Type 2 Diabetes and Cognitive Decline in Middle-Aged Men and Women

The Doetinchem Cohort Study

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OBJECTIVE — To test the hypothesis that type 2 diabetes is associated with greater decline in cognitive function in middle-aged individuals.

RESEARCH DESIGN AND METHODS — In the Dutch prospective Doetinchem Cohort Study, cognitive functioning was measured twice within a 5-year time interval in 2,613 men and women. Participants were aged 43–70 years at baseline (1995–2002), and no one had a history of stroke. Change in scores on global cognitive function as well as on specific cognitive function domains (memory, speed of cognitive processes, and cognitive flexibility) were compared for respondents with and without type 2 diabetes (verified by the general practitioner or random plasma glucose levels ≥11.1 mmol/l).

RESULTS — At the 5-year follow-up, the decline in global cognitive function in diabetic patients was 2.6 times greater than that in individuals without diabetes. For individuals aged ≥60 years, patients with incident and prevalent diabetes showed a 2.5 and 3.6 times greater decline, respectively, in cognitive flexibility than individuals without diabetes. For most cognitive domains, the magnitude of cognitive decline in patients with incident diabetes was intermediate between that of individuals without diabetes and that of patients with diabetes at baseline.

CONCLUSIONS — Middle-aged individuals with type 2 diabetes showed a greater decline in cognitive function than middle-aged individuals without diabetes.

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Type 2 diabetes has been associated with cognitive impairments (1) and higher risks of developing vascular dementia (2,3) and Alzheimer disease (1,3). Cognitive dysfunction in type 2 diabetic patients may result from the interaction among metabolic abnormalities intrinsic to diabetes (hyperglycemia and hyperinsulinemia), diabetes-specific complications (such as retinopathy, nephropathy, and neuropathy), and other diabetes-related disorders (such as ischemic heart disease, cerebrovascular disease, hypertension, low serum HDL cholesterol, central obesity, and depression) (4).

Most studies on cognitive functioning in relation to diabetes have been cross-sectional or focused on elderly individuals (5,6). We found only four longitudinal studies in which changes in cognitive functioning were evaluated in middle-aged populations (7–10). Longitudinal studies are needed to provide insight into the development of cognitive impairment and decline over time in relation to the onset and duration of diabetes. None of the four studies evaluated changes in cognitive functioning in individuals with recently diagnosed diabetes. Yet, to study the relation between onset of diabetes and cognitive decline, it is essential to include this group and measure cognitive function longitudinally, before and after the onset of diabetes. In the present study, we tested the hypothesis that individuals with prevalent diabetes at baseline and those with incident diabetes during follow-up show a greater decline in cognitive functioning than individuals without diabetes.

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RESEARCH DESIGN AND METHODS

— The Doetinchem Cohort Study (DCS) (11) is an ongoing prospective study, initially carried out in a random general population sample of 7,769 men and women aged 20–59 years (1987–1991). The aim of the Doetinchem Cohort Study was to study the impact of (changes in) lifestyle factors and biological risk factors on various aspects of health, such as the incidence of chronic diseases, physical and cognitive functioning, and quality of life. The cohort is reexamined every 5 years. At every reexamination lifestyle factors and biological risk factors are assessed by questionnaires and a physical examination at the research center. Three subsequent examination rounds were completed in the years 1993–1997, 1998–2002, and 2003–2007. All participants gave written informed consent. The study was approved by the external Medical Ethics Committee of the Netherlands Organization of Applied Scientific Research according to the guidelines of the Declaration of Helsinki. Details on the DCS have been extensively described elsewhere (11).

