## SUPPLEMENTAL MATERIAL

# 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

April C.E. van Gennip, Coen D.A. Stehouwer, Martin P. J. van Boxtel, Frans R.J. Verhey, Annemarie Koster, Abraham A. Kroon, Sebastian Köhler, Marleen M.J. van Greevenbroek, Anke Wesselius, Simone J.P.M. Eussen, Walter H. Backes, Jacobus F. Jansen, Miranda T. Schram, Ronald M.A. Henry, Archana Singh-Manoux, Thomas T. van Sloten

Corresponding author: Thomas T. van Sloten, MD, PhD, Department of Internal Medicine, School for Cardiovascular Diseases CARIM, Maastricht University Medical Centre, P. Debyelaan 25, PO Box 5800, 6202 AZ Maastricht, the Netherlands
Phone +31621214590 | Fax + 31433875006 | Email t.vansloten@maastrichtuniversity.nl

## Content

**Supplemental Table S1. Definition of the seven risk factors with cutoffs according to recommendation in current clinical guidelines**

| Risk factor | On target | Not on target |
|---|---|---|
| Glycated hemoglobin level* | <53 mmol/mol (<7%) | ≥53 mmol/mol (≥7%) |
| Blood pressure† | Systolic <130 mmHg and diastolic <80 mmHg | Systolic ≥130 mmHg and diastolic ≥80 mmHg |
| Body mass index | ≥20 and <25 kg/m$^2$ | <20 and ≥25 kg/m$^2$ |
| Smoking | Being a nonsmoker | Current smoker |
| Albuminuria | Absence of micro- or macroalbuminuria<br><br>UK Biobank: <20 mg/l in spot urine samples(1)<br><br>The Maastricht Study: average urinary albumin excretion of <30 mg/24h in two 24-hour urine collections(1) | Micro- or macroalbuminuria<br><br>UK Biobank: ≥20 mg/l in spot urine samples(1)<br><br>The Maastricht Study: average urinary albumin excretion of ≥30 mg/24h in two 24-hour urine collections(1) |
| Physical activity‡ | ≥150 minutes per week moderate-to-vigorous | <150 minutes per week moderate-to-vigorous |
| Dietary habits§ | UK Biobank: ≥3 on a 4-item healthy diet score as defined by the American Heart Association<br>1) ≥2 servings of fruit or vegetables per day<br>2) ≥2 servings of fish per week<br>3) ≥15 slices of bread or bowls of cereal per week<br>4) never/rarely or sometimes adding salt to food<br><br>The Maastricht Study: ≥4 on a 5-item healthy diet score as defined by the American Heart Association(2)<br>1) ≥2 servings of fruit or vegetables per day<br>2) ≥200 gram of fish per week<br>3) ≥3 servings of whole grains per day<br>4) <1,500 mg sodium per day<br>5) ≤450 kilocalories of sugar-sweetened beverages per week | UK Biobank: <3 on a 4-item healthy diet score as defined by the American Heart Association<br>1) <2 servings of fruit or vegetables per day<br>2) <2 servings of fish per week<br>3) <15 slices of bread or bowls of cereal per week<br>4) usually or always adding salt to food<br><br>The Maastricht Study: <4 on a 5-item healthy diet score as defined by the American Heart Association(2)<br>1) <2 servings of fruit or vegetables per day<br>2) <200 gram of fish per week<br>3) <3 servings of whole grains per day<br>4) ≥1,500 mg sodium per day<br>5) >450 kilocalories of sugar-sweetened beverages per week‖ |

* Glycated hemoglobin levels were measured using standardized methods,(3; 4) † Blood pressure was measured twice in UK Biobank(4) and three times in the Maastricht Study(3) in the sitting position using an Omron 705IT monitor in both studies; the average of the readings was used in the analyses; ‡ Physical activity was assessed using adapted questions from the validated short International Physical Activity Questionnaire (IPAQ) in UK Biobank(5) and using the Community Healthy Activities Model Program for Seniors (CHAMPS) Physical Activity Questionnaire(6) in the Maastricht Study; § Dietary habits were assessed using a food frequency questionnaire in both the UK Biobank(7) and the Maastricht Study(8); ‖ Data not available in UK Biobank.

**Supplemental Table S2. UK Biobank: incidence rates for dementia among controls and individuals with type 2 diabetes according to the number of risk factors within target range**

| | Incident dementia | | | |
|---|---|---|---|---|
| | Events/n | Person-years | Incidence rate* (95%CI) | Absolute rate difference* (95%CI) |
| Controls† | 412/77,193 | 693,106 | 0.62 (0.56; 0.68) | Reference |
| Type 2 diabetes | | | | |
| Total subsample | 147/10,663 | 95,162 | 1.19 (1.00; 1.38) | 0.56 (0.36; 0.77) |
| No to 2 risk factors on target | 30/1,875 | 16,710 | 1.55 (0.99; 2.10) | 0.92 (0.36; 1.48) |
| 3 risk factors on target | 48/2,868 | 25,574 | 1.48 (1.06; 1.90) | 0.86 (0.43; 1.28) |
| 4 risk factors on target | 42/3,251 | 29,042 | 1.07 (0.74; 1.40) | 0.45 (0.12; 0.78) |
| 5 to 7 risk factors on target | 27/2,669 | 23,836 | 0.83 (0.52; 1.14) | 0.20 (-0.11; 0.52) |

* Age-, sex- and education-adjusted incidence rates and absolute rate differences per 1,000 person-years; † Controls were defined as individuals without diabetes or prediabetes. 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, ≥20 and <25 kg/m$^2$), smoking (being a nonsmoker), albuminuria (absence of micro- or macroalbuminuria), physical activity (cutoff value, ≥150 minutes per week moderate-to-vigorous physical activity) and dietary habits (optimal as defined by the 5-item healthy diet -score of the American Heart Association(2)). All analyses adjusted for age, sex and education.
CI, confidence interval.

