

# Association of Type 2 Diabetes, According to the Number of Risk Factors Within Target Range, With Structural Brain Abnormalities, Cognitive Performance, and Risk of Dementia

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# Association of Type 2 Diabetes, According to the Number of Risk Factors Within Target Range, With Structural Brain Abnormalities, Cognitive Performance, and Risk of Dementia

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## OBJECTIVE

Type 2 diabetes is associated with increased risks of cognitive dysfunction and brain abnormalities. The extent to which risk factor modification can mitigate these risks is unclear. We investigated the associations between incident dementia, cognitive performance, and brain abnormalities among individuals with type 2 diabetes, according to the number of risk factors on target, compared with control subjects without diabetes.

## RESEARCH DESIGN AND METHODS

Prospective data were from UK Biobank of 87,856 individuals ( $n = 10,663$  diabetes,  $n = 77,193$  control subjects; baseline 2006–2010), with dementia follow-up until February 2018. Individuals with diabetes were categorized according to the number of seven selected risk factors within the guideline-recommended target range (nonsmoking; guideline-recommended levels of glycated hemoglobin, blood pressure, BMI, albuminuria, physical activity, and diet). Outcomes were incident dementia, domain-specific cognitive performance, white matter hyperintensities, and total brain volume.

## RESULTS

After a mean follow-up of 9.0 years, 147 individuals (1.4%) with diabetes and 412 control subjects (0.5%) had incident dementia. Among individuals with diabetes, excess dementia risk decreased stepwise for a higher number of risk factors on target. Compared with control subjects (incidence rate per 1,000 person-years 0.62 [95% CI 0.56; 0.68]), individuals with diabetes who had five to seven risk factors on target had no significant excess dementia risk (absolute rate difference per 1,000 person-years 0.20 [−0.11; 0.52]; hazard ratio 1.32 [0.89; 1.95]). Similarly, differences in processing speed, executive function, and brain volumes were progressively smaller for a higher number of risk factors on target. These results were replicated in the Maastricht Study.

## CONCLUSIONS

Among individuals with diabetes, excess dementia risk, lower cognitive performance, and brain abnormalities decreased stepwise for a higher number of risk factors on target.

Cognitive dysfunction is increasingly recognized as a clinically important complication of type 2 diabetes. The risk of dementia in type 2 diabetes is 1.5- to 2-times higher than in the general population (1). In addition, diabetes is associated with an increased risk of structural brain abnormalities, including higher white matter hyperintensity volume, lower total brain parenchyma volume, and lacunar infarcts (1). These structural brain abnormalities are important risk factors of dementia (2).

Current treatment of type 2 diabetes consists of continuous medical care with comprehensive, multifactorial strategies for reducing adverse outcomes. Recent observational studies (3–5) have shown that individuals with type 2 diabetes who had various risk factors within the recommended target range (e.g., non-smoking; and guideline-recommended levels of glycated hemoglobin, cholesterol, blood pressure, BMI, albuminuria, physical activity, and diet) had little or no excess risk of death or cardiovascular disease compared with the general population. As reviewed previously (2,6), some observational studies, but not all, have shown that individual risk factors in type 2 diabetes (i.e., elevated glycated hemoglobin, high blood pressure, physical inactivity, and albuminuria), longer diabetes duration, and presence of diabetic complications (microvascular or macrovascular) are associated with incident dementia, worse cognitive performance, or structural brain abnormalities. However, the extent to which excess risk of dementia, worse cognitive performance, and higher prevalence of structural brain abnormalities associated with type 2 diabetes may be mitigated by multifactorial risk factor modification is unclear.

Using data from UK Biobank, we evaluated the association between dementia risk, domain-specific cognitive performance (processing speed, memory, and executive function), and prevalence of MRI-determined structural brain abnormalities (white matter hyperintensity volume, total brain parenchyma volume, and lacunar infarcts) among individuals with type 2 diabetes, according to the number of risk factors within target range, compared with control subjects without diabetes. To test the validity of the findings, we replicated the analyses

in the Maastricht Study, a population-based cohort study with oversampling of individuals with type 2 diabetes.

## RESEARCH DESIGN AND METHODS

### Data Source

Primary analysis is based on data from the UK Biobank Study (7), a population-based cohort of >500,000 participants who were recruited from across the U.K. between 2006 and 2010, aged 40 to 69 years. Participants are continuously followed-up for incident dementia. An average of 8.7 (SD 1.7) years after initial recruitment, a subsample of participants also underwent brain MRI. Secondary analysis is based on cross-sectional data from UK Biobank and the Maastricht Study (8). The Maastricht Study is an ongoing cohort study among ~9,000 individuals from the southern part of the Netherlands, aged 40 to 75 years. Individuals are recruited from the general population with an oversampling of individuals with type 2 diabetes (8). For this analysis, cross-sectional data were available from participants who were recruited between 2010 and 2017 ( $n = 7,689$ ). After 2013, a subsample of participants of the Maastricht Study also underwent brain MRI.

UK Biobank received ethical approval from the Research Ethics Committee (reference 11/NW/03820), and the Maastricht Study received ethical approval from Institutional Medical Ethical Committee (reference NL31329.068.10) and from the Ministry of Health, Welfare, and Sports of the Netherlands (Permit 131088-105234-PG). The present analyses were conducted under UK Biobank and the Maastricht Study application numbers 60842 and 351, respectively. All participants gave written informed consent.

