrists for the subjects who were suspected to have cognitive impairment as previously described (1).

Statistical Analysis

The differences in the mean values and the frequencies of risk factors between the subjects with and without diabetes were tested using the *t* test and χ^2 test, respectively. The age- and sex-adjusted or multivariable-adjusted means and 95% CIs of the TBV-to-ICV, HV-to-ICV, and HV-to-TBV ratios were estimated and compared using ANCOVA. The covariates used in the multivariable models were age, sex, education status, hypertension, total cholesterol, BMI, smoking habit, alcohol intake, regular exercise, cerebrovascular lesions on MRI, and/or antidiabetes medication. All statistical analyses were performed using the SAS program, version 9.3 (SAS Institute, Cary, NC). *P* values <0.05 were considered significant.

RESULTS

Supplementary Table 1 shows the baseline characteristics of the study subjects by diabetes status in the health examination. Of the total of 1,238 subjects, 286 (23%) had diabetes. The proportions of men and subjects with hypertension, alcohol intake, and cerebrovascular lesions on MRI scans and the mean values of BMI were significantly higher in the subjects with diabetes compared with those without diabetes, whereas the mean total cholesterol levels were significantly lower in the diabetes group because the proportion of subjects taking lipid-lowering medication was significantly higher in this group.

The adjusted means of the TBV-to-ICV, HV-to-ICV, and HV-to-TBV ratios by diabetes status are presented in Table 1. The subjects with diabetes had significantly lower mean values of all of these MRI parameters of brain atrophy compared with the subjects without diabetes after adjustment for age and sex. These results remained robust even after the adjustment for other confounding factors, namely, education status, hypertension, total cholesterol, BMI, smoking habit, alcohol intake, regular exercise, and cerebrovascular lesions on MRI scans. In the sensitivity analysis with 1,115 subjects who did not have dementia, the associations did not change substantially.

Table 2 shows the association of glucose tolerance status with MRI parameters of brain atrophy in the subgroup of 936 subjects who underwent the 75g-OGTT or had insulin treatment. The mean values of the TBV-to-ICV, HV-to-ICV, and HV-to-TBV ratios were significantly lower in the diabetes group than in the normal glucose tolerance group after adjustment for covariates but not in the IFG or IGT groups. The multivariable-adjusted mean values of the TBV-to-ICV, HV-to-ICV, and HV-to-TBV ratios decreased significantly with elevating 2-h PG levels, while no such associations were observed for the FPG levels. All of these parameters were significantly lower in the subjects with 2-h PG levels ≥11.1 mmol/L compared with those with 2-h PG levels <7.8 mmol/L.

Figure 1 demonstrates the association between the duration of diabetes and the MRI parameters of brain atrophy. Of the 286 subjects with diabetes, 83 had newly diagnosed diabetes, and the remaining 203 subjects had known diabetes. Longer duration of diabetes was significantly associated with lower multivariable-adjusted mean values of the TBV-to-ICV, HV-to-ICV, and HV-to-TBV ratios (all *P* for trend <0.001); all

Table 1—Adjusted mean (95% CI) values of the TBV-to-ICV, HV-to-ICV, and HV-to-TBV ratios by diabetes status

	No. of subjects	TBV-to-ICV ratio (%): indicator of global brain atrophy	HV-to-ICV ratio (%): indicator of hippocampal atrophy	HV-to-TBV ratio (%): indicator of hippocampal atrophy beyond global brain atrophy
Age and sex adjusted				
No diabetes	952	78.1 (78.0–78.2)	0.528 (0.524–0.532)	0.675 (0.670–0.679)
Diabetes	286	77.5 (77.3–77.7)	0.514 (0.507–0.521)	0.662 (0.653–0.670)
P		<0.001	<0.001	0.009
Multivariable adjusted[a]				
No diabetes	952	78.2 (78.0–78.3)	0.529 (0.525–0.533)	0.676 (0.671–0.681)
Diabetes	286	77.6 (77.4–77.8)	0.513 (0.506–0.520)	0.660 (0.651–0.669)
P		<0.001	<0.001	0.002
Multivariable adjusted[a] (in nondemented subjects)[b]				
No diabetes	854	78.4 (78.3–78.5)	0.538 (0.534–0.541)	0.685 (0.680–0.690)
Diabetes	261	77.8 (77.6–78.0)	0.521 (0.514–0.528)	0.669 (0.660–0.677)
P		<0.001	<0.001	0.001

[a]Adjusted for age, sex, education status, hypertension, total cholesterol, BMI, smoking habits, alcohol intake, regular exercise, and cerebrovascular lesions on MRI. [b]Sensitivity analysis that excluded 123 subjects with dementia in 2012.

of these parameters were significantly lower in the subjects with a diabetes duration of ≥17 years compared with the subjects without diabetes.

