Progression of Cerebral Atrophy and White Matter Hyperintensities in Patients With Type 2 Diabetes

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OBJECTIVE — Type 2 diabetes is associated with a moderate degree of cerebral atrophy and a higher white matter hyperintensity (WMH) volume. How these brain-imaging abnormalities evolve over time is unknown. The present study aims to quantify cerebral atrophy and WMH progression over 4 years in type 2 diabetes.

RESEARCH DESIGN AND METHODS — A total of 55 patients with type 2 diabetes and 28 age-, sex-, and IQ-matched control participants had two 1.5T magnetic resonance imaging scans with a 4-year interval. Volumetric measurements of total brain, peripheral cerebrospinal fluid (CSF), lateral ventricles, and WMH were performed with k-nearest neighbor–based probabilistic segmentation. All volumes were expressed as percentage of intracranial volume. Linear regression analyses, adjusted for age and sex, were performed to compare brain volumes between the groups and to identify determinants of volumetric change within the type 2 diabetic group.

RESULTS — At baseline, patients with type 2 diabetes had a significantly smaller total brain volume and larger peripheral CSF volume than control participants. In both groups, all volumes showed a significant change over time. Patients with type 2 diabetes had a greater increase in lateral ventricular volume than control participants (mean adjusted between-group difference in change over time [95% CI]: 0.11% in 4 years [0.00 to 0.22], $P = 0.047$).

CONCLUSIONS — The greater increase in lateral ventricular volume over time in patients with type 2 diabetes compared with control participants shows that type 2 diabetes is associated with a slow increase of cerebral atrophy over the course of years.

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N umerous studies have shown an association between type 2 diabetes and mild to moderate cognitive impairment and an increased risk of dementia (1,2). However, the underlying mechanisms are still unclear. Structural correlates of diabetes-related cognitive impairment can be assessed with brain magnetic resonance imaging (MRI) (3). Cross-sectional studies using either visual rating scales or automated volumetric techniques on magnetic resonance images showed that type 2 diabetes is associated with a moderate degree of cerebral atrophy (rev. in 4). The association of type 2 diabetes and white matter hyperintensities (WMH) is less robust, since some studies found an association to more extensive WMH (5), whereas other studies did not (6). The progression of cerebral atrophy and WMH volume over time in patients with type 2 diabetes is still un-

clear. Consequently, risk factors related to progression of brain abnormalities in type 2 diabetes are largely unknown.

The present study aimed to quantitatively determine the effect of type 2 diabetes on cerebral atrophy and WMH progression over 4 years. Within the group with type 2 diabetes, the relationship between changes in brain volumes and metabolic and vascular risk factors was also assessed.

RESEARCH DESIGN AND
METHODS — At baseline (2002–2004) 122 participants with type 2 diabetes and 56 age-, sex-, and IQ-matched control participants were included; all were between 56 and 80 years of age (7,8). Patients with type 2 diabetes were recruited through their general practitioners. Control participants were recruited among the spouses and acquaintances of the patients. All participants were functionally independent and Dutch speaking. Patients had to have a diabetes duration of at least 1 year. Exclusion criteria were a psychiatric or neurological disorder (unrelated to diabetes) that could influence cognitive functioning, a history of alcohol or substance abuse, or a history of dementia. Control participants with a fasting glucose ≥7.0 were also excluded.

All participants were invited for follow-up 4 years later (2006–2008). Baseline scans that could be used for volumetric analyses were available in 110 participants with type 2 diabetes and in 50 control participants. Of these 160 participants, 6 had died, 4 could not be contacted, 2 were excluded based on the exclusion criteria (1 control participant had a fasting glucose ≥7.0 and 1 patient had severe comorbid disease), and 63 were not able or willing to participate in the follow-up. Reasons for not participating were lack of interest ($n = 26$); comorbidity ($n = 20$; three reported dementia: two patients and one control participant); unwillingness or new contraindications to undergo MRI, such as a pacemaker ($n = 9$); or other reasons ($n = 8$). Two participants were excluded based on artifacts in the scans, which made reliable

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volumetric measurements impossible. This left a total of 83 participants (55 patients and 28 control participants, mean follow-up time: 4.1 ± 0.4 years) for inclusion in the present study.