### Type 2 Diabetes and Control Subjects

In both studies, we selected individuals with type 2 diabetes without baseline dementia and compared them to all individuals without diabetes or prediabetes and without dementia (control subjects). A priori, we excluded individuals with prediabetes from the control group in the main analysis, because prediabetes is associated with a higher risk of dementia, cognitive dysfunction, and structural brain abnormalities in most studies (2,9), but not all (10). In UK Biobank, fasting plasma glucose was used

to classify participants as having no diabetes, prediabetes (i.e., impaired fasting glucose), or diabetes (11). Participants were also considered to have type 2 diabetes if they used glucose-lowering medication or self-reported diabetes. In the Maastricht Study, a 2-h oral glucose tolerance test (8) was used to classify participants as having normal glucose metabolism, prediabetes (i.e., impaired fasting glucose or impaired glucose tolerance), or diabetes based on the World Health Organization 2006 diagnostic criteria (11). Participants were also considered to have type 2 diabetes if they used glucose-lowering medication without a prior diagnosis of type 1 diabetes.

### Risk Factors

Seven risk factors were selected based on recommendations in current clinical guidelines (12–14) and were defined as being within target range based on guideline-recommended target levels: glycated hemoglobin level (cutoff value, <53 mmol/mol [ $<7\%$ ]), blood pressure (cutoff value, <130 mmHg for systolic and <80 mmHg for diastolic blood pressure), BMI (cutoff value,  $\geq 20$  and <25 kg/m<sup>2</sup>), smoking (nonsmoker), albuminuria (absence of micro- or macroalbuminuria), physical activity (cutoff value,  $\geq 150$  min/week of moderate-to-vigorous physical activity), and diet (optimal as defined by the American Heart Association healthy diet score) (Supplementary Table 1). A priori, we did not consider cholesterol as a risk factor, because the association between cholesterol levels and cognitive dysfunction and structural brain abnormalities is inconsistent (1,15,16). In a previous report of the UK Biobank (15), hypercholesterolemia was not associated with structural brain abnormalities.

### Incident All-Cause Dementia (UK Biobank Only)

Incident all-cause dementia was ascertained as described previously (17) from ICD-9 and ICD-10 (*International Classification of Diseases*, 9th and 10th revisions) codes of hospital inpatient records containing data on admissions and diagnoses obtained from the Hospital Episode Statistics for England, Scottish Morbidity Record data for Scotland, and from ICD-10 codes of the Patient Episode Database for Wales, and death registries.

Dementia diagnosis has been validated in English hospital records (sensitivity, 78%; specificity, 92%) (18) and in Scottish routine data (positive predictive value, 83%) (17). Follow-up for dementia was until 14 February 2018.

### Domain-Specific Cognitive Performance (UK Biobank and the Maastricht Study)

Three cognitive domains were evaluated: processing speed and memory in both cohorts, and executive function in the Maastricht Study only, as described previously (8,19). Processing speed was evaluated with the Reaction Time Test in UK Biobank and with the Stroop Color and Word Test Part I and II, Concept Shifting Test Part A and B, and Letter Digit Substitution Test in the Maastricht Study. Memory was evaluated with the Pairs Memory Test in UK Biobank and with the Verbal Learning Test in the Maastricht Study. In the Maastricht Study, executive function was evaluated with the Stroop Color and Word Test Part III and Concept Shifting Test Part C. For conceptual clarity, raw test scores were standardized, and if necessary, inverted so that higher scores indicated better cognitive performance. In the Maastricht Study, domain scores were calculated as the average of all tests for the domain.

### Structural Brain Abnormalities (UK Biobank and the Maastricht Study)

Brain MRI was performed on a 3T MRI scanner in both UK Biobank (Siemens Skyra, Erlangen, Germany) and the Maastricht Study (Siemens Magnetom Prisma<sup>fit</sup> Syngo MR D13D, Erlangen, Germany). We evaluated three MRI-defined structural brain abnormalities: white matter hyperintensity volume and total brain parenchyma volume in both cohorts, and presence of lacunar infarcts (yes/no) in the Maastricht Study only. Image acquisition and analysis were described previously (9,20). In both cohorts, the MRI protocol consisted of a three-dimensional T1-weighted sequence, a T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence, and a susceptibility-weighted imaging sequence. In both cohorts, brain volumes were determined by semiautomated methods. In the Maastricht Study, lacunar infarcts were rated manually.

### Statistical Analysis

We evaluated the association between incident dementia (primary outcome) and domain-specific cognitive performance and structural brain abnormalities (secondary outcomes) among individuals with type 2 diabetes, according to the number of risk factors within target range, compared with control subjects. Among individuals with type 2 diabetes, the following categories were retained in the analysis to include groups that were sufficiently large: 1) no to two risk factors within target range; 2) three risk factors within target range; 3) four risk factors within target range; and 4) five to seven risk factors within target range.

We used Cox regression to estimate hazard ratios (HRs) and 95% CIs for the association with incident dementia with time-in-study as the time scale. Follow-up time was calculated from the UK Biobank baseline examination (2006–2010) to incidence of dementia, death, or 14 February 2018, whichever came first. The proportional hazard assumption was assessed by visual inspection of the Kaplan-Meier curves. Incidence rates for dementia were calculated according to the number of risk factors within target range. In addition, we used linear and logistic regression to estimate regression coefficients ( $\beta$ ) or odds ratios (ORs) for the associations with domain-specific cognitive performance (processing speed, memory, and executive function) and structural brain abnormalities (white matter hyperintensity volume, total brain parenchyma volume, and presence of lacunar infarcts). White matter hyperintensity volume was log-transformed to normalize its skewed distribution.

