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Diabetes mellitus and progression of vascular brain lesions and brain atrophy in patients with symptomatic atherosclerotic disease. The SMART-MR study

Minke Kooistra [a,d], Mirjam I. Geerlings [a,*], Willem P.T.M. Mali [b], Koen L. Vincken [c], Yolanda van der Graaf [a], Geert Jan Biessels [d], on behalf of the SMART-MR Study Group [1]

[a] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands
[b] Department of Radiology, University Medical Center Utrecht, The Netherlands
[c] Image Sciences Institute, University Medical Center Utrecht, The Netherlands
[d] Department of Neurology, Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, The Netherlands

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ABSTRACT

Aim: Diabetes mellitus (DM) is associated with brain atrophy and vascular brain lesions. Cardiovascular disease is a key determinant in this association. We assessed whether DM increased the rate of progression of brain atrophy, vascular brain lesions, and cognitive decline in patients with symptomatic atherosclerotic disease.

Methods: In 663 patients (58 ± 10 years) from the SMART-MR study (n = 89 with DM), 1.5 T MRI and neuropsychological examination were performed at baseline and after 3.9 ± 0.4 years follow-up.

Results: Repeated measures ANCOVA (adjusted for age, sex, and vascular risk factors) showed that patients with DM had smaller total brain volume (mean differences as percentage of intracranial volume (ICV) [95% CI]: −1.36% [−1.81; −0.91]), smaller gray matter volume (−1.23% [−1.85; −0.61]), larger ventricular volume (0.32% [0.14; 0.49]), and larger white matter lesion volume (0.31% [0.09; 0.53]) than patients without DM. Patients with DM had accelerated increase in ventricular volume over time compared with patients without DM (mean differences ventricular volume as percentage of ICV: 0.32% [0.25; 0.39] vs. 0.17% [0.15; 0.19]; p-interaction DM × time < 0.01). Poisson regression showed that patients with DM had an increased risk for incident brain infarcts (relative risk [95% CI]: 1.62 [1.04; 2.53]). Patients with and without DM had similar performance on cognition.

Conclusions: DM on top of existing symptomatic atherosclerotic disease is associated with increased brain atrophy and vascular brain lesion load that proceed at a slightly higher rate than in patients without DM.

1. Introduction

Type 2 diabetes mellitus (DM2) is associated with an increased risk of dementia [1,2]. Moreover, several cross-sectional studies have indicated that non-demented patients with DM2 have worse cognitive performance compared to controls [3,4]. However, it is less clear at which rate cognition declines in non-demented patients with DM2 [5]. Some longitudinal studies have found a decline in cognitive performance that clearly exceeded the rate of normal aging [6–8], but this could not be confirmed by others [9,10].

The cognitive impairments of patients with DM2 are related to changes in brain structures, as can be seen on magnetic resonance imaging (MRI). Patients with DM2 have more vascular brain lesions, like white matter lesions (WMLs) or infarcts, and more cortical and subcortical atrophy than patients without DM2 [3,11,12]. Recently, these MRI abnormalities have also been assessed longitudinally. In a prospective study where patients with DM2 were compared with controls, an accelerated progression of subcortical atrophy, reflected by an increase in ventricular volume, was found in patients with DM2 [13]. Other studies have also found accelerated progression of total brain atrophy in patients with DM when compared with controls [14,15].

Vascular risk factors and vascular disease are important determinants for brain atrophy and vascular brain lesions [16,17]. In patients with DM2, symptomatic atherosclerotic disease was associated with brain MRI abnormalities [18]. Moreover, even among patients with symptomatic atherosclerotic disease, presence of DM was associated with relatively more brain atrophy and more vascular brain lesions in a previous cross-sectional study from our group [19]. However, the association between DM, vascular disease, and progression of brain MRI changes over time has not yet been studied in detail. In the current

* Corresponding author at: Julius Center for Health Sciences and Primary Care, UMC Utrecht, Stratenum 6.131, PO BOX 85500, 3508 GA Utrecht, The Netherlands. Tel.: +31 88 755 9394; fax: +31 88 755 5480.
E-mail address: m.geerlings@umcutrecht.nl (M.I. Geerlings).
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study we investigated whether the presence of DM increases the rate of progression of brain MRI abnormalities and decline in cognition in a population of patients with symptomatic atherosclerotic disease.