Age and sex distribution and estimated IQ at baseline were not significantly different between participants included ($n = 83$) and not included ($n = 77$) in this follow-up MRI study. Importantly, baseline brain volumes (7) were also not significantly different between participants and nonparticipants. The study was approved by the medical ethics committee of the University Medical Center Utrecht, and all participants signed an informed consent form.

Medical history and physical examination

At baseline and follow-up, the same standardized interview was used to question participants about level of education (seven categories), medication use, hypercholesterolemia, smoking, history of a macrovascular event (myocardial infarction or stroke requiring hospitalization or surgical or endovascular treatment of atherosclerotic arterial disease), and diabetes duration. At baseline and follow-up, weight and height were measured and blood samples were taken to determine A1C, fasting glucose, and cholesterol levels. At baseline, blood pressure was measured automatically at home on 10 different time points during the day. At follow-up, blood pressure was measured in a seated position at three time points during the half-day visit. Mean arterial pressures were calculated from these measurements. Hypertension was defined as a systolic blood pressure >160 mmHg or diastolic blood pressure >95 mmHg or self-reported use of blood pressure–lowering drugs prescribed primarily for hypertension. Hypercholesterolemia was defined as a fasting cholesterol >6.2 mmol/l or self-reported use of lipid-lowering drugs. BMI was calculated as weight (in kilograms) divided by the square of height (in meters). All participants had a neurological examination at baseline and follow-up; none of the participants had focal abnormalities suggestive of central lesions, such as infarcts.

IQ was estimated with the Dutch version of the National Adult Reading Test, which is generally accepted to reflect the premorbid level of intellectual functioning (8,9). To control for selective loss to follow-up, the cognitive status of participants (a week after participation in the follow-up examination) and nonparticipants was assessed with the modified Dutch version of the Telephone Interview for Cognitive Status (TICS-m), a screening instrument designed to identify people with dementia (10,11). A cutoff score of 28 is indicative of cognitive impairment (12).

MRI scanning protocol

MRI scans were acquired at baseline and follow-up on a 1.5T Philips magnetic resonance system using a standardized protocol (38 contiguous slices, voxelsize: $0.9 \times 0.9 \times 4.0$ mm) and consisted of an axial T1 (repetition time in ms [TR]: 234, echo time in ms [TE]: 2), T2 (TR: 2,200, TE: 100), proton density (PD) (TR: 2,200, TE: 11), inversion recovery (IR) (TR: 2,919, TE: 22, inversion time in ms [TI]: 410), and fluid-attenuated inversion recovery (FLAIR) (TR: 6,000, TE: 100, TI: 2,000).

Image processing

On both time points, all images (T1, T2, PD, and IR) of each participant were rigidly registered to the FLAIR image by using Elastix (13). Scan inhomogeneities were corrected by a shading correction algorithm (14).

To exclude all nonbrain and non–cerebrospinal fluid (CSF) tissue, a brain mask was created for every participant using all baseline images in a k-means–clustering algorithm with eight clusters (7). The clusters that contained brain and CSF were combined, and additional nonbrain and non-CSF structures in the formed mask were automatically excluded and holes were filled by using a standardized protocol of morphological operators. A 3-voxel dilation of the mask was performed to include all CSF, and the result was manually adjusted to only contain tissue above the foramen magnum.

To construct a follow-up mask with the same brain coverage, the baseline FLAIR was rigidly registered to the follow-up FLAIR of the same participant, and the resulting transform parameters were used to transform the baseline brain mask (13). A standardized combination of morphological operators was applied to fill holes and smooth the follow-up mask. The uncorrected FLAIR images were multiplied voxelwise by the binary brain mask, followed by a shading correction to provide better correction (14).

For the volume measurements on one time point, the brain mask, FLAIR, and IR were used. Volumes were measured by k-nearest neighbor–based probabilistic segmentation, an automatic and validated approach to brain segmentation (15). This method is based on manually classified training data, which consists of FLAIR and IR images of 10 matched subjects with a different extent of cerebral atrophy and WMH made by an identical scanning protocol to the images in this study. Gray and white matter, peripheral CSF (CSF without lateral ventricles), lateral ventricular, and WMH volume were automatically classified.