**Supplemental Table S3. The Maastricht Study: characteristics of controls and individuals with type 2 diabetes**

| | Controls* | Individuals with type 2 diabetes with complete data on all risk factors | | | | |
|---|---|---|---|---|---|---|
| | | Overall | Risk factors within target range | | | |
| | | | 0 to 2 | 3 | 4 | 5 to 7 |
| No. of participants, No (%) | 3,732 (100) | 1,327 (100) | 282 (21.3) | 416 (31.4) | 428 (32.3) | 201 (15.2) |
| Age, years | 58.0 (8.5) | 62.8 (7.7) | 62.4 (7.6) | 63.0 (7.6) | 63.1 (8.0) | 62.4 (7.9) |
| Female sex, No (%) | 2,155 (57.7) | 439 (33.1) | 61 (21.6) | 129 (31.0) | 156 (36.5) | 93 (46.3) |
| Education level† | | | | | | |
| - Low, No (%) | 1,041 (27.9) | 579 (43.6) | 159 (56.4) | 175 (42.1) | 172 (40.2) | 73 (36.3) |
| - Intermediate, No (%) | 1,061 (28.4) | 372 (28.0) | 66 (23.4) | 120 (28.9) | 137 (32.0) | 49 (24.4) |
| - High, No (%) | 1,630 (43.7) | 376 (28.3) | 57 (20.2) | 121 (29.1) | 119 (27.8) | 79 (39.3) |
| Prior cardiovascular disease, No (%) | 449 (12.1) | 348 (26.4) | 106 (37.7) | 109 (26.5) | 99 (23.2) | 34 (17.1) |
| Duration of diabetes, years | - | 4.0 (0.0; 10.0) | 8.0 (3.0; 14.0) | 4.0 (0.0; 10.0) | 3.0 (0.0; 7.0) | 2.0 (0.0; 8.0) |
| Glycated hemoglobin, mmol/mol | 35.3 (3.8) | 50.6 (11.4) | 58.7 (13.4) | 51.7 (11.1) | 46.9 (8.5) | 45.0 (6.7) |
| Glycated hemoglobin, % | 5.4 (0.4) | 6.8 (1.0) | 7.5 (1.2) | 6.9 (1.0) | 6.4 (0.8) | 6.3 (0.6) |
| Glycated hemoglobin <53 mmol/mol (<7%), No (%) | 3,732 (100) | 915 (69.0) | 81 (28.7) | 266 (63.9) | 380 (88.8) | 188 (93.5) |
| Nonsmokers, No (%) | 3,306 (88.6) | 1,144 (86.2) | 191 (67.7) | 361 (86.8) | 397 (92.8) | 195 (97.0) |
| Body mass index, kg/m$^2$ | 25.5 (3.7) | 29.8 (4.8) | 31.7 (4.7) | 30.5 (4.8) | 29.4 (4.3) | 26.5 (4.2) |
| Body mass index ≥20 and <25 kg/m$^2$, No (%) | 1,647 (44.1) | 184 (13.9) | 8 (2.8) | 26 (6.3) | 50 (11.7) | 100 (49.8) |
| Systolic blood pressure, mmHg | 129.8 (16.7) | 141.6 (17.5) | 146.1 (16.0) | 144.5 (16.8) | 141.0 (17.2) | 130.2 (16.6) |
| Diastolic blood pressure, mmHg | 74.7 (9.6) | 77.2 (9.8) | 78.3 (9.5) | 78.5 (9.6) | 77.6 (9.8) | 71.9 (8.9) |
| Systolic <130 and diastolic <80 mmHg, No (%) | 1,822 (48.8) | 286 (21.6) | 17 (6.0) | 44 (10.6) | 101 (23.6) | 124 (61.7) |
| No albuminuria, No (%) | 3,568 (95.6) | 1,080 (81.4) | 136 (48.2) | 240 (81.7) | 407 (95.1) | 197 (98.0) |
| Estimated glomerular filtration rate, ml/min | 82.6 (13.0) | 81.7 (16.2) | 80.1 (18.5) | 81.6 (16.2) | 81.8 (15.3) | 84.2 (14.1) |
| LDL cholesterol, mmol/L | 3.3 (0.9) | 2.4 (0.9) | 2.2 (0.8) | 2.4 (0.9) | 2.5 (0.9) | 2.5 (0.9) |
| Renin-angiotensin-aldosterone system inhibitors, No (%) | 547 (14.7) | 767 (57.6) | 198 (70.2) | 249 (59.9) | 228 (53.3) | 89 (44.3) |
| Moderate-to-vigorous physical activity, minutes/week | 300 (180; 495) | 184 (90; 405) | 60 (0; 135) | 64 (58; 69) | 270 (180; 473) | 360 (225; 540) |
| Moderate-to-vigorous physical activity ≥150 minutes/week, No (%) | 2,926 (78.4) | 798 (60.1) | 56 (19.9) | 202 (48.6) | 344 (80.4) | 196 (97.5) |
| Dietary habits at optimal level‡, No (%) | 806 (21.6) | 159 (12.0) | 2 (0.7) | 9 (2.2) | 33 (7.7) | 49 (24.4) |
| Domain-specific cognitive performance | | | | | | |
| Processing speed, SD | 0.20 (0.72) | -0.24 (0.77) | -0.41 (0.77) | -0.23 (0.76) | -0.18 (0.74) | -0.17 (0.78) |
| Memory, SD | 0.20 (0.90) | -0.33 (0.94) | -0.40 (0.85) | -0.29 (0.95) | -0.28 (0.94) | -0.28 (0.95) |
| Executive function, SD | 0.16 (0.76) | -0.21 (0.82) | -0.37 (0.86) | -0.30 (0.95) | -0.18 (0.80) | -0.11 (0.79) |

**Supplemental Table S3. The Maastricht Study: characteristics of controls and individuals with type 2 diabetes (continued)**

| | Controls* | Individuals with type 2 diabetes with complete data on all risk factors | | | | |
|---|---|---|---|---|---|---|
| | | Overall | Risk factors within target range | | | |
| | | | 0 to 2 | 3 | 4 | 5 to 7 |
| Structural brain abnormalities§ | | | | | | |
| White matter hyperintensity volume, ml | 0.2 (0.1; 0.5) | 0.4 (0.1; 1.2) | 0.4 (0.1; 1.4) | 0.3 (0.1; 1.0) | 0.4 (1.1; 1.5) | 0.3 (0.1; 1.1) |
| Total brain parenchyma volume, ml | 1,148 (110) | 1,114 (107) | 1,107 (104) | 1,113 (105) | 1,123 (117) | 1,110 (96) |
| Presence of lacunar infarcts, No (%) | 79 (2.8) | 61 (7.2) | 16 (10.4) | 17 (6.4) | 20 (7.0) | 8 (5.4) |

Data are means (standard deviation) or median (interquartile range). All p values for comparison between controls and individuals with type 2 diabetes according to the number of risk factors within target range <.05.