In addition, the multivariable-adjusted mean values of the TBV-to-ICV ratio were significantly decreased in both the subjects with late-life and the subjects with midlife diabetes compared with those without diabetes, whereas the subjects with midlife diabetes had significantly lower HV-to-ICV and HV-to-TBV ratios compared with those without diabetes or with late-life diabetes (Fig. 2).

CONCLUSIONS

The results of the current study clearly demonstrated that in an elderly Japanese population, the subjects with diabetes, particularly those with higher 2-h PG levels, had significantly lower global brain and HVs compared with those without these characteristics. These associations remained unchanged after adjustment for potential confounding factors and after the exclusion of subjects with dementia. Thus, diabetes is a possible risk factor for hippocampal atrophy, which precedes the onset of dementia among subjects with diabetes.

Intriguingly, our findings showed that the subjects with diabetes had significantly lower mean HV-to-TBV ratio values, indicating not that hippocampal atrophy simply reflects global brain atrophy in subjects with diabetes but, rather, that the hippocampus is predominantly affected by diabetes. In addition, in our subjects a longer duration and a midlife onset of diabetes were significantly associated with a lower HV, possibly suggesting that a long exposure of diabetes particularly worsens hippocampal atrophy. Our findings highlight the importance of the prevention and

Table 2—Multivariable-adjusted mean (95% CIs) values of the TBV-to-ICV, HV-to-ICV, and HV-to-TBV ratios by glucose tolerance status and fasting and 2-h PG levels

	No. of subjects	TBV-to-ICV ratio (%): indicator of global brain atrophy	HV-to-ICV ratio (%): indicator of hippocampal atrophy	HV-to-TBV ratio (%): indicator of hippocampal atrophy beyond global brain atrophy
Glucose tolerance[a]				
Normal (reference)	367	78.6 (78.4–78.8)	0.540 (0.534–0.547)	0.687 (0.679–0.694)
IFG	53	78.7 (78.2–79.1)	0.533 (0.517–0.549)	0.677 (0.658–0.697)
IGT	280	78.5 (78.3–78.7)	0.537 (0.530–0.544)	0.684 (0.675–0.692)
Diabetes	236	77.9 (77.7–78.1)*	0.518 (0.510–0.526)*	0.664 (0.655–0.674)*
FPG levels (mmol/L)[b]				
<6.1 (reference)	608	78.4 (78.3–78.6)	0.536 (0.532–0.541)	0.683 (0.677–0.689)
6.1–6.9	186	78.4 (78.1–78.6)	0.528 (0.519–0.536)	0.673 (0.662–0.683)
≥7.0	142	78.2 (77.9–78.5)	0.528 (0.517–0.539)	0.674 (0.661–0.688)
P for trend		0.21	0.07	0.11
2-h PG levels (mmol/L)[b]				
<7.8 (reference)	430	78.6 (78.4–78.7)	0.539 (0.533–0.544)	0.685 (0.678–0.692)
7.8–11.0	319	78.5 (78.3–78.6)	0.537 (0.530–0.543)	0.684 (0.676–0.692)
≥11.1	165	78.1 (77.8–78.4)*	0.518 (0.508–0.529)*	0.663 (0.650–0.675)*
P for trend		0.03	0.007	0.02

[a]Adjusted for age, sex, education status, hypertension, total cholesterol, BMI, smoking habits, alcohol intake, regular exercise, and cerebrovascular lesions on MRI. [b]Adjusted for age, sex, education status, hypertension, total cholesterol, BMI, smoking habits, alcohol intake, regular exercise, cerebrovascular lesions on MRI, and antidiabetes medication. *$P < 0.05$ vs. reference group.