The results of the probabilistic classification of all tissues were visually checked for all participants, and incorrectly classified images were excluded. In two participants, a small meningioma was found, which was manually excluded. To reduce the effects of noise, the WMH classification was thresholded on a 0.5 probability, after which isolated classified voxels were automatically excluded. The automated segmentation tends to classify the gliotic core around infarcts as WMH. Because this confounds the measurement of WMH volume, infarcts were manually segmented from the WMH volume and added to the total brain volume. The total volume of the individual tissues was calculated by multiplying the probabilities by the voxel volume. To correct for between-subject differences in intracranial volume (volume of all classified tissues combined), all baseline and follow-up volumes were expressed as a percentage of intracranial volume. Total brain volume (gray and white matter + WMH + infarcts) was calculated on both time points. The total brain, peripheral CSF, lateral ventricular, and WMH volume were analyzed.

Statistical analysis

Participant characteristics were compared between the type 2 diabetic group and the control group using independent-samples t tests. TICS-m scores were compared between participants and nonparticipants at the follow-up examination by an independent-samples t test and differences in loss to follow-up between groups were assessed by Pearson χ^2 tests. Within-group changes in brain volumes over time were assessed by using paired t tests. Because of nonnormal distribution (Kolmogorov-Smirnov, $P < 0.05$), progression of WMH volume was analyzed by a Wilcoxon signed-rank test. Linear regression analyses adjusted for age and sex were performed to assess the relationship between baseline brain volumes and

Table 1—*Baseline participant characteristics*

	Control participants	Patients with type 2 diabetes	P values
Demographics			
Men/women	12/16	26/29	0.71
Age (years)	64.2 ± 4.3	65.9 ± 5.4	0.16
Level of education*	4.5 ± 1.3	4.2 ± 1.5	0.47
Estimated IQ	98 ± 15	97 ± 14	0.66
Time to follow-up (years)	4.1 ± 0.4	4.1 ± 0.4	0.58
Risk factors for heart and vessel disease			
Mean arterial pressure (mmHg)	107 ± 13	113 ± 14	0.07
Use of antihypertensive drugs (%)	29	66	0.001
Hypercholesterolemia (%)†	46	60	0.25
Smoking ever (%)	50	67	0.13
BMI (kg/m²)	27	28	0.20
Any macrovascular event (%)‡	7	31	0.004
Brain infarcts on MRI (%)	21	25	0.69
Diabetes-related factors			
Diabetes duration (years)	—	9.5 ± 6.6	—
A1C level (%)	5.5 ± 0.3	7.0 ± 1.1	<0.001
Fasting glucose (mmol/l)	5.6 ± 0.6	8.8 ± 2.8	<0.001
Use of insulin (%)	—	31	—

Data are means ± SD or percentages of total group. *Seven categories. †Defined as a fasting cholesterol >6.2 mmol/l or self-reported use of lipid-lowering drugs. ‡Defined as a myocardial infarction or stroke requiring hospitalization or surgical or endovascular treatment of atherosclerotic arterial disease.

group and the relationship between volume change over time and group. Baseline WMH volume was multiplied by 100 and naturally log transformed because of nonnormal distribution. Additionally, separate analyses were done for men and women, because differences in cerebral tissue volumes were found at the baseline examination (7).

To identify possible determinants of baseline brain volume and volume change over time, linear regression analyses adjusted for age and sex were performed within the type 2 diabetic group.

Determinants that were considered included diabetes duration, A1C levels, mean arterial pressure, hypertension, total cholesterol levels, hypercholesterolemia, BMI, and history of a macrovascular event.

RESULTS— Table 1 shows the baseline characteristics of the patients with type 2 diabetes and the control participants. The groups are similar with regard to age, sex distribution, and estimated IQ ($P > 0.05$). As expected, the groups differed on vascular risk factors and glyce-

mic control. At follow-up, nine patients and three control participants had new brain infarcts. Levels of risk factors remained unchanged over time.