* Controls were defined as individuals without diabetes or prediabetes; † Education level was classified into low (none, primary or lower vocational education only), intermediate (intermediate general secondary, intermediate vocational or higher general secondary education) or high (higher vocational education or university level of education); ‡ Dietary habits at optimal level was defined as a score ≥4 on a 5-item healthy diet score as defined by the American Heart Association,(2) with one point given for the following items: 1) ≥2 servings of fruit or vegetables per day; 2) ≥200 grams of fish per week; 3) ≥3 servings of whole grains per day; 4) <1,500 mg sodium per day and 5) ≤450 kilocalories of sugar-sweetened beverages per week; § Data available in a subsample of 3,707 individuals.

LDL, low-density lipoprotein; SD, standard deviation.

**Supplemental Table S4. Interactions with age and sex for the associations of incident dementia, domain-specific cognitive performance and structural brain abnormalities according to the number of risk factors within target range among individuals with type 2 diabetes as compared to controls**

| | Incident dementia | Domain-specific cognitive performance | | | Structural brain abnormalities | | |
|---|---|---|---|---|---|---|---|
| | | Processing speed (SD) | Memory (SD) | Executive function (SD) | White matter hyperintensity (log2-transformed ml) | Total brain parenchyma volume (ml) | Presence of Lacunes |
| | P-values for interaction | | | | | | |
| *UK Biobank* | | | | | | | |
| Interaction with age (continuous) | 0.750 | 0.605 | 0.404 | n/a | 0.737 | 0.353 | n/a |
| Interaction with sex | 0.483 | 0.353 | <0.001* | n/a | 0.283 | 0.066 | n/a |
| *The Maastricht Study* | | | | | | | |
| Interaction with age (continuous) | n/a | 0.357 | 0.115 | 0.348 | 0.891 | 0.003† | 0.078 |
| Interaction with sex | n/a | 0.786 | 0.396 | 0.124 | 0.873 | 0.003‡ | 0.732 |

All analyses adjusted for age, sex and education. Analyses with structural brain abnormalities were additionally adjusted for time between baseline examination and MRI examination, and analyses with brain volumes were additionally adjusted for total intracranial volume.

* Association was stronger in women compared to men; † Association was stronger with increasing age; ‡ Association was stronger in men compared to women.

SD, standard deviation; n/a, not applicable; MRI, Magnetic Resonance Imaging.

**Supplemental Table S5. UK Biobank: adjusted hazard ratios for incident dementia according to the number of risk factors within target range among individuals with type 2 diabetes as compared to controls – results of additional analyses**

| | Incident dementia |
|---|---|
| | Hazard Ratio (95% confidence interval) |
| **Additional adjustment for diabetes duration*** | |
| Controls† | Reference |
| No to 2 risk factors on target | 2.17 (1.49; 3.18) |
| 3 risk factors on target | 2.05 (1.50; 2.81) |
| 4 risk factors on target | 1.63 (1.18; 2.24) |
| 5 to 7 risk factors on target | 1.33 (0.90; 1.96) |
| **Cutoff value for HbA1c, ≥42 and <53 mmol/mol (≥6 and <7%) instead of <53 mmol/mol (<7%)** | |
| Controls† | Reference |
| No to 2 risk factors on target | 2.19 (1.54; 3.11) |
| 3 risk factors on target | 2.30 (1.74; 3.05) |
| 4 risk factors on target | 1.50 (1.07; 2.11) |
| 5 to 7 risk factors on target | 1.50 (0.94; 2.26) |
| **Cutoff value for office blood pressure, systolic <140 mmHg and diastolic <90 mmHg instead of systolic <130 mmHg and diastolic <80 mmHg** | |
| Controls† | Reference |
| No to 2 risk factors on target | 2.27 (1.49; 3.46) |
| 3 risk factors on target | 2.49 (1.83; 3.40) |
| 4 risk factors on target | 1.73 (1.25; 2.39) |
| 5 to 7 risk factors on target | 1.45 (1.04; 2.02) |
| **Cutoff value for body mass index ≤30 kg/m$^2$ instead of ≥20 and <25 kg/m$^2$** | |
| Controls† | Reference |
| No to 2 risk factors on target | 2.91 (1.95; 4.33) |
| 3 risk factors on target | 1.91 (1.33; 2.73) |
| 4 risk factors on target | 2.18 (1.61; 2.94) |
| 5 to 7 risk factors on target | 1.35 (0.98; 1.86) |
| **LDL cholesterol level as additional risk factor, cutoff value <2.5 mmol/L** | |
| Controls† | Reference |
| No to 2 risk factors on target | 2.33 (1.45; 3.74) |
| 3 risk factors on target | 2.20 (1.54; 3.14) |
| 4 risk factors on target | 2.28 (1.71; 3.06) |
| 5 to 8 risk factors on target | 1.47 (1.07; 2.00) |
| **Additional adjustment for use of renin-angiotensin-aldosterone system inhibitors** | |
| Controls† | Reference |
| No to 2 risk factors on target | 2.55 (1.54; 3.30) |
| 3 risk factors on target | 2.18 (1.60; 2.97) |
| 4 risk factors on target | 1.59 (1.15; 2.20) |
| 5 to 7 risk factors on target | 1.25 (0.84; 1.85) |
| **Additional adjustment for estimated glomerular filtration rate** | |
| Controls† | Reference |
| No to 2 risk factors on target | 2.43 (1.67; 3.54) |
| 3 risk factors on target | 2.32 (1.71; 3.15) |
| 4 risk factors on target | 1.76 (1.28; 2.42) |
| 5 to 7 risk factors on target | 1.38 (0.93; 2.03) |