From 1995 onward, cognitive testing for DCS participants aged ≥45 years was introduced. In the years 1995–1997, a random sample of one-third of participants aged ≥45 years was enrolled in the study on cognitive functioning, and a random sample of two-thirds was enrolled in an additional dietary study. Those participating in the dietary study during 1995–1997 had their baseline measurement of cognitive functioning during 2000–2002. Between 1995 and 2002, 3,350 respondents aged 43–70 years, 96% of all respondents invited, participated in cognitive testing for the first time. Five years later, between 2000 and 2007, 2,690 of them (80%) participated in cognitive testing again. At the first cognitive testing,

55% of the population were ≤55 years and 88% were ≤65 years of age. Participants who reported (at baseline or at follow-up) having experienced a stroke (n = 77) were excluded from the analyses, because stroke has direct effects on brain functions and cognition. A total of 2,613 people (1,288 men and 1,325 women) who participated in two cognitive measurements were included in this study.

Cognitive tests

The neuropsychological test battery included four tests, the 15-word Verbal Learning Test (VLT), the Stroop Color and Word Test (SCWT), a fluency test, and the Letter Digit Substitution Test (LDST), to measure global cognitive function and specific cognitive domains, namely memory, speed of cognitive processes, and cognitive flexibility (i.e., higher order information processing). In the VLT, 15 monosyllabic words printed on paper are displayed, one by one, in three subsequent trials, with a free recall procedure immediately after each presentation (immediate recall). After a delay of about 15 min, there is an additional free recall trial (delayed recall). The VLT total is calculated by summation of the words recalled correctly on the three immediate recalls. The VLT maximal represents the highest score on one of the three immediate recalls. In the SCWT, three skills are tested: *1*) to read 40 written color names, *2*) to name the color of 40 colored patches, and *3*) to name the color of the ink in which 40 incongruously named color words are printed (so, e.g., the word "blue" is printed in red). In the fluency test, the participant is asked to name as many animals as possible within 1 min. In the LDST, nine letters are given a unique digit code (1 to 9) in a key displayed on the same sheet of paper. The participant is asked to fill in the correct digits corresponding to the letters, as fast as possible. These tests are described in more detail elsewhere (12). The tests are sensitive to age, also in the middle-age range. Cognitive tests were performed by trained investigators and took ~20 min to complete.

Distributions of scores on the SCWT were normalized (distributions were unimodal and skewed to the right). For each cognitive test, a z score was computed for each participant at baseline and at follow-up, based on the means and SDs of the test scores at baseline. In this way we were able to examine changes over time. Standardized scores on the SCWT were inverted, so that higher scores represent better cognition. All (inverted) standardized scores were then combined to form scores for specific cognitive domains, i.e., scores for memory function, speed of cognitive processes, and cognitive flexibility, and a summary score for global cognitive function, as follows:

$$\text{Memory function} = (z\text{VLT}_{\text{total}} + z\text{VLT}_{\text{maximal}} + z\text{VLT}_{\text{delayed recall}})/3$$

$$\text{Speed of cognitive processes} = (-z\ln(\text{SCWT}_{\text{color names}}) - z\ln(\text{SCWT}_{\text{color patches}}) + z\text{LDST})/3$$

$$\text{Cognitive flexibility} = -z\ln(\text{SCWT}_{\text{color link}})$$

$$\text{Global cognitive function} = (-z\ln(\text{SCWT}_{\text{color link}}) + z\text{LDST} + z\text{VLT}_{\text{total}} + z\text{VLT}_{\text{delayed recall}} + z_{\text{fluency}})/5$$

Diabetes status

At baseline and at follow-up, participants were asked whether they had diabetes by means of a self-administered questionnaire. For all patients with self-reported diabetes who had given written informed consent for it, their general practitioner was contacted for verification via mailed questionnaires. Almost all participants gave consent (98.2%). For 90% of patients with self-reported diabetes at baseline and for 88% of those with self-reported diabetes at follow-up, information regarding their diabetes status was obtained. Individuals with type 1 diabetes (n = 5) or with an unknown type of diabetes (n = 4) were excluded from the analyses. Three individuals with self-reported diabetes for whom the general practitioner did not confirm the diagnosis and women with gestational diabetes mellitus in the past but no diabetes at present were classified as not having diabetes. In addition, in the entire cohort a random (nonfasting) venous blood sample was taken to determine the plasma glucose level with the hexokinase method (13). For three individuals, plasma glucose could not be determined. In conclusion, diabetes was defined on the basis of self-report confirmed by the general practitioner, self-report alone (when no general practitioner verification was available), or a random plasma glucose of ≥11.1 mmol/l (14).