2. Methods

2.1. SMART-MR study

Data were used from the Second Manifestations of ARTerial disease—Magnetic Resonance (SMART-MR) study, a prospective cohort study aimed to investigate brain changes on MRI in independently living patients with symptomatic atherosclerotic disease [16,20]. Between May 2001 and December 2005, all patients newly referred to the University Medical Center Utrecht with manifest coronary artery disease, cerebrovascular disease, peripheral arterial disease or an abdominal aortic aneurysm, and without MR contraindications were invited to participate. During a one-day visit, an MRI of the brain was performed, in addition to a physical examination, ultrasonography of the carotid arteries, and blood and urine sampling. Risk factors, medical history, and functioning were assessed with questionnaires. Neuropsychological assessment was introduced in the SMART-MR study in January 2003 and was performed on the same day as the MRI and other investigations. Between January 2006 and May 2009, all participants still alive were invited for follow-up measurements, including MRI of the brain and neuropsychological assessment. The SMART-MR study was approved by the ethics committee of our institution and written informed consent was obtained from all participants.

2.2. Diabetes mellitus

Diabetes mellitus (DM) at baseline was defined as a known history of DM, self-reported or registered glucose-lowering therapy, or glucose $\geq$11.1 mmol/L. Patients not meeting these criteria, but with a fasting plasma glucose level $\geq$7.0 mmol/L at baseline, were considered to have DM at baseline if they received treatment with glucose-lowering agents within 1 year after baseline [21].

2.3. MRI protocol

MRI investigations were performed on a 1.5 Tesla whole-body system (Gyroscan ACS-NT, Philips Medical Systems, Best, The Netherlands). The protocol consisted of transversal T1-weighted gradient-echo (repetition time (TR)/echo time (TE): 235/2 ms), transversal T2-weighted turbo spin-echo (TR/TE: 2200/11 ms and 2200/100 ms; turbo factor 12), fluid-attenuated inversion recovery (FLAIR) (TR/TE/inversion time (TI): 6000/100/2000 ms), and transversal inversion recovery (IR) (TR/TE/TI: 2900/22/410 ms) sequences (field of view 230 × 230 mm; matrix size, 180 × 256; slice thickness, 4 mm; no slice gap; 38 slices).

2.4. Brain segmentation

We used the T1-weighted gradient-echo, IR sequence and FLAIR sequence for brain segmentation. The probabilistic segmentation technique has been described elsewhere [22,23]. The segmentation program distinguishes cortical gray matter, white matter, sulcal and ventricular cerebrospinal fluid (CSF), and WMLs. The automatic segmentation was visually checked for presence of infarcts and adapted if necessary to make a distinction between WMLs and infarct volumes. Total brain volume was calculated by summing the volumes of gray and white matter and, if present, the volumes of WMLs and infarcts. All volumes cranial to the foramen magnum were included. As a result, the total brain volume includes the cerebrum, brainstem and cerebellum. Total intracranial volume (ICV) was calculated by summing the total brain volume and the volumes of sulcal and ventricular CSF.

2.5. Brain infarcts and white matter lesions

At baseline and follow-up, infarcts were rated visually by an investigator and neuroradiologist, blinded to clinical characteristics and were re-evaluated in a consensus meeting. Infarcts were defined as focal hyperintensities on T2-weighted images of >3 mm in diameter. These T2 hyperintensities, when located in the white matter, also had to be hypointense on T1-weighted and FLAIR images to distinguish them from WMLs. Patients with an increase in number of infarcts between baseline and follow-up were considered to have incident infarcts. Volumes of WMLs obtained with the segmentation program consisted of periventricular and deep lesions and were summed to obtain the total volume of WMLs. WML volumes were normalized for ICV and natural log transformed.