**Supplemental Table 5. UK Biobank: adjusted hazard ratios for incident dementia according to the number of risk factors within target range among individuals with type 2 diabetes as compared to controls – results of additional analyses (continued)**

| | Incident dementia |
|---|---|
| | Hazard Ratio (95% confidence interval) |
| **Controls defined as individuals without diabetes or prediabetes who had 4 risk factors on target** | |
| Controls | Reference |
| No to 2 risk factors on target | 2.25 (1.52; 3.33) |
| 3 risk factors on target | 2.16 (1.56; 3.00) |
| 4 risk factors on target | 1.57 (1.11; 2.21) |
| 5 to 7 risk factors on target | 1.22 (0.81; 1.84) |
| **Controls defined as individuals without diabetes, including individuals with prediabetes in the control group** | |
| Controls | Reference |
| No to 2 risk factors on target | 2.46 (1.69; 3.56) |
| 3 risk factors on target | 2.36 (1.75; 3.19) |
| 4 risk factors on target | 1.72 (1.25; 2.36) |
| 5 to 7 risk factors on target | 1.33 (0.90; 1.97) |
| **Accounting for death as a competing risk using Fine and Gray proportional subdistributional hazard regression** | |
| Controls† | Reference |
| No to 2 risk factors on target | 2.41 (1.66; 3.50) |
| 3 risk factors on target | 2.32 (1.71; 3.14) |
| 4 risk factors on target | 1.69 (1.23; 2.33) |
| 5 to 7 risk factors on target | 1.32 (0.89; 1.95) |
| **Excluding glycated hemoglobin as a risk factor** | |
| Controls† | Reference |
| No to 2 risk factors on target | 2.55 (1.92; 3.37) |
| 3 risk factors on target | 1.79 (1.34; 2.40) |
| 4 risk factors on target | 1.36 (0.94; 1.98) |
| 5 or 6 risk factors on target | 1.75 (0.93; 3.27) |
| **Excluding body mass index as a risk factor** | |
| Controls† | Reference |
| No to 2 risk factors on target | 2.47 (1.72; 3.54) |
| 3 risk factors on target | 2.40 (1.80; 3.21) |
| 4 risk factors on target | 1.64 (1.20; 2.26) |
| 5 or 6 risk factors on target | 1.17 (0.75; 1.82) |
| **Excluding physical activity as a risk factor** | |
| Controls† | Reference |
| No to 2 risk factors on target | 2.21 (1.66; 2.93) |
| 3 risk factors on target | 1.05 (1.56; 2.71) |
| 4 risk factors on target | 1.44 (0.98; 2.11) |
| 5 or 6 risk factors on target | 1.09 (0.49; 2.44) |

All analyses adjusted for age, sex and education.

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, ≥20 and <25 kg/m$^2$), smoking (being a nonsmoker), albuminuria (absence of micro- or macroalbuminuria), physical activity (cutoff value, ≥150 minutes per week moderate-to-vigorous physical activity) and dietary habits (optimal as defined by the 5-item healthy diet score of the American Heart Association(2)).

* Duration of diabetes was centralized around the grand mean (the mean duration among all individuals) for individuals with type 2 diabetes, and set to 0 years for controls; † Controls were defined as individuals without diabetes or prediabetes. LDL, low-density lipoprotein.

**Supplemental Table S6. Adjusted regression coefficients for domain-specific cognitive performance according to the number of risk factors within target range among individuals with type 2 diabetes as compared to controls – results of additional analyses**

| | Processing speed (SD) | Memory (SD) | Executive function (SD) |
|---|---|---|---|
| | B (95% confidence interval) | | |
| **Additional adjustment for diabetes duration*** | | | |
| *UK Biobank* | | | |
| Controls† | Reference | | |
| No to 2 risk factors on target | -0.17 (-0.21; -0.12) | 0.04 (0.00; 0.09) | n/a |
| 3 risk factors on target | -0.11 (-0.15; -0.08) | 0.06 (0.02; 0.10) | n/a |
| 4 risk factors on target | -0.10 (-0.13; -0.06) | 0.03 (-0.01; 0.06) | n/a |
| 5 to 7 risk factors on target | -0.09 (-0.13; -0.05) | 0.01 (-0.03; 0.05) | n/a |
| *The Maastricht Study* | | | |
| Controls† | Reference | | |
| No to 2 risk factors on target | -0.23 (-0.31; -0.15) | -0.20 (-0.31; -0.10) | -0.24 (-0.33; -0.16) |
| 3 risk factors on target | -0.11 (-0.18; -0.05) | -0.10 (-0.19; -0.02) | -0.09 (-0.16; -0.02) |
| 4 risk factors on target | -0.09 (-0.15; -0.03) | -0.13 (-0.21; -0.04) | -0.10 (-0.17; -0.03) |
| 5 to 7 risk factors on target | -0.15 (-0.24; -0.06) | -0.26 (-0.37; -0.14) | -0.07 (-0.17; -0.03) |
| **Cutoff value for HbA1c, ≥42 and <53 mmol/mol (≥6 and <7%) instead of <53 mmol/mol (<7%)** | | | |
| *UK Biobank* | | | |
| Controls† | Reference | | |
| No to 2 risk factors on target | -0.16 (-0.20; -0.12) | 0.04 (0.00; 0.08) | n/a |
| 3 risk factors on target | -0.09 (-0.12; -0.05) | 0.04 (0.00; 0.07) | n/a |
| 4 risk factors on target | -0.10 (-0.14; -0.07) | 0.04 (0.01; 0.07) | n/a |
| 5 to 7 risk factors on target | -0.10 (-0.15; -0.06) | 0.00 (-0.04; 0.04) | n/a |
| *The Maastricht Study* | | | |
| Controls† | Reference | | |
| No to 2 risk factors on target | -0.26 (-0.33; -0.19) | -0.22 (-0.32; -0.13) | -0.25 (-0.33; -0.17) |
| 3 risk factors on target | -0.14 (-0.20; -0.07) | -0.09 (-0.17; -0.01) | -0.14 (-0.21; -0.07) |
| 4 risk factors on target | -0.12 (-0.18; -0.05) | -0.15 (-0.23; -0.06) | -0.11 (-0.18; -0.03) |
| 5 to 7 risk factors on target | -0.17 (-0.27; -0.07) | -0.22 (-0.36; -0.21) | -0.07 (-0.18; 0.04) |