All analyses were adjusted for baseline age, sex, and education (low or high in UK Biobank; low, intermediate, or high in the Maastricht Study). Analyses with structural brain abnormalities as the outcome were additionally adjusted for time between baseline examination and MRI examination, and analyses with brain volumes as the outcome were additionally adjusted for intracranial volume.

We tested interaction terms with age and sex to examine whether the associations investigated differed by age and sex.

We did several additional analyses. First, analyses were repeated using different cutoff values for glycated hemoglobin ( $\geq 42$  and  $< 53$

mmol/mol [ $\geq 6$  and  $< 7\%$ ]), blood pressure (systolic blood pressure  $< 140$  mmHg and diastolic blood pressure  $< 90$  mmHg), and BMI ( $\geq 20$  and  $\leq 30$  kg/m<sup>2</sup>). In addition, we used 24-h ambulatory blood pressure instead of office blood pressure to define recommended levels of blood pressure (cutoff value, systolic blood pressure  $< 130$  mmHg and diastolic blood pressure  $< 80$  mmHg; data available in the Maastricht Study only). Second, we additionally adjusted for diabetes duration, use of renin-angiotensin-aldosterone system inhibitors, and estimated glomerular filtration rate. Adjustment for diabetes duration was done by centralizing duration of diabetes around the grand mean (the mean duration among all individuals) for individuals with type 2 diabetes and setting diabetes duration to 0 years for control subjects. Third, analyses were repeated considering LDL cholesterol levels as an additional risk factor (cutoff value,  $< 2.5$  mmol/L). Fourth, analyses were repeated defining control subjects as individuals without diabetes or prediabetes who had four risk factors within target range (median number of risk factors within target range among all control subjects), and defining control subjects as individuals without diabetes, including individuals with prediabetes in the control group. Fifth, analyses were repeated after excluding glycated hemoglobin, BMI, or physical activity as risk factors. Sixth, the analysis on incident dementia was repeated accounting for death as a competing risk using Fine and Gray proportional subdistribution hazard regression. Seventh, given that risk factor levels might be affected by the preclinical phase of dementia (21), we repeated the analysis on incident dementia with consecutive exclusion of the first 5 years of follow-up. Eighth, among individuals with type 2 diabetes, we evaluated the associations of the individual risk factors with each outcome and the association between the number of risk factors within target range on a continuous scale with each outcome.

Statistical analyses were performed with Stata 14.1 software.

## RESULTS

The study population of UK Biobank included 10,663 individuals with type 2

diabetes and 77,193 control subjects (i.e., without diabetes or prediabetes), who had complete data on all seven risk factors and were free of dementia at baseline (Supplementary Fig. 1). Their mean age was 57.1 (SD 8.2) years, and 49.4% were women (Table 1). Median number of risk factors within target range among individuals with type 2 diabetes was 4 (interquartile range 3; 5) and among control subjects was 4 (4; 5).

#### UK Biobank: Incident Dementia

After a mean follow-up of 9.0 (SD 0.9) years, 147 individuals (1.4%) with type 2 diabetes and 412 control subjects (0.5%) had incident all-cause dementia. Figure 1 and Supplementary Table 2 show the incidence rates, absolute rate differences, and adjusted HRs for incident dementia for individuals with type 2 diabetes compared with control subjects and according to the number of risk factors within target range. Compared with control subjects, individuals with type 2 diabetes had a higher incidence of dementia (HR 1.88 [95% CI 1.55; 2.27]). The risk of dementia was progressively lower in individuals with type 2 diabetes who had a higher number of risk factors within target range compared with control subjects. Among individuals with type 2 diabetes who had five to seven risk factors within target range, the risk of dementia was not statistically significantly different from that in control subjects (HR 1.32 [0.89; 1.95]).

#### UK Biobank: Domain-Specific Cognitive Performance and Structural Brain Abnormalities

Individuals with type 2 diabetes, compared with control subjects, had worse scores on processing speed ( $\beta$  per SD:  $-0.11$  [95% CI  $-0.13$ ;  $-0.09$ ]), but not on memory ( $\beta$  per SD:  $0.03$  [0.01; 0.05]), and higher white matter hyperintensity volume ( $\beta$ :  $0.16$  [0.09; 0.22] log-transformed mL) and lower total brain parenchyma volume ( $\beta$ :  $-5$  [ $-7$ ;  $-3$ ] mL). The difference in processing speed, white matter hyperintensity volume, and total brain parenchyma volume was progressively smaller for a higher number of risk factors within target range among individuals with type 2 diabetes compared with control subjects (Fig. 2). Among individuals with type 2 diabetes

who had five to seven risk factors within target range, compared with control subjects, the  $\beta$  for processing speed (per SD) was  $-0.08$  (95% CI  $-0.11$ ;  $-0.04$ ), and there was no statistically significantly higher prevalence of structural brain abnormalities (Fig. 2).