A TICS-m was obtained from 51 (76% with diabetes) of 67 nonparticipants at follow-up who were still alive and could be contacted and from 79 (66% with diabetes) of 83 participants. The TICS-m score was similar and normally distributed for participants and nonparticipants (participants mean 36.9 ± 4.4, nonparticipants 35.1 ± 6.0, $P > 0.05$). Among all nonparticipants, three patients with type 2 diabetes (3% of baseline sample) and two control participants (4% of baseline) had marked cognitive impairment based on caregiver-reported dementia or a TICS-m score <28 [χ^2 (1) = 0.34, $P = 0.56$] (10). Table 2 shows baseline volumes and differences between baseline and follow-up volumes. In both groups, total brain volume decreased over time and peripheral CSF, lateral ventricular, and WMH volume increased over time (all $P \leq 0.001$ in both groups).

At baseline, patients with type 2 diabetes had a significantly smaller total brain volume (adjusted difference between type 2 diabetes and control group [95% CI] −1.36% [−2.31 to −0.40], $P = 0.006$) and larger peripheral CSF volume (0.98% [0.07 to 1.90], $P = 0.036$). The lateral ventricular volume showed a greater increase over time in patients with type 2 diabetes than in control participants (adjusted difference in change over time between type 2 diabetes and control group [95% CI] 0.11% in 4 years [0.00 to 0.22], $P = 0.047$). Relative to the baseline ventricular volume, this reflects a 3.6% larger increase in the diabetic than in the

Table 2—*Mean volumes and changes in volumes over time in patients with type 2 diabetes and control participants*

	Total brain	Peripheral CSF	Lateral ventricles	WMH*
Control participants				
Volume at baseline (%)	79.9 ± 2.0	18.1 ± 1.6	2.01 ± 1.18	0.28 ± 0.42
Change over time (%)	−1.21 ± 0.66†	0.96 ± 0.62†	0.23 ± 0.21†	0.12 ± 0.28‡
Patients with type 2 diabetes				
Volume at baseline (%)	78.1 ± 2.6	19.4 ± 2.4	2.49 ± 1.05	0.39 ± 0.78
Change over time (%)	−1.46 ± 0.71†	1.10 ± 0.64†	0.36 ± 0.25†	0.14 ± 0.18†
Differences between patients and control participants				
Difference in baseline volume	−1.36 (−2.31 to −0.40)‡	0.98 (0.07 to 1.90)§	0.37 (−0.12 to 0.87)	0.35 (−0.13 to 0.83)
Difference in change over time	−0.18 (−0.49 to 0.13)	0.09 (−0.20 to 0.38)	0.11 (0.00 to 0.22)§	0.02 (−0.09 to 0.12)

Data are unadjusted mean relative brain volumes ± SD and changes in brain volume over time ± SD (mean difference between relative baseline and relative follow-up volume) or adjusted (age and sex) between-group differences (regression B coefficients (95% CI)) in relative baseline volumes and relative change in brain volumes over time. *For the differences in WMH volume between patients and control participants, baseline WMH volumes were multiplied by 100 and naturally log transformed. †$P < 0.001$; ‡$P < 0.01$; within-group change, paired t test or Wilcoxon signed-rank test. ‡$P < 0.01$; §$P < 0.05$; between-group differences, linear regression analyses.

Table 3—Relationship between baseline determinants and baseline volumes and volume change over time in patients with type 2 diabetes