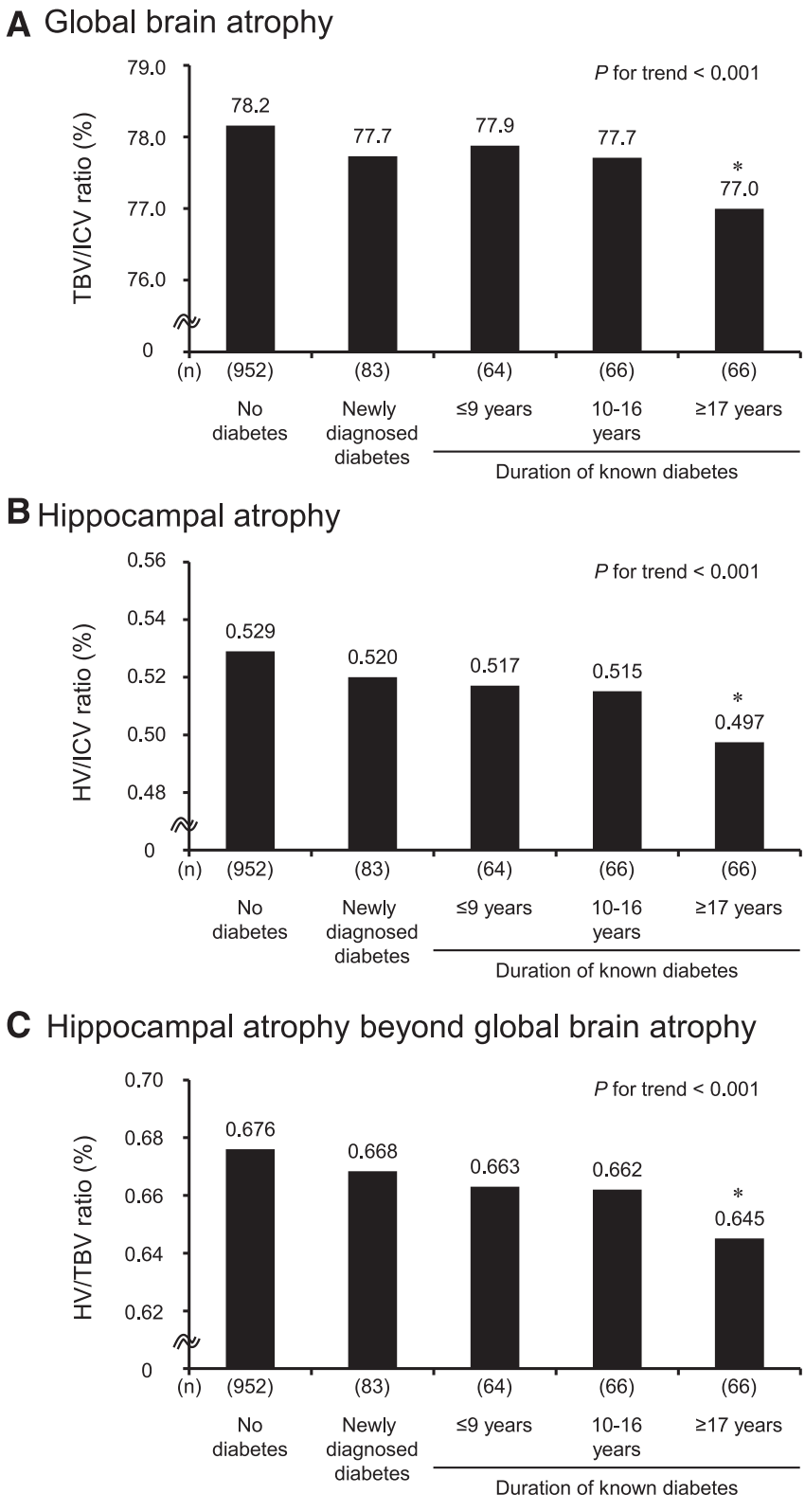

Figure 1—Multivariable-adjusted TBV-to-ICV (*A*), HV-to-ICV (*B*), and HV-to-TBV (*C*) ratios according to duration of diabetes. Values were adjusted for age, sex, education status, hypertension, total cholesterol, BMI, smoking habits, alcohol intake, regular exercise, and cerebrovascular lesions on MRI. Seven subjects with missing values of duration of known diabetes were excluded from the analysis. *$P < 0.05$ vs. no diabetes group.

early management of diabetes toward reducing the risk of global brain and hippocampal atrophy and subsequent dementia in late life.

In prior epidemiological studies of general populations, a positive association between diabetes and global brain atrophy has consistently been demonstrated (5,15,16). However, there have been conflicting results regarding the association between diabetes and hippocampal atrophy in some population-based cross-sectional (3–6) and hospital-based studies (7). The Rotterdam Study (3) and the Honolulu-Asia Aging Study (4) revealed that diabetes was significantly associated with hippocampal atrophy, which is in accord with our present findings. In contrast, the Framingham Offspring Study (5), the Sydney Memory and Ageing Study (6), and the pooled analyses of three hospital-based studies in the Netherlands (7) showed no significant association.