#### The Maastricht Study: Domain-Specific Cognitive Performance and Structural Brain Abnormalities

The study population of the Maastricht Study included 1,327 individuals with type 2 diabetes and 3,732 control subjects (Supplementary Fig. 1). Their mean age was 59.3 (SD 8.6) years, and 51.2% were women (Supplementary Table 3). Individuals with type 2 diabetes had worse scores than control subjects on processing speed ( $\beta$  per SD:  $-0.16$  [95% CI  $-0.21$ ;  $-0.12$ ]), executive function ( $\beta$  per SD:  $-0.15$  [ $-0.19$ ;  $-0.10$ ]), and memory ( $\beta$  per SD:  $-0.17$  [ $-0.22$ ;  $-0.11$ ]), and higher white matter hyperintensity volume ( $\beta$ :  $0.40$  [0.29; 0.51] log-transformed mL), lower total brain parenchyma volume ( $\beta$ :  $-13$  [ $-16$ ;  $-11$ ] mL), and a higher prevalence of lacunar infarcts (OR 1.73 [1.18; 2.46]). As in UK Biobank, differences in processing speed and executive function, but not memory, and structural brain abnormalities were progressively smaller for a higher number of risk factors within target range among individuals with type 2 diabetes compared with control subjects (Fig. 3).

#### Additional Analyses

Additional analyses were done in both UK Biobank and the Maastricht Study. There were no consistent interactions with age or sex over the outcomes and across both studies (Supplementary Table 4). Analysis with different cutoff values for glycated hemoglobin, office blood pressure, and BMI, and with 24-h ambulatory blood pressure instead of office blood pressure provided results that were consistent with the main analysis (Supplementary Tables 5–7). After additional adjustment for diabetes duration, use of renin-angiotensin-aldosterone system inhibitors, and estimated glomerular filtration rate, after considering LDL cholesterol as an additional risk factor and after excluding glycated hemoglobin, BMI, or physical activity as risk factors, results were qualitatively similar (Supplementary Tables 5–7). Results were similar with control

subjects defined as individuals without diabetes and prediabetes who had four risk factors within target range and with control subjects defined as individuals without diabetes, including individuals with prediabetes in the control group (Supplementary Tables 5–7). Results on incident dementia did not change after accounting for death as a competing risk (Supplementary Table 5) or after the consecutive exclusion of the first 5 years of follow-up (Supplementary Fig. 2). Of the individual risk factors among individuals with type 2 diabetes, a low glycated hemoglobin, being a non-smoker, and absence of albuminuria were most strongly associated with most of the outcomes in both cohorts (Supplementary Table 8). In UK Biobank, among individuals with type 2 diabetes, a higher number of risk factors within target range was associated with a lower risk of dementia (HR per additional risk factor within target range  $0.80$  [95% CI  $0.70$ ;  $0.91$ ]), higher scores on processing speed ( $\beta$ :  $0.03$  [0.01; 0.05] SD per additional risk factor within target range), lower white matter hyperintensity volume ( $\beta$ :  $-0.09$  [ $-0.14$ ;  $-0.04$ ] log-transformed mL per additional risk factor within target range), and higher total brain parenchyma volume ( $\beta$ :  $2$  [0; 3] mL per additional risk factor within target range) (Supplementary Table 9). Similar associations were found in the Maastricht Study (Supplementary Table 9).

#### CONCLUSIONS

In this analysis based on 87,856 individuals from UK Biobank, the excess risk of dementia was progressively lower in individuals with type 2 diabetes who had a higher number of risk factors within target range compared with control subjects without diabetes. In addition, differences in domain-specific cognitive performance and prevalence of structural brain abnormalities were progressively smaller for a higher number of risk factors within target range among individuals with type 2 diabetes compared with control subjects without diabetes. Results on domain-specific cognitive performance and structural brain abnormalities were replicated among 5,059 individuals from the Maastricht Study. We did not observe consistent interactions with age and sex over the outcomes and across both studies.