	Total brain	Peripheral CSF	Lateral ventricles	WMH*
Baseline				
Age (per 5 years)	−1.00 (−1.59 to −0.41)†	0.93 (0.38 to 1.48)†	0.07 (−0.20 to 0.35)	0.17 (−0.08 to 0.43)
Male sex	−1.16 (−2.43 to 0.10)	1.01 (−0.17 to 2.19)	0.16 (−0.42 to 0.74)	−0.23 (−0.77 to 0.32)
Diabetes duration (per 5 years)	0.03 (−0.49 to 0.55)	0.03 (−0.46 to 0.52)	−0.06 (−0.30 to 0.18)	−0.16 (−0.37 to 0.06)
A1C level (%)	0.00 (−0.58 to 0.57)	−0.05 (−0.58 to 0.49)	0.05 (−0.22 to 0.31)	−0.02 (−0.26 to 0.23)
Mean arterial pressure (per 10 mmHg)	0.02 (−0.45 to 0.48)	−0.01 (−0.45 to 0.42)	−0.01 (−0.22 to 0.21)	0.11 (−0.09 to 0.31)
Hypertension‡	−0.49 (−1.89 to 0.92)	0.28 (−1.04 to 1.60)	0.20 (−0.45 to 0.85)	−0.22 (−0.82 to 0.39)
Total cholesterol (mmol/l)	−0.28 (−1.00 to 0.44)	0.06 (−0.62 to 0.73)	0.23 (−0.10 to 0.55)	0.00 (−0.31 to 0.31)
Hypercholesterolemia§	0.22 (−1.20 to 1.64)	0.08 (−1.25 to 1.42)	−0.31 (−0.96 to 0.34)	−0.04 (−0.65 to 0.57)
BMI (kg/m^2)	−0.05 (−0.21 to 0.12)	0.10 (−0.05 to 0.25)	−0.05 (−0.13 to 0.02)	−0.03 (−0.10 to 0.04)
Macrovascular event‖	−1.11 (−2.49 to 0.26)	0.86 (−0.44 to 2.16)	0.24 (−0.41 to 0.88)	−0.15 (−0.75 to 0.46)
Longitudinal change over 4 years				
Age (per 5 years)	−0.25 (−0.42 to −0.08)†	0.21 (0.05 to 0.36)¶	0.04 (−0.02 to 0.10)	0.01 (−0.03 to 0.06)
Male sex	−0.06 (−0.42 to 0.31)	0.12 (−0.21 to 0.45)	−0.06 (−0.20 to 0.07)	−0.06 (−0.16 to 0.04)
Diabetes duration (per 5 years)	0.07 (−0.08 to 0.22)	−0.05 (−0.19 to 0.08)	−0.01 (−0.07 to 0.04)	−0.01 (−0.05 to 0.03)
A1C level (%)	0.02 (−0.15 to 0.18)	−0.05 (−0.20 to 0.10)	0.03 (−0.03 to 0.10)	0.03 (−0.01 to 0.08)
Mean arterial pressure (per 10 mmHg)	−0.08 (−0.21 to 0.06)	0.06 (−0.06 to 0.18)	0.02 (−0.04 to 0.07)	−0.01 (−0.04 to 0.03)
Hypertension‡	−0.43 (−0.81 to −0.04)¶	0.49 (0.15 to 0.83)†	−0.06 (−0.22 to 0.09)	−0.06 (−0.17 to 0.05)
Total cholesterol (mmol/l)	−0.04 (−0.25 to 0.16)	−0.01 (−0.20 to 0.18)	0.05 (−0.03 to 0.13)	0.00 (−0.06 to 0.06)
Hypercholesterolemia§	0.01 (−0.40 to 0.42)	0.03 (−0.35 to 0.40)	−0.03 (−0.19 to 0.12)	−0.02 (−0.13 to 0.09)
BMI (kg/m^2)	−0.01 (−0.06 to 0.04)	0.02 (−0.02 to 0.06)	−0.01 (−0.03 to 0.01)	0.00 (−0.02 to 0.01)
Macrovascular event‖	−0.12 (−0.52 to 0.29)	0.12 (−0.25 to 0.49)	0.00 (−0.15 to 0.15)	0.04 (−0.07 to 0.15)

Data are regression B coefficients (95% CI) for each determinant, adjusted for age and sex. Baseline volumes and change in volumes over time are described separately. Relative total brain volume decreases and relative peripheral CSF, lateral ventricular, and WMH volume increases over time. Therefore, negative B values in change over time reflect a greater decrease in relative total brain volume, whereas in the other volumes positive B values reflect a greater increase of these volumes. *Relative baseline WMH volumes were multiplied by 100 and naturally log transformed. †$P < 0.01$. ‡Defined as a systolic blood pressure >160 mmHg or diastolic blood pressure >95 mmHg or self-reported use of blood pressure–lowering drugs prescribed primarily for hypertension. §Defined as a fasting cholesterol >6.2 mmol/l or self-reported use of lipid-lowering drugs. ‖Defined as a myocardial infarction or stroke requiring hospitalization or surgical or endovascular treatment of atherosclerotic arterial disease. ¶$P < 0.05$.