**Supplemental Table S6. Adjusted regression coefficients for domain-specific cognitive performance according to the number of risk factors within target range among individuals with type 2 diabetes as compared to controls – results of additional analyses (continued)**

| | Processing speed (SD) | Memory (SD) | Executive function (SD) |
|---|---|---|---|
| | B (95% confidence interval) | | |
| **Cutoff value for office blood pressure, systolic <140 mmHg and diastolic <90 mmHg instead of systolic <130 mmHg and diastolic <80 mmHg** | | | |
| *UK Biobank* | | | |
| Controls† | Reference | | |
| No to 2 risk factor on target | -0.19 (-0.24; -0.14) | 0.05 (0.00; 0.10) | n/a |
| 3 risk factors on target | -0.12 (-0.16; -0.08) | 0.06 (0.03; 0.10) | n/a |
| 4 risk factors on target | -0.10 (-0.13; -0.06) | 0.02 (-0.01; 0.06) | n/a |
| 5 to 7 risk factors on target | -0.09 (-0.12; -0.05) | 0.01 (-0.02; 0.04) | n/a |
| *The Maastricht Study* | | | |
| Controls† | Reference | | |
| No to 2 risk factors on target | -0.33 (-0.42; -0.24) | -0.23 (-0.35; -0.12) | -0.28 (-0.38; -0.18) |
| 3 risk factors on target | -0.14 (-0.20; -0.07) | -0.16 (-0.25; -0.07) | -0.16 (-0.23; -0.08) |
| 4 risk factors on target | -0.13 (-0.19; -0.06) | -0.08 (-0.16; 0.00) | -0.10 (-0.17; -0.03) |
| 5 to 7 risk factors on target | -0.15 (-0.22; -0.08) | -0.26 (-0.35; -0.17) | -0.12 (-0.20; -0.04) |
| **24-hour ambulatory blood pressure‡ instead of office blood pressure, with a cutoff value for systolic <130 mmHg and diastolic <80 mmHg** | | | |
| *The Maastricht Study* | | | |
| Controls† | Reference | | |
| No to 2 risk factor on target | -0.32 (-0.43; -0.22) | -0.17 (-0.29; -0.05) | -0.30 (-0.41; -0.20) |
| 3 risk factors on target | -0.18 (-0.26; -0.10) | -0.12 (-0.22; -0.03) | -0.13 (-0.21; -0.04) |
| 4 risk factors on target | -0.11 (-0.17; -0.04) | -0.12 (-0.21; -0.03) | -0.11 (-0.19; -0.03) |
| 5 to 7 risk factors on target | -0.15 (-0.21; -0.08) | -0.20 (-0.29; -0.11) | -0.08 (-0.16; 0.00) |

**Supplemental Table S6. Adjusted regression coefficients for domain-specific cognitive performance according to the number of risk factors within target range among individuals with type 2 diabetes as compared to controls – results of additional analyses (continued)**

| | Processing speed (SD) | Memory (SD) | Executive function (SD) |
|---|---|---|---|
| | B (95% confidence interval) | | |
| **Cutoff value for body mass index ≤30 kg/m$^2$ instead of ≥20 and <25 kg/m$^2$** | | | |
| *UK Biobank* | | | |
| Controls† | Reference | | |
| No to 2 risk factor on target | -0.17 (-0.23; -0.12) | 0.06 (0.01; 0.12) | n/a |
| 3 risk factors on target | -0.12 (-0.16; -0.08) | 0.04 (0.00; 0.08) | n/a |
| 4 risk factors on target | -0.11 (-0.15; -0.08) | 0.05 (0.01; 0.08) | n/a |
| 5 to 7 risk factors on target | -0.08 (-0.11; -0.05) | 0.00 (-0.03; 0.04) | n/a |
| *The Maastricht Study* | | | |
| Controls† | Reference | | |
| No to 2 risk factors on target | -0.32 (-0.41; -0.23) | -0.17 (-0.29; -0.06) | -0.28 (-0.38; -0.18) |
| 3 risk factors on target | -0.17 (-0.24; -0.10) | -0.20 (-0.30; -0.10) | -0.17 (-0.25; -0.08) |
| 4 risk factors on target | -0.11 (-0.18; -0.05) | -0.11 (-0.19; -0.03) | -0.10 (-0.18; -0.03) |
| 5 to 7 risk factors on target | -0.14 (-0.20; -0.07) | -0.20 (-0.28; -0.12) | -0.11 (-0.19; -0.04) |
| **LDL cholesterol level as additional risk factor, cutoff value <2.5 mmol/L** | | | |
| *UK Biobank* | | | |
| Controls† | Reference | | |
| No to 2 risk factor on target | -0.18 (-0.23; -0.12) | 0.05 (0.00; 0.10) | n/a |
| 3 risk factors on target | -0.14 (-0.18; -0.10) | 0.04 (0.00; 0.08) | n/a |
| 4 risk factors on target | -0.09 (-0.12; -0.05) | 0.04 (0.01; 0.08) | n/a |
| 5 to 8 risk factors on target | -0.10 (-0.13; -0.07) | 0.01 (-0.02; 0.04) | n/a |
| *The Maastricht Study* | | | |
| Controls† | Reference | | |
| No to 2 risk factors on target | -0.25 (-0.36; -0.15) | -0.21 (-0.34; -0.07) | -0.35 (-0.37; -0.23) |
| 3 risk factors on target | -0.17 (-0.25; -0.10) | -0.14 (-0.24; -0.05) | -0.13 (-0.22; -0.05) |
| 4 risk factors on target | -0.17 (-0.23; -0.10) | -0.17 (-0.25; -0.09) | -0.14 (-0.21; -0.07) |
| 5 to 8 risk factors on target | -0.13 (-0.19; -0.07) | -0.17 (-0.25; -0.09) | -0.10 (-0.17; -0.03) |