**Table 1—UK Biobank: characteristics of control subjects and individuals with type 2 diabetes**

	Control subjects*	Overall	Individuals with type 2 diabetes with complete data on all risk factors				
			Risk factors within target range				
			0 to 2	3	4	5 to 7	
Participants, n (%)	77,193 (100)	10,663 (100)	1,875 (17.6)	2,868 (26.9)	3,251 (30.5)	2,669 (25.0)	
Age, years	56.7 (8.2)	59.7 (7.1)	58.7 (7.1)	59.4 (7.2)	60.1 (7.0)	60.2 (7.1)	
Female sex, n (%)	36,352 (47.1)	7,078 (66.4)	498 (26.6)	818 (28.5)	1,147 (35.3)	1,122 (42.0)	
Education level†							
Low, n (%)	51,687 (67.0)	7,897 (74.1)	1,444 (77.0)	2,167 (75.6)	2,390 (73.5)	1,896 (71.0)	
High, n (%)	25,506 (33.0)	2,766 (25.9)	431 (23.0)	701 (24.4)	861 (26.5)	773 (29.0)	
Prior cardiovascular disease, n (%)	4,507 (5.9)	1,941 (18.2)	409 (21.9)	552 (19.3)	569 (17.5)	411 (15.4)	
Duration of diabetes, years	—	4.0 (0.0; 8.0)	5.0 (2.0; 11.0)	4.0 (1.0; 9.0)	3.0 (0.0; 8.0)	2.0 (0.0; 6.0)	
Glycated hemoglobin, mmol/mol	35.3 (4.2)	52.2 (15.3)	62.9 (16.4)	55.8 (15.6)	49.8 (13.6)	43.9 (9.2)	
Glycated hemoglobin, %	5.4 (0.4)	7.0 (1.4)	7.9 (1.5)	7.3 (1.4)	6.7 (1.2)	6.2 (0.8)	
Glycated hemoglobin <53 mmol/mol (<7%), n (%)	77,118 (99.9)	6,558 (61.5)	417 (22.2)	1,373 (47.9)	2,290 (70.4)	2,478 (92.8)	
Nonsmokers, n (%)	67,968 (88.1)	9,474 (88.9)	1,316 (70.2)	2,484 (86.6)	3,057 (94.0)	2,617 (98.1)	
BMI, kg/m <sup>2</sup>	27.9 (4.9)	31.6 (18.3)	33.5 (6.0)	32.5 (5.4)	31.5 (5.3)	29.4 (5.7)	
BMI ≥20 and <25 kg/m <sup>2</sup> , n (%)	20,589 (26.7)	990 (9.3)	29 (1.6)	88 (3.1)	209 (6.4)	664 (24.9)	
Systolic blood pressure, mmHg	141.0 (19.9)	143.6 (18.3)	147.4 (17.0)	145.2 (17.6)	144.5 (17.8)	137.9 (19.4)	
Diastolic blood pressure, mmHg	84.3 (10.9)	83.0 (10.3)	85.6 (10.0)	84.3 (10.1)	83.1 (10.0)	79.4 (10.2)	
Systolic <130 and diastolic <80 mmHg, n (%)	17,247 (22.3)	1,792 (16.8)	81 (4.3)	287 (10.0)	431 (13.3)	993 (37.2)	
No albuminuria, n (%)	60,519 (78.4)	6,245 (58.6)	415 (22.1)	1,289 (44.9)	2,281 (70.2)	2,435 (91.2)	
Estimated glomerular filtration rate, mL/min	87.6 (14.8)	83.8 (18.0)	82.9 (20.2)	83.0 (19.1)	83.9 (16.9)	85.0 (16.2)	
LDL cholesterol, mmol/L	3.6 (0.9)	2.9 (0.9)	2.9 (0.9)	2.9 (0.9)	2.9 (0.9)	2.9 (0.9)	
Renin-angiotensin-aldosterone system inhibitors, n (%)	9,411 (12.2)	4,761 (44.7)	938 (50.0)	1,359 (47.4)	1,458 (44.9)	1,006 (37.7)	
Moderate-to-vigorous physical activity, min/week	200 (840; 2,120)	540 (80; 1,680)	0 (0; 360)	280 (0; 1,280)	720 (240; 1,840)	1,080 (448; 2,180)	
Moderate-to-vigorous physical activity ≥150 min/week, n (%)	60,328 (78.2)	7,409 (69.5)	594 (31.7)	1,691 (59.0)	2,620 (80.6)	2,504 (93.8)	
Dietary habits at optimal level‡, n (%)	40,128 (52.0)	6,245 (58.6)	411 (21.9)	1,392 (48.5)	2,116 (65.1)	2,326 (87.2)	
Incident dementia, n (%)	412 (0.5)	147 (1.4)	30 (1.6)	38 (1.7)	42 (1.3)	27 (1.0)	
Domain-specific cognitive performances§							
Processing speed	0.01 (1.0)	-0.18 (1.1)	-0.21 (1.1)	-0.17 (1.1)	-0.18 (1.0)	-0.17 (1.1)	
Memory	-0.02 (1.0)	-0.02 (1.0)	0.00 (1.0)	0.01 (1.0)	-0.03 (1.0)	-0.05 (1.0)	

Continued on p. 2498



**Table 1—Continued**

	Control subjects*	Risk factors within target range				
		Overall	0 to 2	3	4	5 to 7
Structural brain abnormalities						
White matter hyperintensity volume, mL	3.0 (1.6; 6.2)	4.6 (2.5; 8.5)	4.9 (3.0; 9.9)	5.2 (2.8; 10.0)	4.7 (2.5; 8.3)	3.6 (1.9; 8.4)
Total brain parenchyma volume, mL	1,169 (113)	1,150 (107)	1,146 (103)	1,146 (111)	1,167 (107)	1,136 (104)

Data are means (SD) or median (interquartile range), unless indicated otherwise. *P* < 0.05 for all comparisons between control subjects and individuals with type 2 diabetes according to the number of risk factors within target range. \*Control subjects were defined as individuals without diabetes or prediabetes. †Education level was classified into low (no college or university degree level education) or high (college or university degree education). ‡Dietary habits at optimal level was defined as a score ≥3 on a four-item healthy diet score as defined by the American Heart Association (30), with 1 point given for the following items: 1) ≥2 servings of fruit or vegetables per day; 2) ≥2 servings of fish per week; 3) ≥15 slices of bread or bowls of cereal per week; and 4) never, rarely, or sometimes adding salt to food. §Data available in a subsample of 87,075 individuals. ¶Data available in a subsample of 6,004 individuals.

We are not aware of other observational studies that have investigated the association between multiple risk factors and the risk of cognitive dysfunction or structural brain abnormalities in type 2 diabetes. Additionally, randomized trials investigating the effect of multifactorial risk factor intervention in individuals with diabetes with cognitive decline or structural brain abnormalities as outcomes are scarce. In accordance with our study findings, the 2-year Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) multidomain lifestyle intervention (diet, exercise, cognition, and vascular risk management) trial that included 1,260 individuals, 12.7% of whom had diabetes, demonstrated beneficial effects on cognitive function with consistent results among individuals with and without high baseline fasting glucose levels (22). Additionally, the Look Action for Health in Diabetes (Look AHEAD) trial was a multisite randomized clinical trial done in the U.S. that included 5,145 individuals with type 2 diabetes (23). An intensive lifestyle intervention of weight loss and exercise compared with the control intervention (regular diabetes support and education) had beneficial effects on white matter hyperintensities (24) and ventricle volume (a measure of total brain atrophy) (24), although no effect was found on cognitive function (25). Another trial that included 183 individuals with type 2 diabetes identified no effect of an intensive multifactorial intervention (diet, physical activity, smoking, and strict regulation of glycated hemoglobin, blood pressure, and cholesterol) compared with the control intervention on cognitive function (26). Other trials evaluated the effect of targeting isolated risk factors in type 2 diabetes such as glycated hemoglobin and blood pressure. These studies have shown beneficial effects on some structural brain abnormalities, including white matter hyperintensity volume (27) or total brain parenchyma volume (28,29), but mostly no effects on cognitive function (30–34).