Other measures

Several measures that are potentially associated with diabetes and/or cognitive function were assessed. Each assessment round included a physical examination at the research center, involving height, weight, waist circumference, and blood pressure measurements and obtaining nonfasting blood samples. BMI was determined as weight in kilograms divided by the square of height in meters. Blood pressure was measured with the subject in the sitting position using a random zero sphygmomanometer. Total and HDL cholesterol were measured using standardized enzymatic methods (11).

In every assessment, information on demographic characteristics (e.g., age and educational level), lifestyle factors (e.g., smoking, alcohol consumption, and physical activity), and history of chronic diseases (e.g., myocardial infarction) was also collected using standardized questionnaires. Educational level was evaluated as the highest level reached and classified into five categories: *1*) primary school, *2*) lower vocational education, *3*) intermediate secondary education, *4*) intermediate vocational or higher secondary education, and *5*) higher vocational education or university. Smoking status was defined as being a nonsmoker (never or former smoker) or smoker (of cigarettes) and further according to the number of pack-years smoked at baseline. One pack-year corresponds to smoking 20 cigarettes/day for 1 year (or, e.g., smoking 1 cigarette/day for 20 years). Alcohol consumption was classified into five categories: *1*) abstainers, *2*) 0–1 glasses/day, *3*) 1–2 glasses/day, *4*) 2–4 glasses/day, and 5) >4 glasses/day. Physical activity level was assessed by the use of the validated European Prospective Investigation into Cancer and Nutrition (EPIC) questionnaire on physical activity (15) and classified into four categories: inactive, moderately inactive, moderately active, and active (16).

Depressive symptoms were assessed using the Dutch version (17) of the SF-36 (18). The scales "mental health" and "vitality" evaluate symptoms of depression. Scores on both scales range from 0 to 100 in which higher scores represent better (mental) health.

Statistical analyses

Multivariate linear regression analyses and ANCOVA were used to study the association between diabetes status and changes in cognitive function over follow-

up. Changes in cognitive domains and global cognitive function were analyzed as continuous outcome measures, with diabetes status as the main independent measure. Two models were tested. First, we tested a basic model, adjusting for age, sex, level of education, and baseline level of cognitive function. Second, to find out whether associations between diabetes and change in cognitive function could be explained by other diabetes-related factors, we tested the basic model with additional adjustment for factors of the metabolic syndrome (waist circumference, systolic blood pressure, use of blood pressure-lowering medication, and HDL cholesterol level), physical activity, alcohol consumption, smoking, and history of myocardial infarction. Because depression is quite common among people with diabetes and depression negatively affects cognitive function, we additionally adjusted this second model for depressive symptoms (mental health and vitality). For all these covariates, baseline measures were taken for inclusion in the analyses.

To test whether the association between diabetes and cognitive function was different at both ends of the middle-age range, additional analyses were performed including an interaction term of diabetes and age (≤60 vs. >60 years). All analyses were performed using SAS (version 9.2; SAS Institute, Cary, NC).

Table 1—*General baseline characteristics of the study population by diabetes status*