2.6. Brain volumes

All brain volumes (total brain volume, cortical gray matter volume, ventricular volume) were expressed relative to ICV. Total brain volume was used as an indicator of global brain atrophy, cortical gray matter volume as an indicator of cortical brain atrophy, and ventricular volume as an indicator of subcortical brain atrophy.

2.7. Neuropsychological assessment

At baseline and follow-up, memory and executive functioning were assessed with neuropsychological tests, sensitive to mild impairments as described earlier [24]. Composite z-scores for the domains memory and executive functioning were calculated based on the total study population. The composite score for memory included immediate and delayed recall and the retention score of the 15-word learning test (a modification of the Rey Auditory Verbal Learning test), and the delayed recall of the Rey–Osterrieth Complex Figure test. The composite score for executive function included the Visual Elevator test, the Brixton Spatial Anticipation test and the Verbal Fluency test (letter N for baseline and letter A for follow-up, 1 minute time frame). Composite z-scores were computed by converting raw scores to standardized z-scores and averaging them of all subtests per domain. Before calculating z-scores, the scores of the Visual Elevator test and the Brixton Spatial Anticipation test were multiplied by minus one so that lower scores represented poorer performance. The composite z-scores at follow-up were calculated by using the means and standard deviations of the baseline test scores. Premorbid intellectual functioning was estimated using the Dutch version of the National Adult Reading Test (DART) [25]. Educational level was recorded and divided into eight categories, graded from primary school to academic degree, according to the Dutch educational system.

2.8. Covariates

An overnight fasting venous blood sample was taken to determine lipid levels. Hyperlipidemia (yes/no) was defined as total cholesterol >5.0 mmol/L, low-density lipoprotein cholesterol >3.2 mmol/L, or self-reported use of lipid-lowering drugs. Height and weight were measured without shoes and heavy clothing, and body mass index (BMI) was calculated (kg/m^2). Systolic and diastolic blood pressure (mm Hg) were measured twice in supine position with a sphygmomanometer and averaged. Pack-years of smoking were calculated, and alcohol intake was categorized into never, former and current.

2.9. Study sample

Of the 1309 patients at baseline, 19 had no MRI, 14 had no FLAIR sequence and in 44 patients brain volume data were missing due to motion or artifacts. As a result, baseline MRI data were available in 1232 patients. Of the 1232 patients, 718 patients participated in the

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follow-up examination (n = 16 lost to follow-up, n = 432 refused, n = 66 died). Of these 718 patients, 38 had no MRI, and in 17 patients brain volume data were missing due to motion or artifacts. This resulted in 663 patients (89 patients (13%) with DM) with available MRI data at baseline and follow-up. Since neuropsychological assessment was introduced later in the study, data on neuropsychological testing were available in 473 patients (59 patients (12%) with DM) both at baseline and follow-up.

2.10. Data analysis

Baseline characteristics were calculated for the study sample of 663 patients, and for patients with and without DM. Between group differences in characteristics were analyzed with independent t-tests, Mann–Whitney U test for non-parametric data, and chi-square tests for proportions. Associations between presence of DM and progression of brain abnormalities and changes in cognition over time were analyzed with repeated-measures analyses of covariance (ANCOVA), including the effect of group, time, and the time × group interaction. The effect of group reflects the mean difference between patients with DM and patients without DM; the effect of time reflects the mean change in measures of brain volume (% ICV) or mean change in z-score of cognition for the study sample during follow-up (n = 663 and n = 473 respectively); the time × group interaction reflected the additional change over time attributable to DM status. p-Values <0.05 were considered statistically significant.

For the association between presence of DM and incidence of brain infarcts we used Poisson regression models with log-link function and robust standard errors to estimate relative risks (RR) and accompanying confidence intervals (CI) rather than odds ratio which overestimate the relative risk, particularly for outcomes that are common (>10%) [26,27]. A distinction between lacunar and cortical infarcts was not made, because groups would become too small to gain enough power for the analyses.