These conflicting results may be related to a difference in the diagnostic criteria for diabetes. In the two studies reporting the significant association, diabetes was diagnosed by means of the 75g-OGTT (3,4), as in our study, but this was not the case in the other studies (5–7). The current study showed that 2-h PG levels after the 75g-OGTT were significantly associated with hippocampal atrophy independent of other risk factors, but the FPG levels were not. All of these findings suggest that the association of diabetes and hippocampal atrophy can be explained mainly by elevated 2-h PG levels, a marker for postprandial hyperglycemia.

Several pathophysiological mechanisms can explain the association between diabetes or elevated 2-h PG levels and hippocampal atrophy. First, it is reported that elevated 2-h PG values are considered a good marker for oxidative stress arising from postprandial hyperglycemia (17) and correlate with insulin resistance (18). Hyperglycemia increases oxidative stress and produces advanced glycation end products, resulting in an accumulation of amyloid β-protein and neurodegeneration in the brain (2,19). In addition, in subjects with insulin resistance or hyperinsulinemia, abnormally elevated insulin levels in the brain are suggested to stimulate amyloid β-protein secretion and inhibit the extracellular degradation of amyloid

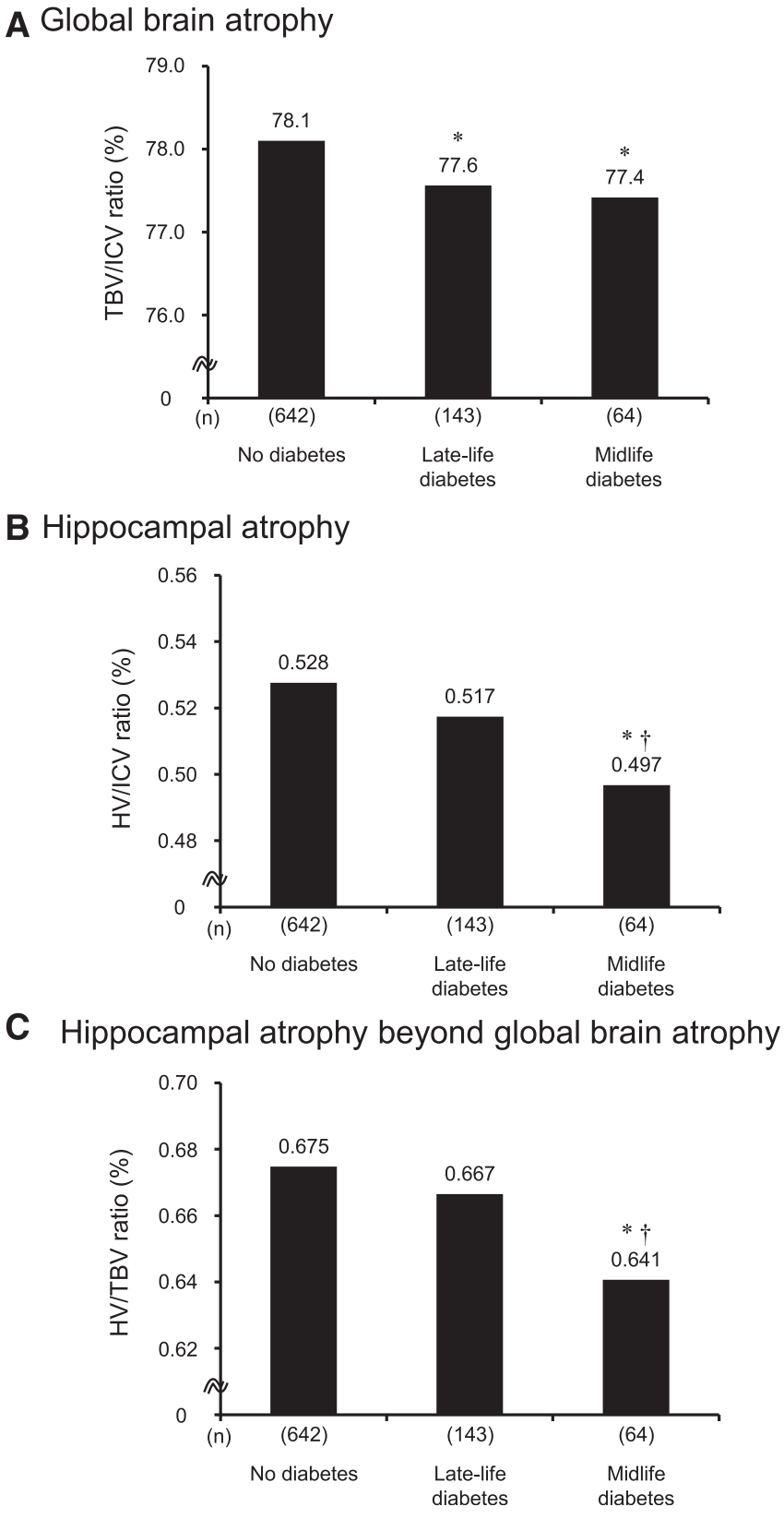

Figure 2—Multivariable-adjusted TBV-to-ICV (*A*), HV-to-ICV (*B*), and HV-to-TBV (*C*) ratios by the time of diabetes diagnosis. Values were adjusted for age, sex, education status, hypertension, total cholesterol, BMI, smoking habit, alcohol intake, regular exercise, and cerebrovascular lesions on MRI. *$P < 0.05$ vs. no diabetes group, †$P < 0.05$ vs. late-life diabetes group.

β-protein by competition for insulin-degrading enzyme (2). Since insulin receptors are selectively distributed in the hippocampus and cerebral cortex (20), insulin resistance and hyperinsulinemia may particularly contribute to atrophy in these areas. Some observational studies reported that insulin resistance was associated with brain and hippocampal atrophy (21,22), which supports this hypothesis.

These hypotheses are also supported by our previous reports from the cohort and clinicopathological studies that demonstrated that elevated 2-h PG levels were significantly associated with increased risks of development of Alzheimer disease (8) and the formation of neuritic plaques (9). For the other potential mechanisms, diabetes may cause brain atrophy as a result of microvascular ischemic disease (2) or elevated cortisol levels by the impaired feedback mechanism in the hypothalamic-pituitary-adrenal axis (23). Since it is reported that the hippocampus is more vulnerable to hypoglycemia, hypoxia (24,25), and elevated cortisol levels (23) than other brain regions, atrophy may occur more predominantly in the hippocampus compared with other brain regions.