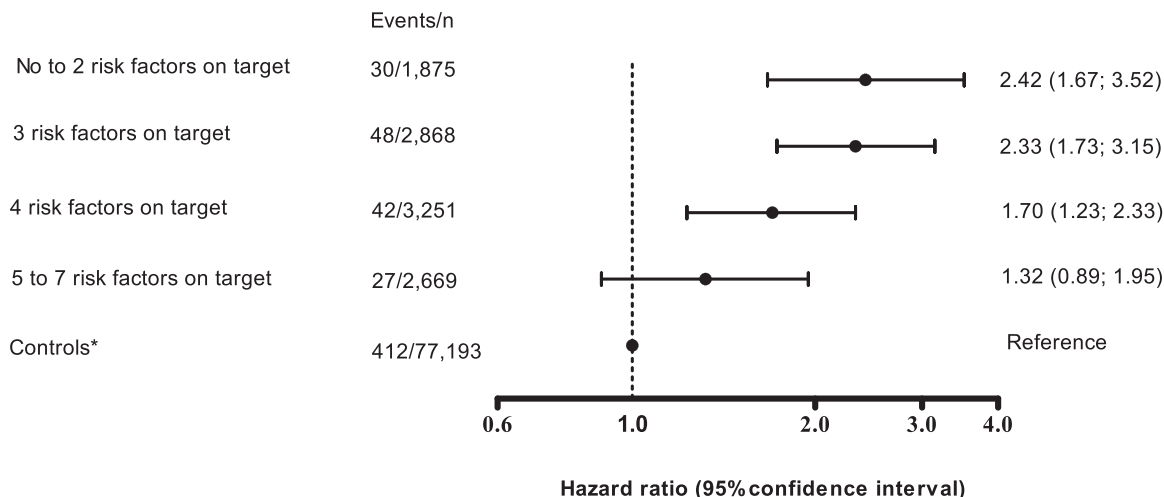
Our findings are biologically plausible. The pathophysiology of type 2 diabetes-related dementia is likely determined by multiple etiologies, including large-vessel disease, microvascular dysfunction, and neurodegeneration. Given the multifactorial nature of dementia in diabetes, it has been suggested (35) that interventions

targeting several risk factors and mechanisms simultaneously may be required for optimal preventive effects. The seven selected risk factors (smoking, elevated levels of glycated hemoglobin, hypertension, obesity, albuminuria, physical inactivity, and unhealthy diet) have each been associated with one or more of these etiologies (36).

A part of the worse scores on domain-specific cognitive performance and the higher prevalence of structural brain abnormalities associated with diabetes remained unexplained after taking into account the number of risk factors within target range in UK Biobank and the Maastricht Study. This remaining association may potentially be due to risk factors that we did not take into account (e.g., diabetes-related neuropsychiatric symptoms [37] and atrial fibrillation [37]). In addition, the effect of risk factor control in diabetes early in life (prior to midlife before inception of the present cohort studies) may impact the risk of dementia.

Results in our study were consistent for all outcomes, except memory. In UK Biobank, individuals with type 2 diabetes did not have worse scores on memory compared with control subjects. In the Maastricht Study, individuals with type 2 diabetes had worse scores on memory compared with control subjects, but lower scores were not related to the number of risk factors within target range. The interpretation of memory tests is complex. The cognitive domain memory includes various subdomains (e.g., verbal and nonverbal, short- and long-term, and declarative and nondeclarative memory), and the effect of diabetes might differ according to which subdomain is tested. UK Biobank and the Maastricht Study both had a single memory test, and these tests evaluated different subdomains (i.e., visuospatial working memory in UK Biobank and long-term verbal-declarative memory in the Maastricht Study, respectively). This makes it difficult to compare the results of both cohorts. Previous studies that evaluated the association between diabetes and the selected risk factors on memory also used different tests and showed inconsistent results (38). Further study with more extensive batteries of neuropsychological tests is needed to better understand the effect of diabetes on memory.

**Incident dementia in relation to risk factor control**

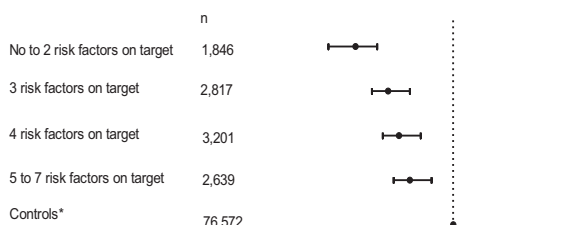


**Figure 1**—UK Biobank: adjusted HRs for incident dementia according to the number of risk factors within target range among individuals with type 2 diabetes compared with control subjects. The following seven risk factors were considered with cutoff values based on recommendations in current clinical guidelines: glycated hemoglobin level (cutoff value, <53 mmol/mol [ $<7\%$ ]), systolic and diastolic blood pressure (cutoff value, <130 mmHg for systolic blood pressure and <80 mmHg for diastolic blood pressure), BMI (cutoff value,  $\geq 20$  and <25 kg/m<sup>2</sup>), smoking (being a nonsmoker), albuminuria (absence of micro- or macroalbuminuria), physical activity (cutoff value,  $\geq 150$  min/week moderate-to-vigorous physical activity), and dietary habits (optimal as defined by the five-item healthy diet score of the American Heart Association [13]). All analyses adjusted for age, sex, and education. \*Control subjects were defined as individuals without diabetes or prediabetes.