All abovementioned models were adjusted for age and sex (model 1; for the association with cognitive decline educational level and DART-score were also included in the model). In model 2 we additionally adjusted for vascular risk factors (systolic and diastolic blood pressure, BMI, hyperlipidemia, smoking and alcohol) and history of cerebrovascular disease. For the association between presence of DM and incidence of brain infarcts we additionally adjusted for presence of brain infarcts at baseline (model 3).

In secondary analyses, we excluded 42 patients who developed DM during the follow-up period from the non-diabetic group and we repeated the analyses.

We used multiple imputation [28] (10 datasets) to address missing values in the study sample, using the statistical program R (AregImpute). Data were analyzed using IBM SPSS Statistics version 20.0 (IBM, New York, NY, USA), by pooling the 10 imputed datasets.

3. Results

Mean [SD] age of the study population was 58 [10] years and the majority was men (81%). Patients with DM were on average older (61 [9] vs. 57 [9]), had a higher BMI (27.8 [3.8] vs. 26.6 [3.4]), systolic blood pressure (143 [17] vs. 140 [20]) and more often a history of cerebrovascular disease or cerebrovascular disease at inclusion (30% vs. 22%) than patients without DM (Table 1). The follow-up assessment took place at 3.9 [0.4] years after baseline in both groups.

3.1. Presence of DM and progression of brain MRI abnormalities

Results of the repeated measures ANCOVA on the association between DM and progression of brain MRI abnormalities are presented in Table 2 and Fig. 1. Brain MRI abnormalities were more pronounced in patients with DM than in patients without DM (Table 2). This was represented by a smaller total brain volume (mean difference in brain volume as percentage of ICV [95% CI] for patients with DM compared with patients without DM: −1.36% [−1.81; −0.91]), a smaller gray matter volume (−1.23% [−1.85; −0.61]), a larger ventricular volume (0.32% [0.14; 0.49]), and a larger WML volume (0.31% [0.09; 0.53]). Furthermore, brain MRI abnormalities progressed significantly over time in both groups (Table 2). Total brain volume and gray matter volume decreased over time (mean change as percentage of ICV over the follow-up period [95% CI] in total brain volume = −1.01% [−1.12; −0.90] and in gray matter volume = −1.77% [−2.01; −1.52]), and ventricular volume and WML volume increased over time for the whole study sample (ventricular volume = 0.23% [0.20; 0.26] and WML volume = 0.12% [0.05; 0.20]).

Patients with DM showed an accelerated increase in ventricular volume over time relative to patients without DM (mean differences in ventricular volume as percentage of ICV [95% CI]: 0.32% [0.26; 0.39] vs. 0.17% [0.15; 0.19]; p-value time × group interaction < 0.01). Total brain volume, gray matter volume and WML volume showed no accelerated changes in patients with DM (p-value time × group interaction > 0.05). Additional adjustment for vascular risk factors and history of cerebrovascular disease only slightly attenuated the results (Table 2).

There were 82 patients with incident brain infarcts (n = 19 with DM vs. n = 63 without DM). The risk for incident brain infarcts was increased in patients with DM relative to patients without DM (RR = 1.62, 95% CI

Table 1
Baseline characteristics of the study sample.

	Total (n = 663)	Diabetes (n = 89)	Non-diabetes (n = 574)	p-Values
Age (years)	57.5 ± 9.5	60.6 ± 9.3	57.0 ± 9.4	<0.01
Sex (% male)	81.3	79.8	81.5	0.69
Educational level (1–7)[a]	3 (2–6)	3 (1–6)	4 (2–6)	0.14
DART-score[a]	82 (58–97)	81 (61–97)	82 (57–97)	0.98
Follow-up time (years)	3.9 ± 0.4	3.9 ± 0.4	3.9 ± 0.4	0.80
Vascular risk factors				
BMI (kg/m^2)	26.8 ± 3.5	27.8 ± 3.4	26.6 ± 3.5	<0.01
Systolic BP (mm Hg)	140 ± 20	143 ± 17	140 ± 20	0.14
Diastolic BP (mm Hg)	81 ± 10	81 ± 10	82 ± 11	0.35
Hyperlipidemia (% yes)	78%	78%	78%	0.82
Smoking (pack years)[a]	20.2 (0–49)	22.4 (0–55)	19.5 (0–47)	0.07
Alcohol intake (% current)	79%	66%	80%	<0.01
Vascular disease category				
Coronary artery disease (%)	62%	61%	62%	0.81
Cerebrovascular disease (%)	23%	30%	22%	0.14
Peripheral arterial disease (%)	18%	24%	18%	0.15
Abdominal aortic aneurysm (%)	6%	8%	6%	0.39