control group (relative increase in ventricular volume: patients: 15.2 ± 12.9%, control participants: 11.6 ± 7.8%). Total brain, peripheral CSF, and WMH volume showed no significant between-group differences in change over time ($P > 0.05$). At follow-up, 14 control participants had impaired fasting glucose levels (5.6–6.9 mmol/l). Brain volumes at baseline and changes in volume over time in this group were similar to the other control participants. Moreover, if these 14 individuals were removed from the comparison between the diabetic and control group, the results remained essentially the same.

In separate analyses for individuals below and above the age of 65 years, the differences between the diabetic and control group remained largely identical (data not shown). In separate analyses for men and women, female patients with type 2 diabetes compared with female control participants had a smaller baseline total brain volume (−2.07% [−3.36 to −0.78], $P = 0.002$), a larger baseline peripheral CSF (1.28% [0.09 to 2.47],

$P = 0.036$) and lateral ventricular (0.78% [0.25 to 1.32], $P = 0.005$) volume, and a greater increase in lateral ventricular volume over time (0.21% in 4 years [0.04 to 0.37], $P = 0.016$). Although the directions of these effects were similar in male participants, no significant baseline or longitudinal between-group differences were found for male participants ($P > 0.05$).

In Table 3, the secondary analyses on metabolic and vascular risk factors within the type 2 diabetic group are shown adjusted for age and sex. Increasing age was associated with a smaller total brain volume (volume difference per 5-year increase of age [95% CI] −1.00% [−1.59 to −0.41], $P = 0.001$) and a larger peripheral CSF volume (0.93% [0.38 to 1.48], $P = 0.001$). Increasing age was also associated with a greater decrease in total brain volume over time (difference in change over time per 5-year increase of age −0.06% per year [−0.10 to −0.02], $P = 0.005$) and a greater increase in peripheral CSF volume (0.05% per year

[0.01 to 0.09], $P = 0.010$). The presence of hypertension at baseline was not associated with baseline brain volumes, but hypertension was associated with a greater decrease in total brain volume over time (difference in change over time between patients with hypertension versus no hypertension −0.10% per year [−0.20 to −0.01], $P = 0.033$) and a greater increase in peripheral CSF volume (0.12% per year [0.04 to 0.20], $P = 0.006$). No significant associations between baseline brain volumes or brain volume change and sex, diabetes duration, A1C level, mean arterial pressure, total cholesterol levels, hypercholesterolemia, BMI, and history of a macrovascular event were found ($P > 0.05$).

CONCLUSIONS — At baseline patients with type 2 diabetes had more cerebral atrophy than control participants. Both the control and the type 2 diabetic group showed a significant progression of cerebral atrophy and WMH volume over 4 years. Patients with type 2 diabetes had

a greater increase in lateral ventricular volume than control participants. In explorative analyses on risk factors within the type 2 diabetic group, increasing age was associated with more cerebral atrophy and increasing age and the presence of hypertension at baseline were associated with greater progression of cerebral atrophy.

The baseline findings of our study are in line with previous cross-sectional studies, which consistently report an association between type 2 diabetes and modest cerebral atrophy (rev. in 3). To the best of our knowledge, no longitudinal studies that specifically addressed progression of cerebral atrophy over time in type 2 diabetes have been published. However, in a longitudinal study on cardiovascular risk factors and dementia in the elderly, diabetes was found to be associated with a greater increase in lateral ventricular volume (16). Moreover, some cross-sectional studies observed an association between diabetes duration and severity of cerebral atrophy (6,17) but not invariably (7). In combination with the results of these previous studies, our results suggest that cerebral atrophy in patients with type 2 diabetes progresses only slowly relative to control participants over the course of years. Hence, the average rate of decline in patients with type 2 diabetes stayed within the range of normal ageing and does not approach the accelerated loss that is observed in disease states such as Alzheimer's disease (18). It is important to note that in our study population, cognitive decline was also not accelerated in the type 2 diabetic group relative to control participants (10).