	No diabetes	Incident diabetes	Prevalent diabetes
n	2,460	78	61
Age (years)	55.0 ± 6.8	57.4 ± 6.6	60.6 ± 6.5
Sex (% women)	51.0	46.2	49.2
Level of education (% highly educated)	26.8	12.8	13.1
Cognitive function domain scores (*z* scores)			
Memory function	0.01 ± 0.94	0.00 ± 0.89	−0.53 ± 0.87
Speed of cognitive processes	0.02 ± 0.83	−0.18 ± 0.88	−0.51 ± 0.95
Cognitive flexibility	0.02 ± 0.99	−0.33 ± 1.00	−0.30 ± 1.41
Global cognitive function	0.02 ± 0.72	−0.19 ± 0.66	−0.45 ± 0.75
Random glucose level (mmol/l)	5.3 ± 0.9	6.9 ± 1.6	11.4 ± 3.9
Systolic blood pressure (mmHg)	130 ± 17	143 ± 19	142 ± 18
Diastolic blood pressure (mmHg)	82 ± 10	88 ± 11	84 ± 12
Use of blood pressure lowering medication (%)	10.0	21.8	41.0
Total cholesterol (mmol/l)	5.84 ± 1.00	6.09 ± 1.19	5.70 ± 1.02
HDL cholesterol (mmol/l), men	1.23 ± 0.32	1.04 ± 0.26	1.17 ± 0.36
HDL cholesterol (mmol/l), women	1.55 ± 0.38	1.20 ± 0.33	1.23 ± 0.23
History of myocardial infarction (%)	1.6	3.9	6.6
BMI (kg/m^2)	26.1 ± 3.6	30.0 ± 4.9	29.6 ± 4.9
Waist circumference (cm), men	98.3 ± 8.9	105.7 ± 7.9	106.1 ± 14.1
Waist circumference (cm), women	88.8 ± 10.5	102.1 ± 12.5	103.3 ± 10.8
Physical activity (% inactive)*	24.6	24.4	37.7
Alcohol consumption (% >4 glasses/day)	4.8	9.0	1.6
Smoking (%)	22.2	23.4	14.8
Mental health*	77 ± 15	78 ± 13	77 ± 18
Vitality*	68 ± 17	66 ± 17	65 ± 18

Data are means ± SD unless otherwise indicated. Diabetes is defined as self-reported diabetes (verified by the general practitioner) or having a random plasma glucose level ≥11.1 mmol/l. *Physical inactivity is defined as being classified in the lowest two of four categories (inactive and moderately inactive) according the Wareham classification for physical activity (16). Mental health and vitality scores are based on the SF-36 and represent depressive symptoms. Scores range from 0 to 100 in which higher scores represent better (mental) health (18).

RESULTS — Nonparticipants and individuals lost to follow-up were slightly older and less educated than individuals who completed the follow-up assessment. Individuals lost to follow-up scored ~0.4 SDs lower at baseline on all cognitive domains. In addition, the prevalence of several cardiovascular risk factors was higher among the dropouts, and the prevalence of type 2 diabetes (self-report or plasma glucose level ≥11.1 mmol/l) among them was also higher (6.2 vs. 2.6% in the follow-up group).

At follow-up, 139 individuals were classified as having type 2 diabetes: 129 based on self-report (113 verified by the general practitioner) and 10 based on their elevated plasma glucose levels. Of those 139, 61 (2.3% of the total population; 31 men and 30 women) had prevalent diabetes at baseline, and 78 (3.0% of the total population; 42 men and 36 women) developed type 2 diabetes during follow-up (incident cases).

Patients with prevalent and incident diabetes were older and less educated and had higher systolic blood pressure and BMI at baseline than individuals without diabetes. Furthermore, baseline cognitive function in diabetic patients was worse than that of individuals without diabetes (Table 1).

Changes in cognitive function

We observed an interaction effect of diabetes with age (≤60 vs. >60 years) on the association between diabetes and change in cognitive flexibility. Therefore, results for change in cognitive flexibility will be presented separately for individuals aged ≤60 years and those aged >60 years.

Prevalent diabetic patients showed statistically significantly greater declines in memory function, cognitive flexibility, and global cognitive function than individuals without diabetes after adjustment for age, sex, and educational level. Incident diabetic patients showed about twice the decline observed in individuals without diabetes, but this decline was statistically significant for memory, speed, and flexibility (for individuals aged ≥60 years) only (Table 2).