Percentage of missing values before imputation: educational level (38%), DART-score (37%), BMI (0.2%), hyperlipidemia (1.8%), alcohol (0.5%), smoking (0.3%), all other variables 0.0%.
[a] Median (10th–90th percentile).

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Table 2
Differences in brain volumes between patients with and without diabetes and over time for the whole study group.

	Model	Mean differences between DM and non-DM[a]	Mean change over time[b]	Time × group interaction p-Value
Total brain volume (% of ICV)	1	−1.36 (−1.81; −0.91)	−1.01 (−1.12; −0.90)	n.s.
	2	−1.19 (−1.64; −0.75)	−1.00 (−1.11; −0.88)	n.s.
Gray matter volume (% of ICV)	1	−1.23 (−1.85; −0.61)	−1.77 (−2.01; −1.52)	n.s.
	2	−1.07 (−1.69; −0.45)	−1.75 (−2.00; −1.50)	n.s.
Ventricular volume (% of ICV)	1	0.32 (0.14; 0.49)	0.23 (0.20; 0.26)	<0.01
	2	0.28 (0.11; 0.45)	0.23 (0.20; 0.26)	<0.01
WML volume[c]	1	0.31 (0.09; 0.53)	0.12 (0.05; 0.20)	n.s.
	2	0.29 (0.07; 0.50)	0.14 (0.06; 0.22)	n.s.

Data are brain volumes as percentage of ICV (95% confidence interval) with repeated-measures analysis of covariance. Model 1 adjusted for age and sex, model 2 additionally adjusted for BMI, alcohol, smoking, hyperlipidemia, systolic and diastolic blood pressure, and cerebrovascular disease. Percentage of missing values before imputation: gray matter fraction (17.5%), all other variables (0.0%).
DM = diabetes mellitus; WML = white matter lesion; ICV = intracranial volume.
[a] Non-DM group is reference.
[b] For the whole study sample (n = 663).
[c] Log transformed WML volume.

1.04–2.53, adjusted for age and sex). The increased risk was attenuated after additional adjustment for vascular risk factors and history of cerebrovascular disease (model 2; RR = 1.45, 95% CI 0.92–2.29), and presence of brain infarcts at baseline (model 3; RR = 1.30, 95% CI 0.81–2.06; stratified for respectively presence or absence of infarcts at baseline RR = 1.26, 95% CI 0.71–2.23 and RR = 1.55, 95% CI 0.73–3.31).

3.2. Presence of DM and cognitive decline

Results of the repeated measures ANCOVA of the analyses on the association between DM and cognitive decline are presented in Table 3. Patients with and without DM had similar performance on memory as well as executive functioning (Table 3). After four years of follow-up, memory performance and executive functioning did not decline for the whole study sample. Decline in memory performance or executive functioning was not accelerated in patients with DM compared to those without DM (p-value time × group interaction > 0.05).

In secondary analyses, exclusion of patients who developed DM during the follow-up period (n = 42) from the non-diabetic group did not change the results (data not shown).

4. Discussion

In a population of patients with symptomatic atherosclerotic disease, patients with DM had more brain atrophy and vascular brain lesions (WMLs and infarcts) than patients without DM. Brain atrophy and vascular brain lesions progressed over four years in both groups, and this progression was accelerated in patients with DM. Cognitive performance did not differ between the groups and patients with DM did not show accelerated cognitive decline compared with patients without DM.