**Supplemental Table S6. Adjusted regression coefficients for domain-specific cognitive performance outcomes according to the number of risk factors within target range among individuals with type 2 diabetes as compared to controls – results of additional analyses (continued)**

| | Processing speed (SD) | Memory (SD) | Executive function (SD) |
|---|---|---|---|
| | B (95% confidence interval) | | |
| **Additional adjustment for use of renin-angiotensin-aldosterone system inhibitors** | | | |
| *UK Biobank* | | | |
| Controls† | Reference | | |
| No to 2 risk factor on target | -0.16 (-0.21; -0.12) | 0.04 (0.00; 0.09) | n/a |
| 3 risk factors on target | -0.10 (-0.14; -0.06) | 0.06 (0.02; 0.10) | n/a |
| 4 risk factors on target | -0.08 (-0.11; -0.04) | 0.02 (-0.01; 0.06) | n/a |
| 5 to 7 risk factors on target | -0.06 (-0.10; -0.02) | 0.01 (-0.03; 0.05) | n/a |
| *The Maastricht Study* | | | |
| Controls† | Reference | | |
| No to 2 risk factors on target | -0.26 (-0.34; -0.18) | -0.21 (-0.32; -0.11) | -0.28 (-0.37; -0.19) |
| 3 risk factors on target | -0.13 (-0.20; -0.06) | -0.12 (-0.20; -0.03) | -0.12 (-0.19; -0.04) |
| 4 risk factors on target | -0.10 (-0.16; -0.03) | -0.14 (-0.22; -0.05) | -0.12 (-0.19; -0.04) |
| 5 to 7 risk factors on target | -0.16 (-0.25; -0.07) | -0.26 (-0.37; -0.14) | -0.09 (-0.19; 0.01) |
| **Additional adjustment for estimated glomerular filtration rate** | | | |
| *UK Biobank* | | | |
| Controls† | Reference | | |
| No to 2 risk factor on target | -0.19 (-0.24; -0.15) | 0.04 (-0.01; 0.08) | n/a |
| 3 risk factors on target | -0.12 (-0.16; -0.08) | 0.06 (0.02; 0.10) | n/a |
| 4 risk factors on target | -0.09 (-0.13; -0.06) | 0.02 (-0.01; 0.06) | n/a |
| 5 to 7 risk factors on target | -0.08 (-0.11; -0.04) | 0.00 (-0.04; 0.04) | n/a |
| *The Maastricht Study* | | | |
| Controls† | Reference | | |
| No to 2 risk factors on target | -0.28 (-0.35; -0.20) | -0.22 (-0.32; -0.12) | -0.28 (-0.37; -0.19) |
| 3 risk factors on target | -0.14 (-0.21; -0.08) | -0.12 (-0.20; -0.03) | -0.12 (-0.19; -0.05) |
| 4 risk factors on target | -0.11 (-0.17; -0.04) | -0.14 (-0.22; -0.05) | -0.11 (-0.19; -0.04) |
| 5 to 7 risk factors on target | -0.16 (-0.25; -0.07) | -0.26 (-0.37; -0.14) | -0.09 (-0.19; 0.01) |

**Supplemental Table S6. Adjusted regression coefficients for domain-specific cognitive performance outcomes according to the number of risk factors within target range among individuals with type 2 diabetes as compared to controls – results of additional analyses (continued)**

| | Processing speed (SD) | Memory (SD) | Executive function (SD) |
|---|---|---|---|
| | B (95% confidence interval) | | |
| **Controls defined as individuals without diabetes and prediabetes who had 4 risk factors on target** | | | |
| *UK Biobank* | | | |
| Controls | Reference | | |
| No to 2 risk factor on target | -0.18 (-0.23; -0.14) | 0.05 (0.00; 0.09) | n/a |
| 3 risk factors on target | -0.12 (-0.16; -0.08) | 0.06 (0.03; 0.10) | n/a |
| 4 risk factors on target | -0.10 (-0.13; -0.06) | 0.03 (-0.01; 0.06) | n/a |
| 5 to 7 risk factors on target | -0.07 (-0.11; -0.03) | 0.01 (-0.03; 0.05) | n/a |
| *The Maastricht Study* | | | |
| Controls | Reference | | |
| No to 2 risk factors on target | -0.31 (-0.40; -0.23) | -0.21 (-0.32; -0.10) | -0.33 (-0.42; -0.23) |
| 3 risk factors on target | -0.18 (-0.25; -0.10) | -0.10 (-0.20; -0.01) | -0.15 (-0.23; -0.07) |
| 4 risk factors on target | -0.14 (-0.21; -0.07) | -0.12 (-0.22; -0.03) | -0.14 (-0.23; -0.06) |
| 5 to 7 risk factors on target | -0.20 (-0.29; -0.10) | -0.24 (-0.37; -0.12) | -0.11 (-0.22; 0.00) |
| **Controls defined as individuals without diabetes, including individuals with prediabetes in the control group** | | | |
| *UK Biobank* | | | |
| Controls | Reference | | |
| No to 2 risk factors on target | -0.18 (-0.23; -0.14) | 0.04 (0.00; 0.09) | n/a |
| 3 risk factors on target | -0.12 (-0.15; -0.08) | 0.06 (0.02; 0.10) | n/a |
| 4 risk factors on target | -0.10 (-0.13; -0.06) | 0.02 (-0.01; 0.06) | n/a |
| 5 to 7 risk factors on target | -0.08 (-0.11; -0.04) | 0.01 (-0.03; 0.04) | n/a |
| *The Maastricht Study* | | | |
| Controls | Reference | | |
| No to 2 risk factors on target | -0.26 (09,34; -0.18) | -0.21 (-0.31; -0.11) | -0.27 (-0.36; -0.19) |
| 3 risk factors on target | -0.13 (-0.19; -0.07) | -0.11 (-0.19; -0.03) | -0.11 (-0.18; -0.04) |
| 4 risk factors on target | -0.10 (-0.16; -0.03) | -0.13 (-0.21; -0.05) | -0.11 (-0.18; -0.04) |
| 5 to 7 risk factors on target | -0.15 (-0.24; -0.06) | -0.25 (-0.37; -0.14) | -0.08 (-0.18; 0.02) |