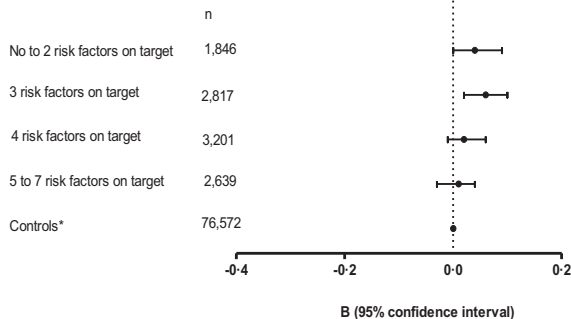
**A**

**Domain-specific cognitive performance in relation to risk factor control**

**1. Processing speed (SD)**



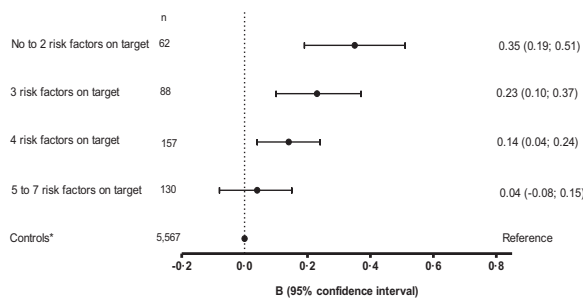
**2. Memory (SD)**



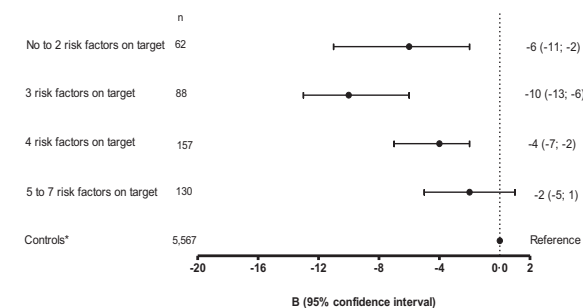
**B**

**Structural brain abnormalities in relation to risk-factor control**

**1. White matter hyperintensity volume (log-transformed mL)**

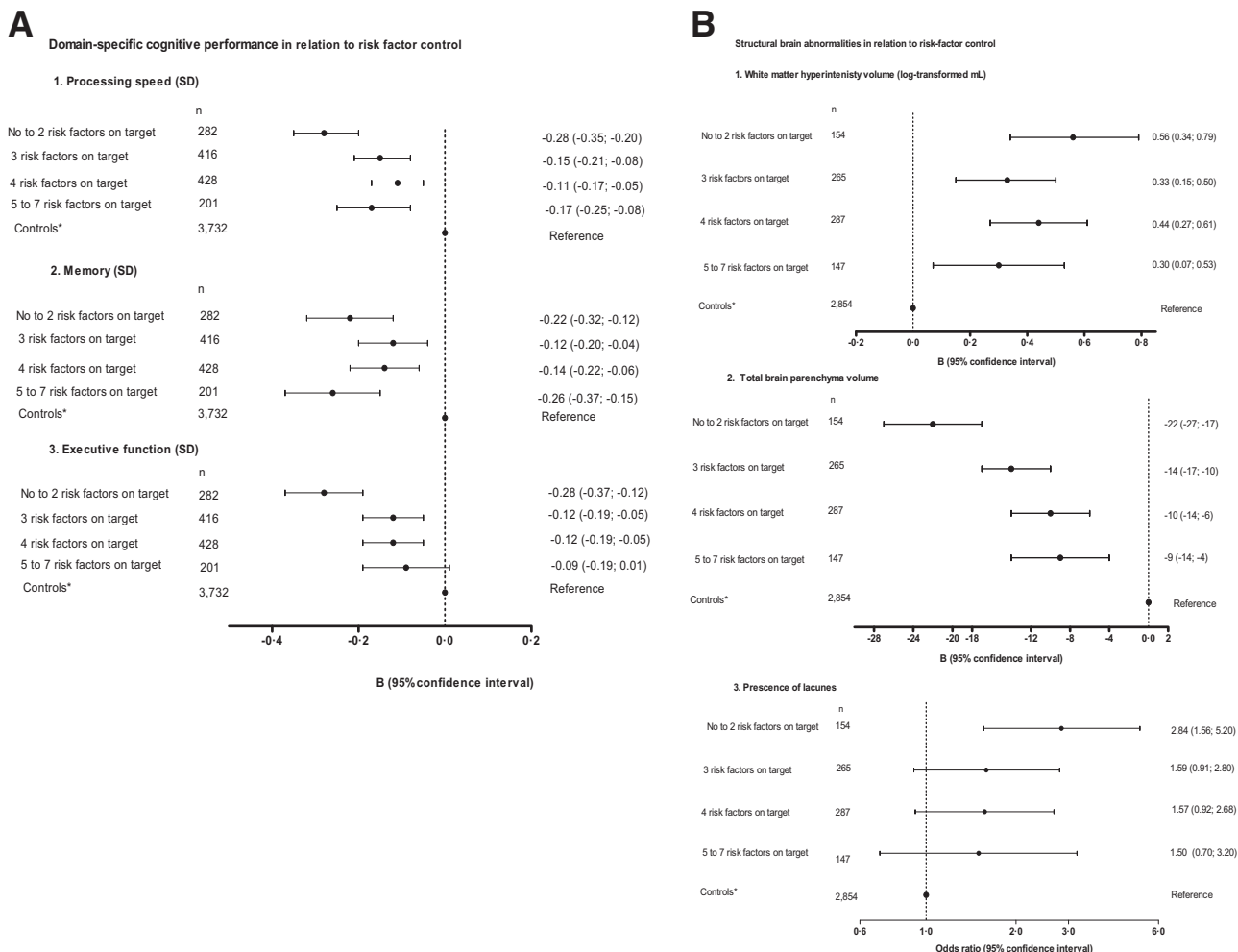


**2. Total brain parenchyma volume (ml)**



**Figure 2**—UK Biobank: adjusted regression coefficients for domain-specific cognitive performance (A) and structural brain abnormalities (B) according to the number of risk factors within target range among individuals with type 2 diabetes compared with control subjects. The following seven risk factors were considered with cutoff values based on recommendations in current clinical guidelines: glycated hemoglobin level (cutoff value, <53 mmol/mol [ $<7\%$ ]), systolic and diastolic blood pressure (cutoff value, <130 mmHg for systolic blood pressure and <80 mmHg for diastolic blood pressure), BMI (cutoff value,  $\geq 20$  and <25 kg/m<sup>2</sup>), smoking (being a nonsmoker), albuminuria (absence of micro- or macroalbuminuria), physical activity (cutoff value,  $\geq 150$  min/week moderate-to-vigorous physical activity), and dietary habits (optimal as defined by the five-item healthy diet score of the American Heart Association [13]). All analyses adjusted for age, sex, and education. Analyses with structural brain abnormalities as the outcome were additionally adjusted for time between baseline examination and MRI examination and intracranial volume. \*Control subjects were defined as individuals without diabetes or prediabetes.





**Figure 3**—The Maastricht Study: adjusted effect estimates for domain-specific cognitive performance (A) and structural brain abnormalities (B) according to the number of risk factors within target range among individuals with type 2 diabetes compared with control subjects. The following seven risk factors were considered with cutoff values based on recommendations in current clinical guidelines: glycated hemoglobin level (cutoff value, <53 mmol/mol (<7%)), systolic and diastolic blood pressure (cutoff value, <130 mmHg for systolic blood pressure and <80 mmHg for diastolic blood pressure), body mass index (cutoff value,  $\geq 20$  and <25 kg/m<sup>2</sup>), smoking (being a nonsmoker), albuminuria (absence of micro- or macroalbuminuria), physical activity (cutoff value,  $\geq 150$  min/week moderate-to-vigorous physical activity), and dietary habits (optimal as defined by the five-item healthy diet score of the American Heart Association [13]). All analyses adjusted for age, sex, and education. Analyses with structural brain abnormalities as the outcome were additionally adjusted for time between baseline examination and MRI examination, and analyses with brain volumes as the outcome were additionally adjusted for intracranial volume. \*Control subjects were defined as individuals without diabetes or prediabetes.