In the fully adjusted model, cognitive decline in memory, flexibility, and global cognitive function in prevalent diabetic patients was about 3 times greater than that in individuals without diabetes, although this decline was statistically significant only for flexibility (for individuals aged ≥60 years) and global cognitive function. Differences in cognitive decline in memory and speed between incident diabetic patients and individuals without diabetes were no longer statistically significant in the fully adjusted model (Table 2). Results of the fully adjusted model are presented in Fig. 1. Associations between diabetes status and changes in cognitive function were not statistically significantly different for men compared with women.

CONCLUSIONS — In the present study, diabetic patients showed a greater

Table 2—*Relative changes in cognitive function scores by diabetes status*

	Basic model*			Fully adjusted model†		
	No diabetes	Incident diabetes	Prevalent diabetes	No diabetes	Incident diabetes	Prevalent diabetes
Memory function	−1.0	−2.4§	−2.9§	−1.0	−1.9	−2.5‡
Speed of cognitive processes	−1.0	−1.9§	−1.2	−1.0	−1.5	−1.0
Cognitive flexibility						
≤60 years	−1.0	0.9	−3.2	−1.0	0.6	−3.4
>60 years	−1.0	−2.6§	−3.7‖	−1.0	−2.5‡	−3.6‖
Global cognitive function	−1.0	−1.9	−2.8‖	−1.0	−1.6	−2.6§

Relative decline in cognitive domain scores is shown with individuals with no diabetes as the reference group: in the reference group of "healthy" individuals, we set the cognitive decline to −1.0. The numbers in the columns of patients with diabetes reflect how many times stronger the cognitive decline was among diabetic patients compared with individuals without diabetes. No diabetes indicates no diabetes at baseline or at follow-up ($n = 2,460$). Incident diabetes indicates no diabetes at baseline and diabetes at follow-up ($n = 78$). Prevalent diabetes indicates diabetes at baseline and at follow-up ($n = 61$). Diabetes was defined as reporting to have diabetes (verified by the general practitioner) or having random plasma glucose levels ≥11.1 mmol/l. *Change scores are adjusted for age, sex, level of education, and baseline cognitive score. †Change scores are adjusted for age, sex, level of education, waist circumference, HDL cholesterol level, systolic blood pressure, use of blood pressure-lowering medication, history of myocardial infarction, depressive symptoms (vitality and mental health), physical activity, alcohol consumption, smoking, and baseline cognitive score. ‡Different from no diabetes group at $P < 0.10$; §$P < 0.05$; ‖$P < 0.01$.

decline in cognitive function (cognitive flexibility and global cognitive function) than individuals without diabetes. The magnitude of decline in cognitive function in individuals who developed diabetes during follow-up was between that of individuals without diabetes and those who had diabetes at baseline but was not statistically significantly different from either group after adjustment for other cardiovascular risk factors.

Strengths of the present study are its prospective design, the relatively young population, and the long follow-up period with repeated assessment of cognitive function using a sensitive cognitive test battery. For most patients who reported diabetes, the diagnosis could be verified with their general practitioner. Further, a large number of covariates were assessed, which enabled adjustment for a broad array of potential confounders.

Limitations of the present study can be found in the dropout of individuals during follow-up. Although dropout of this order of magnitude (20%) is inherent to cohort studies, there are reasons to believe that in our study it was selective to some extent. Overall, cognitive function was better in the follow-up group and especially among individuals without diabetes. Based on associations in the follow-up group, some of these observed differences in baseline characteristics between the group of dropouts and the follow-up group would weaken associations between diabetes and change in cognitive function, whereas other observed differences would make these associations stronger. In addition, associations were adjusted for these confounding characteristics. Therefore, the effect of dropouts on the results will be only marginal.

Furthermore, we may have missed some cases of diabetes because we measured random glucose levels rather than fasting glucose levels, and we did this only once. To diagnose diabetes, two measurements of glucose levels are recommended. In addition, although most self-reported cases of diabetes were verified with the general practitioner, we cannot exclude the possibility of some misclassifications in the diabetic groups either. Because of these possible misclassifications, the observed differences may be underestimations. In addition, no data on A1C were available. Therefore, we could not relate longer-term glucose levels to changes in cognitive function.