**Supplemental Table S6. Adjusted regression coefficients for domain-specific cognitive performance outcomes according to the number of risk factors within target range among individuals with type 2 diabetes as compared to controls – results of additional analyses (continued)**

| | Processing speed (SD) | Memory (SD) | Executive function (SD) |
|---|---|---|---|
| | B (95% confidence interval) | | |
| **Excluding glycated hemoglobin as a risk factor** | | | |
| *UK Biobank* | | | |
| Controls† | Reference | | |
| No to 2 risk factors on target | -0.16 (-0.19; -0.12) | 0.05 (0.01; 0.08) | n/a |
| 3 risk factors on target | -0.09 (-0.12; -0.06) | 0.03 (0.00; 0.06) | n/a |
| 4 risk factors on target | -0.09 (-0.13; -0.06) | 0.03 (0.00; 0.07) | n/a |
| 5 or 6 risk factors on target | -0.11 (-0.18; -0.04) | -0.03 (-0.10; 0.04) | n/a |
| *The Maastricht Study* | | | |
| Controls† | Reference | | |
| No to 2 risk factors on target | -0.20 (-0.26; -0.14) | -0.20 (-0.31; -0.10) | -0.21 (-0.28; -0.15) |
| 3 risk factors on target | -0.12 (-0.17; -0.06) | -0.10 (-0.19; -0.02) | -0.10 (-0.17; -0.04) |
| 4 risk factors on target | -0.20 (-0.29; -0.11) | -0.13 (-0.21; -0.04) | -0.06 (-0.17; 0.03) |
| 5 or 6 risk factors on target | -0.13 (-0.30; 0.04) | -0.26 (-0.37; -0.14) | -0.19 (-0.38; 0.00) |
| **Excluding body mass index as a risk factor** | | | |
| *UK Biobank* | | | |
| Controls† | Reference | | |
| No to 2 risk factors on target | -0.20 (-0.25; -0.16) | 0.05 (0.00; 0.09) | n/a |
| 3 risk factors on target | -0.11 (-0.15; -0.08) | 0.05 (0.02; 0.09) | n/a |
| 4 risk factors on target | -0.09 (-0.12; -0.05) | 0.03 (0.00; 0.06) | n/a |
| 5 or 6 risk factors on target | -0.07 (-0.11; -0.03) | -0.01 (-0.05; 0.03) | n/a |
| *The Maastricht Study* | | | |
| Controls† | Reference | | |
| No to 2 risk factors on target | -0.29 (-0.37; -0.22) | -0.23 (-0.33; -0.14) | -0.29 (-0.37; -0.20) |
| 3 risk factors on target | -0.13 (-0.20; -0.07) | -0.14 (-0.22; -0.06) | -0.12 (-0.19; -0.05) |
| 4 risk factors on target | -0.10 (-0.16; -0.03) | -0.10 (-0.18; -0.02) | -0.11 (-0.18; -0.04) |
| 5 or 6 risk factors on target | -0.20 (-0.31; -0.09) | -0.33 (-0.47; -0.20) | -0.05 (-0.17; 0.07) |

**Supplemental Table S6. Adjusted regression coefficients for domain-specific cognitive performance outcomes according to the number of risk factors within target range among individuals with type 2 diabetes as compared to controls – results of additional analyses (continued)**

| | Processing speed (SD) | Memory (SD) | Executive function (SD) |
|---|---|---|---|
| | B (95% confidence interval) | | |
| **Excluding physical activity as a risk factor** | | | |
| *UK Biobank* | | | |
| Controls† | Reference | | |
| No to 2 risk factors on target | -0.15 (-0.18; -0.11) | 0.05 (0.02; 0.09) | n/a |
| 3 risk factors on target | -0.11 (-0.14; -0.07) | 0.02 (-0.01; 0.06) | n/a |
| 4 risk factors on target | -0.08 (-0.12; -0.04) | 0.02 (-0.01; 0.06) | n/a |
| 5 or 6 risk factors on target | -0.08 (-0.15; -0.01) | -0.01 (-0.08; 0.06) | n/a |
| *The Maastricht Study* | | | |
| Controls† | Reference | | |
| No to 2 risk factors on target | -0.22 (-0.28; -0.16) | -0.15 (-0.23; -0.07) | -0.19 (-0.27; -0.13) |
| 3 risk factors on target | -0.12 (-0.18; -0.07) | -0.16 (-0.23; -0.09) | -0.11 (-0.17; -0.05) |
| 4 risk factors on target | -0.17 (-0.25; -0.08) | -0.18 (-0.28; -0.07) | -0.14 (-0.23; -0.05) |
| 5 or 6 risk factors on target | -0.08 (-0.27; 0.10) | 0.41 (-0.64; -0.17) | -0.11 (-0.31; 0.10) |

All analyses adjusted for age, sex and education.

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, ≥20 and <25 kg/m$^2$), smoking (being a nonsmoker), albuminuria (absence of micro- or macroalbuminuria), physical activity (cutoff value, ≥150 minutes per week moderate-to-vigorous physical activity) and dietary habits (optimal as defined by the 5-item healthy diet score of the American Heart Association(2)).

* Duration of diabetes was centralized around the grand mean (the mean duration among all individuals) for individuals with type 2 diabetes, and set to 0 years for controls; † Controls were defined as individuals without diabetes or prediabetes; ‡ Data not available in UK Biobank.

SD, standard deviation; n/a, not applicable; LDL, low-density lipoprotein.

**Supplemental Table S7. Adjusted regression coefficients for structural brain abnormalities according to the number of risk factors within target range among individuals with type 2 diabetes as compared to controls – results of additional analyses**

| | White matter hyperintensity volume (log2-transformed ml) | Total brain parenchyma volume (ml) | Presence of lacunes |
|---|---|---|---|
| | B (95%CI) | | Odds Ratio (95%CI) |
| **Additional adjustment for diabetes duration*** | | | |
| *UK Biobank* | | | |
| Controls† | Reference | | |
| No to 2 risk factors on target | 0.37 (0.21; 0.53) | -7 (-11; -2) | n/a |
| 3 risk factors on target | 0.29 (0.15; 0.43) | -11 (-15; -7) | n/a |
| 4 risk factors on target | 0.17 (0.06; 0.28) | -5 (-8; -2) | n/a |
| 5 to 7 risk factors on target | 0.07 (-0.05; 0.19) | -3 (-6; 0) | n/a |
| *The Maastricht Study* | | | |
| Controls† | Reference | | |
| No to 2 risk factors on target | 0.79 (0.53; 1.05) | -25 (-31; -19) | 2.64(1.45; 4.80) |
| 3 risk factors on target | 0.68 (0.48; 0.88) | -22 (-27; -18) | 1.82 (1.05; 3.16) |
| 4 risk factors on target | 0.89 (0.70; 1.08) | -23 (-24; -12) | 2.17 (1.31; 3.62) |
| 5 to 7 risk factors on target | 0.61 (0.35; 0.87) | -18 (-1; -0.7) | 1.77 (0.84; 3.73) |
| **Cutoff value for HbA1c, ≥42 and <53 mmol/mol (≥6 and <7%) instead of <53 mmol/mol (<7%)** | | | |
| *UK Biobank* | | | |
| Controls† | Reference | | |
| No to 2 risk factors on target | 0.33 (0.19; 0.47) | -4 (-8; -1) | n/a |
| 3 risk factors on target | 0.16 (0.04; 0.27) | -7 (-10; -4) | n/a |
| 4 risk factors on target | 0.11 (0.00; 0.21) | -3 (-6; -1) | n/a |
| 5 to 7 risk factors on target | 0.07 (-0.07; 0.21) | -5 (-9; -1) | n/a |
| *The Maastricht Study* | | | |
| Controls† | Reference | | |
| No to 2 risk factors on target | 0.52 (0.31; 0.73) | -20 (-25; -16) | 3.05 (1.78; 5.22) |
| 3 risk factors on target | 0.32 (0.16; 0.49) | -11 (-14; -7) | 1.13 (0.63; 2.03) |
| 4 risk factors on target | 0.48 (0.30; 0.66) | -12 (-16; -8) | 1.50 (0.85; 2.64) |
| 5 to 7 risk factors on target | 0.28 (0.02; 0.54) | -10 (-15; -4) | 1.89 (0.88; 4.07) |