Cross-sectional studies on the association between type 2 diabetes and WMH, as assessed with visual rating scales, showed inconsistent results (rev. in 4). However, when detailed rating scales were used, a modest association with deep WMH was observed (5,8). Recent longitudinal studies (19,20) on the association between WMH progression and vascular risk factors in the elderly reported an association between diabetes and an increased WMH progression rate. We found no significant association between type 2 diabetes and WMH volume for cross-sectional as well as longitudinal measurements in the present study, whereas we did observe an association in our baseline cohort (7). This discrepancy can be explained by the relatively large interindividual variability in WMH volume, the small difference in WMH volume between groups combined with the relatively limited sample size of the present study. Volumetric methods that can also make a distinction in periventricular and deep WMH and a larger sample size are needed to look at this association in more detail.

The sex-related differences in baseline brain volumes between groups observed in our study were comparable to the differences found in our baseline study in which between-group brain volume differences were also only significant for female participants (7). Previous studies on cognitive functioning or dementia in patients with diabetes did not observe sex-specific increases in the rate of cognitive decrements (2). However, it must be noted that the effect of sex on brain volume change and cognition in diabetes has not yet been analyzed systematically, and this is a topic that will need to be addressed in further studies.

Relatively few studies have specifically examined metabolic and vascular determinants of brain-imaging abnormalities in patients with type 2 diabetes. Cross-sectional studies (7,17,21,22) report hypertension, diabetes duration, and history of macrovascular events as determinants of cerebral atrophy and diabetes duration as a determinant of WMH volume. In the present study, hypertension was a determinant of cerebral atrophy progression. Cross-sectional studies in community-dwelling elderly subjects showed A1C level as a determinant of WMH volume and A1C and BMI as determinants of cerebral atrophy (23,24). Furthermore, in longitudinal population-based studies, not specifically in individuals with diabetes, a history of stroke was found as a determinant of WMH progression, and A1C levels, and BMI and severe WMH were found as determinants of cerebral atrophy progression (19,24). Studies on cognitive dysfunction in type 2 diabetes have identified both vascular factors and elevated A1C as possible determinants (8,25), but results are not always consistent across studies. Importantly, no causality can be inferred from such associations. Although experimental studies identify several possible mechanisms that may contribute to cerebral damage in type 2 diabetes, including glucose toxicity, vascular disturbances, and abnormal insulin signaling in the brain, it is yet unclear which of these factors are the main causal factors of cerebral damage in humans (2).

The strength of the present study is the prospective design in combination with precise automatic brain volume measurements and detailed assessment of metabolic and vascular determinants in patients and control participants. The observed changes in brain volumes over time are well outside the error of measurement of our method. Limitations include the loss to follow-up, which can lead to possible selection bias. Nevertheless, compared with the participants at follow-up, nonparticipants were similar in age, sex distribution, estimated IQ, and baseline brain volumes. The results of the TICS-m also show no selection bias due to drop out of participants with severely impaired cognitive functioning. However, the relatively healthy patient population and the risk factor profile of the control participants could have underestimated the effects of type 2 diabetes. Finally, the analyses of the determinants were affected by the modest sample size and difficulties inherent to the assessment of these determinants. Diabetes duration, for example, cannot be firmly established because diabetes develops insidiously and tends to be undiagnosed during the first years after onset. In addition, the actual levels of risk factors such as A1C and blood pressure, change over time and under the influence of treatment.

In conclusion, the greater increase in lateral ventricular volume over time in patients with type 2 diabetes as compared with control participants shows that type 2 diabetes is associated with a slow increase of cerebral atrophy over the course of years.

APPENDIX — The Utrecht Diabetic Encephalopathy Study Group consists of (in alphabetical order): A. Algra, E.v.d.B., G.J.B., A.M.A. Brands, M.A. Breedijk, J.d.B., J. van Gijn, W.H. Gispen, J. van der Grond, E.H.F. de Haan, A.C. van Huffelen, C.J., L.J.K., R.P.C. Kessels, W.P.M., S.M. Manschot, J.P.W. Pluim, Y.D.R., G.E.H.M. Rutten, A.M.T., H.W. de Valk, M.A.V.

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