The relation between diabetes and cognitive decline in middle-aged individuals was evaluated in three previous longitudinal studies (7–10). In the Atherosclerosis Risk in Communities (ARIC) Study, diabetic patients showed greater declines over 6 and 14 years in scores representing speed of cognitive processes and verbal fluency but not in scores for memory (7,8). In the Interdisciplinary Longitudinal Study of Aging (ILSE) diabetic patients showed a greater decline at 4 years of follow-up in intelligence tasks but not in memory and speed than individuals without diabetes (10). Finally, in a study by van den Berg et al. (9), no differences in cognitive decline on several tests were observed between individuals with and without diabetes over a 4-year period. However, our study differs from these studies as to the tests used to determine cognitive domain functions. Different tests might reveal different patterns of decline. In addition, the age ranges of the subjects were different among the studies. Studying different age-groups can result in different conclusions, as reflected by the interaction between age and diabetes in our study. With one exception (9), the overall conclusion of the previous studies and ours is that diabetes is associated with greater cognitive decline in middle-aged individuals, but that it remains uncertain which cognitive domain is affected most.

Associations between incident diabetes and cognitive decline have not been studied before. The magnitude of cognitive decline in incident diabetic patients tended to be somewhere between the cognitive decline in individuals without diabetes and that of patients with diabetes at baseline, but the observed association was not significant. Incident diabetic patients may thus also benefit from timely and appropriate treatment at the level of cognitive functions (19). Improved glycemic control reduces the damaging effects of hyperglycemia on neuronal and microvascular structures (5). In this respect, it is remarkable that random plasma glucose levels of incident diabetic patients were similar to those of prevalent diabetic patients (8.5 and 8.6 mmol/l, respectively), which might be an indication that treatment was insufficient. However, random plasma glucose is not the best indicator of glycemic control.

Results of our study seem to indicate that hyperglycemia affects different domains of cognitive functioning at different stages of the disease process. For instance, memory seems to be affected continuously (lower score at baseline and a [borderline significantly] greater decline during follow-up for diabetic patients), whereas speed of cognitive processes seems to be affected during the first years of hyperglycemia only (worse score at baseline, but no greater decline over follow-up for diabetic patients than for individuals without diabetes, whereas incident diabetic patients show a greater decline in speed of cognitive processes). These results suggest that early treatment of hyperglycemia could prevent some of the decline in speed of cognitive processes, but probably less so in the case of memory.