In addition to previous studies that showed multifactorial risk factor modification might reduce the excess risk of dementia in the general population (39,40), the current study suggests that such an approach also might potentially reduce the excess risk of dementia in type 2 diabetes. This provides important evidence to promote current multifactor risk factor treatment strategies in diabetes and to encourage adoption of healthy habits. Our findings suggest that treatment-recommended levels of glycated hemoglobin, being a non-smoker, and absence of albuminuria are particularly important targets of the

selected risk profile to prevent cognitive decline.

Key strengths of this study include the large sample size, which enabled study of the combination of risk factors among individuals with type 2 diabetes compared with control subjects. Furthermore, data were included on domain-cognitive specific performance and MRI-defined structural brain abnormalities, findings were replicated in an independent cohort, and multiple sensitivity analyses were done to evaluate potential bias.

This study has several limitations. First, the observational design precludes causal conclusions and a complete

comparison of the effect of treating risk factors, because some individuals may have had a risk factor within target range without treatment. Second, the analyses on domain-specific cognitive performance and structural brain abnormalities were based on cross-sectional data. Third, not all individual categories of the number of risk factors within target range could be examined due to low numbers in some categories. Fourth, given the long preclinical phase of dementia, our mean follow-up time of 9.0 years is still relatively short. Nevertheless, our results were unaffected by excluding the first 5 years of follow-up.

Fifth, both study populations consisted mostly of middle-aged, Caucasian individuals. The results may therefore not apply to other age- or ethnic groups.

In conclusion, the current study shows that excess risk of dementia was progressively lower in individuals with type 2 diabetes who had a higher number of risk factors within target range compared with control subjects without diabetes.

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**Author Contributions.** A.C.E.v.G., C.D.A.S., A.S.-M., and T.T.v.S. developed the statistical analysis. A.C.E.v.G. and T.T.v.S. drafted the manuscript. C.D.A.S., M.P.J.v.B., F.R.J.V., A.K., A.A.K., S.K., M.M.J.v.G., A.W., S.J.P.M.E., W.H.B., J.F.J., M.T.S., R.M.A.H., and A.S.-M. critically reviewed the manuscript for important intellectual content. T.T.v.S. generated the idea for the study. T.T.v.S. is the guarantor of this work, and as such, had full access to the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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