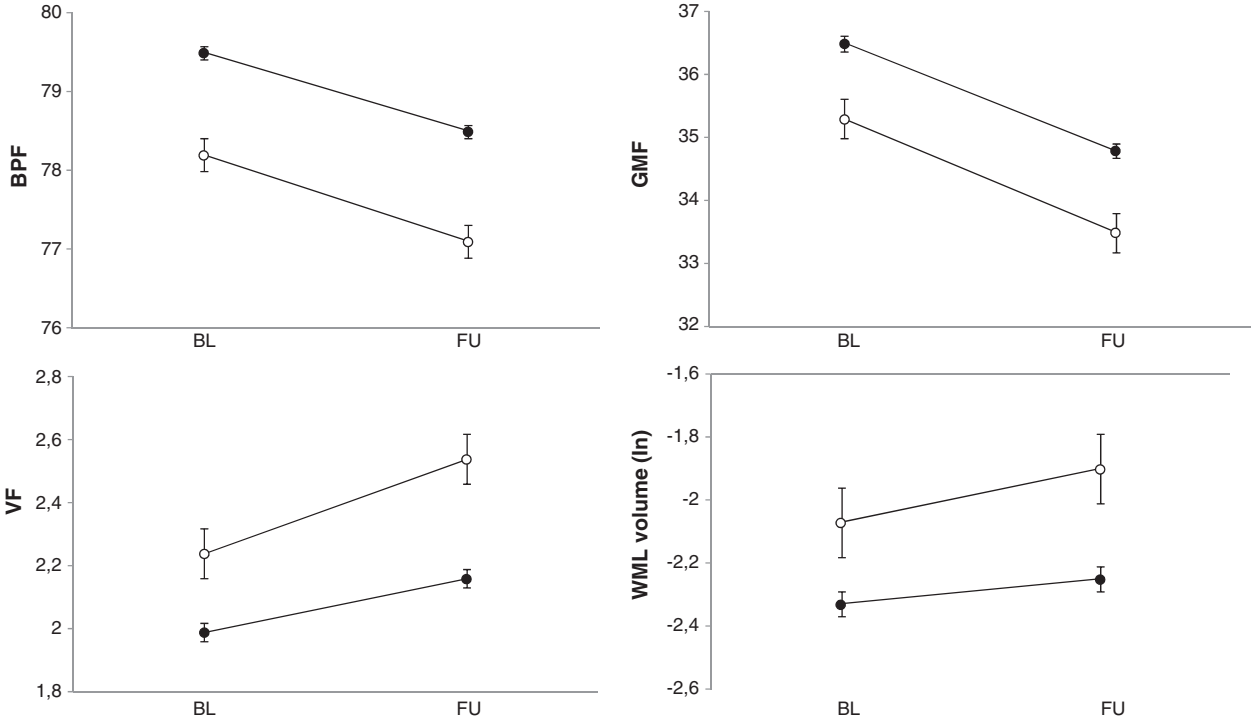

Fig. 1. Brain volumes and white matter lesion volume (as percentage of intracranial volume; mean ± SEM) for patients with diabetes (white circles; n = 89) and patients without diabetes (black circles; n = 574) at baseline (BL) and follow-up (FU). Analyses are adjusted for age and sex. BPF = brain parenchymal fraction; GMF = gray matter fraction; VF = ventricular fraction; WML volume (ln) = log transformed white matter lesion volume.

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Table 3
Differences in cognitive domain z-scores for patients with and without diabetes and over time for the whole study group.

	Model	Mean differences between DM and non-DM[a]	Mean change over time[b]	Time × group interaction p-Value
Memory performance (z-score)	1	−0.07 (−0.27; 0.13)	0.07 (−0.03; 0.17)	n.s.
	2	−0.03 (−0.23; 0.18)	0.07 (−0.03; 0.17)	n.s.
Executive functioning (z-score)	1	−0.04 (−0.22; 0.15)	−0.04 (−0.15; 0.07)	n.s.
	2	−0.01 (−0.19; 0.18)	−0.04 (−0.15; 0.07)	n.s.