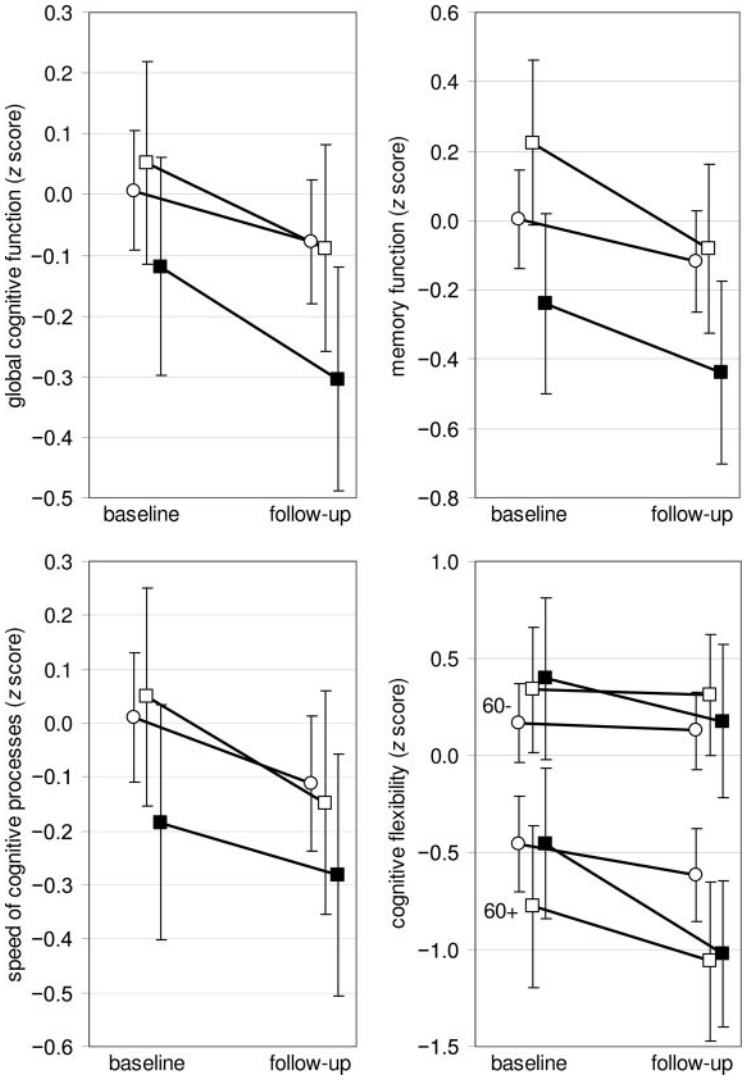

Figure 1—*Average cognitive function with 95% CI at baseline and at follow-up for individuals with no diabetes (○——○), incident diabetes (□——□), and prevalent diabetes (■——■). For change in cognitive flexibility, an interaction effect was observed for diabetes status and age. Therefore, cognitive flexibility is displayed for individuals aged ≤60 years (upper lines) and individuals aged >60 years (lower lines) separately.*

Several pathways have been hypothesized between type 2 diabetes and cognitive decline. For example, hyperglycemia causes oxidative stress and glycation of important functional and structural proteins (20), which can have a direct detrimental effect on brain cells and the microcirculation in the brain (21). In addition, higher fasting plasma glucose has been associated with functional changes in regional cerebral perfusion (22). In addition, type 2 diabetes is associated with increased central arterial stiffness (23), which has been shown to be a strong predictor of loss in cognitive function in older individuals (24). Improvement in glycemic control may improve cognitive functioning in adults with type 2 diabetes (19) and reduce the risk for (cardiovascular) complications.

Because we observed that cognitive decline was greater in prevalent diabetic patients than in incident diabetic patients and individuals without diabetes, duration of exposure to hyperglycemia could be the main factor that induces and maintains cognitive decline. To further explore this hypothesis, we performed ad hoc analyses on a subset of our data, relating diabetes duration to cognitive decline. A verified date of diagnosis of diabetes was available for 109 (57 incident and 52 prevalent) diabetic patients at follow-up. On average, diabetes in these patients had been diagnosed 6.5 ± 6.8 (mean ± SD) years before the follow-up assessment. We did not observe an association between duration of diabetes and change in cognitive functioning within this subgroup of diabetic patients. Thus, this result did not confirm our hypothesis.

Type 2 diabetes is often associated with other conditions that may influence cognitive function, such as hypertension, hypercholesterolemia, and central obesity. Therefore, we adjusted for these cardiovascular risk factors. However, trends observed in the fully adjusted model were similar to those in the basic model, indicating that comorbidities of diabetes only partly explain the associations between diabetes and cognitive decline.

In summary, middle-aged diabetic patients have greater cognitive decline than individuals without diabetes. Therefore, cognitive function should be assessed and monitored in middle-aged individuals with type 2 diabetes.

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A.C.J.N. analyzed data, interpreted results, and wrote the manuscript. C.A.B. originated the idea for analyses, interpreted results, and reviewed/edited the manuscript. A.M.W.S. interpreted results and reviewed/edited the manuscript. W.M.M.V. supervised data collection, interpreted results, and reviewed/edited the manuscript.

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