In the current study, longer duration of diabetes and younger onset of diabetes were significantly associated with hippocampal atrophy. The Mayo Clinic Study of Aging (26) also demonstrated that midlife diabetes—but not late-life diabetes—was associated with hippocampal atrophy. Thus, hippocampal atrophy is likely to occur as a result of a long exposure to glucose toxicity, abnormal insulin metabolism, microvascular disease, and dysregulation of the hypothalamic-pituitary-adrenal axis in individuals with diabetes.

The strengths of the current study included its population-based design, the large sample size with volumetric MRI, the accurate determination of diabetes and glucose tolerance status, and the detailed evaluation of confounding factors. Nevertheless, several limitations should be noted. First, since the current study was a cross-sectional design, it is difficult to infer a causal association between diabetes and brain atrophy. However, we contend that diabetes causes hippocampal atrophy because midlife diabetes diagnosed at least 24 years

earlier and a long duration of diabetes were linked with the extent of the hippocampal atrophy. Second, the diagnosis of diabetes and glucose tolerance status was based on a single measurement of glucose levels or a single 75g-OGTT in each health examination (in 1988 and in 2012). This limitation might have led to a misclassification of diabetes diagnosis and glucose tolerance status and might have weakened the association found in the current study, biasing the results toward the null hypothesis. Thus, the true association may be stronger than that observed in the present analysis. Third, 75g-OGTT data were missing for 324 subjects (mainly elderly subjects aged ≥80 years). However, the sensitivity analysis after exclusion of those without available 75g-OGTT data did not change the study conclusions substantially (data not shown).

In conclusion, our data suggest that a longer duration of diabetes and a midlife onset of diabetes are significant risk factors for hippocampal atrophy, a main morphological feature of Alzheimer disease. In addition, the significant association between elevated 2-h PG levels (a marker of postprandial hyperglycemia) and hippocampal atrophy suggests that the careful control of postprandial plasma glucose levels is important to prevent hippocampal atrophy and the subsequent development of dementia in individuals with diabetes. Further prospective cohort studies and experimental studies are needed to clarify the association between hyperglycemia and hippocampal atrophy.

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