Data are z-scores (95% confidence interval) analyzed with repeated-measures analysis of covariance. Model 1 adjusted for age, sex, educational level and DART-score, model 2 additionally adjusted for BMI, alcohol, smoking, hyperlipidemia, systolic and diastolic blood pressure, and history of cerebrovascular disease.
DM = diabetes mellitus.
[a] Non-DM group is reference.
[b] For the whole study sample (n = 473).

The observed association between DM and brain atrophy is in line with results from previous cross-sectional studies, which consistently report lower brain volumes and ventricular widening in patients with DM [13,15,19,29]. Previous longitudinal studies have reported an accelerated change in total brain volume [14] and ventricular volume [13,30] in patients with DM relative to patients without DM. Overall, the picture that emerges from previous and present observations, is that brain volume changes in patients with DM progress insidiously over the years, at a rate that only slightly exceeds that of normal aging.

For the association between DM and vascular brain lesions, the results of previous studies were inconsistent [12]. Some studies reported larger WML volumes cross-sectionally [3,11] and an accelerated increase in WML volume [31] in patients with DM over time, but this was not confirmed by others [13,14]. In the present study we found an association between DM and larger WML volume, and also a slightly accelerated increase in WML volume in patients with DM. In line with previous findings, the current longitudinal analyses showed a higher incidence of brain infarcts in patients with DM relative to patients without DM, partly explained by presence of brain infarcts at baseline and a history of cerebrovascular disease [32].

Cognitive performance did not change significantly over four years of follow-up in the two groups. This could be caused by the fact that the study included late middle-aged individuals with relatively intact cognition. In contrast with previous findings [9,10], cognitive performance was similar in patients with and without DM. The most likely explanation is that our whole study cohort consisted of patients with symptomatic atherosclerotic disease. Compared with controls, patients with vascular disease are generally found to be more vulnerable for modest cognitive decrements [33], possibly obscuring additional effects of DM. Despite the absence of a difference in cognition relative to the patients without DM, there was an additional effect of DM on brain MRI abnormalities, which was independent of vascular risk factors. Although several potential mechanisms (e.g. vascular disturbances, glucose toxicity, and abnormal insulin signaling in the brain) have been identified that may contribute to the brain abnormalities in DM2, it is yet unclear which of these factors are the main causal factors of brain abnormalities in humans [2].

Probably brain MRI measures are more sensitive than cognitive dysfunction to detect differences between patients with and without DM and may precede differences in cognitive decline. Progression of brain atrophy and vascular brain lesions seems to be a linear process, whereas decline in cognition is probably not linear but stepwise. According to the cognitive reserve capacity, a critical threshold should be reached before clinically relevant deficits emerge [34]. High vascular burden will lower the threshold, but additional presence of DM does not increase this process.

Strengths of this study are the prospective design and the large number of patients investigated with brain MRI and in the majority of cases also with a neuropsychological assessment. The volumetric assessment of brain atrophy and WMLs made it possible to investigate the associations on a continuous scale, without loss of information due to categorization of data. Our automated method is less influenced by observer bias than visual rating methods and enabled us to accurately measure WMLs and brain volumes. The large scale of the study limited us to extend the neuropsychological assessment with measures of cognitive decline on other domains besides memory and executive functioning. Furthermore, as in many other follow-up studies of aging, a limitation of this study is that individuals who participated in the follow-up examination represented a relatively healthy group. The selective loss to follow-up may have led to an underestimation of the effects. Also, the duration of DM was unknown and we were not able to distinguish between type 1 and type 2 DM. However, considering the mean age of the population, it seems plausible that most DM patients had type 2 DM.

To summarize, in this prospective study we have shown that the presence of DM on top of existing symptomatic atherosclerotic disease is associated with increased brain atrophy and vascular brain lesion load, at a rate that only slightly exceeds that of patients without DM.

Disclosure statement

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All other authors confirm that they have no actual or potential conflict of interest to disclose.

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