**Supplemental Table S7. Adjusted regression coefficients for structural brain abnormalities according to the number of risk factors within target range among individuals with type 2 diabetes as compared to controls – results of additional analyses (continued)**

| | White matter hyperintensity volume (log2-transformed ml) | Total brain parenchyma volume (ml) | Presence of Lacunes |
|---|---|---|---|
| | B (95%CI) | | Odds Ratio (95%CI) |
| **Cutoff value for office blood pressure, systolic <140 mmHg and diastolic <90 mmHg instead of systolic <130 mmHg and diastolic <80 mmHg** | | | |
| *UK Biobank* | | | |
| Controls† | Reference | | |
| No to 2 risk factor on target | 0.45 (0.25; 0.65) | -5 (-10; 1) | n/a |
| 3 risk factors on target | 0.23 (0.08; 0.37) | -12 (-16; -8) | n/a |
| 4 risk factors on target | 0.11 (0.00; 0.22) | -3 (-6; -1) | n/a |
| 5 to 7 risk factors on target | 0.10 (0.00; 0.19) | -3 (-6; -1) | n/a |
| *The Maastricht Study* | | | |
| Controls† | Reference | | |
| No to 2 risk factors on target | 0.57 (0.31; 0.83) | -24 (-30; -18) | 2.60 (1.33; 5.06) |
| 3 risk factors on target | 0.53 (0.33; 0.72) | -13 (-18; -9) | 1.56 (0.85; 2.85) |
| 4 risk factors on target | 0.33 (0.17; 0.50) | -12 (-16; -8) | 1.83 (1.11; 3.00) |
| 5 to 7 risk factors on target | 0.30 (0.12; 0.49) | -9 (-14; -5) | 1.25 (0.65; 2.42) |
| **24-hour ambulatory blood pressure‡ instead of office blood pressure, with a cutoff value for systolic <130 mmHg and diastolic <80 mmHg** | | | |
| *The Maastricht Study* | | | |
| Controls† | Reference | | |
| No to 2 risk factor on target | 0.53 (0.26; 0.79) | -21 (-27; -16) | 2.89 (1.45; 5.65) |
| 3 risk factors on target | 0.36 (0.15; 0.56) | -17 (-12; -12) | 2.29 (1.29; 4.07) |
| 4 risk factors on target | 0.45 (0.27; 0.64) | -10 (-14; -6) | 1.53 (0.86; 2.74) |
| 5 to 7 risk factors on target | 0.21 (0.12; 0.50) | -10 (-14; -6) | 1.26 (0.65; 2.45) |

**Supplemental Table S7. Adjusted regression coefficients for structural brain abnormalities according to the number of risk factors within target range among individuals with type 2 diabetes as compared to controls – results of additional analyses (continued)**

| | White matter hyperintensity volume (log2-transformed ml) | Total brain parenchyma volume (ml) | Presence of Lacunes |
|---|---|---|---|
| | B (95%CI) | | Odds Ratio (95%CI) |
| **Cutoff value for body mass index ≤30 kg/m$^2$ instead of ≥20 and <25 kg/m$^2$** | | | |
| *UK Biobank* | | | |
| Controls† | Reference | | |
| No to 2 risk factor on target | 0.34 (0.16; 0.52) | -8(-12; -3) | n/a |
| 3 risk factors on target | 0.33 (0.19; 0.48) | -8 (-12; -5) | n/a |
| 4 risk factors on target | 0.11 (0.00; 0.22) | -4 (-7; -1) | n/a |
| 5 to 7 risk factors on target | 0.07 (-0.02; 0.17) | -4 (-6; -1) | n/a |
| *The Maastricht Study* | | | |
| Controls† | Reference | | |
| No to 2 risk factors on target | 0.63 (0.36; 0.91) | -25 (-31; -19) | 2.97 (1.48; 5.94) |
| 3 risk factors on target | 0.38 (0.17; 0.58) | -12 (-16; -7) | 1.80 (0.98; 3.32) |
| 4 risk factors on target | 0.38 (0.21; 0.56) | -14 (-18; -11) | 1.58 (0.92; 2.70) |
| 5 to 7 risk factors on target | 0.35 (0.18; 0.52) | -8 (-12; -5) | 1.39 (0.80; 2.43) |
| **LDL cholesterol level as additional risk factor, cutoff value <2.5 mmol/L** | | | |
| *UK Biobank* | | | |
| Controls† | Reference | | |
| No to 2 risk factor on target | 0.31 (0.11; 0.51) | -6 (-11; -1) | n/a |
| 3 risk factors on target | 0.30 (0.15; 0.44) | -7 (-12; -4) | n/a |
| 4 risk factors on target | 0.16 (0.04; 0.28) | -5 (-8; -2) | n/a |
| 6 to 8 risk factors on target | 0.06 (-0.03; 0.16) | -3 (-6; -1) | n/a |
| *The Maastricht Study* | | | |
| Controls† | Reference | | |
| No to 2 risk factors on target | 0.78 (0.46; 1.11) | -21 (-28; -14) | 2.64 (1.14; 6.11) |
| 3 risk factors on target | 0.36 (0.16; 0.56) | -15 (-20; -11) | 1.36 (0.70; 2.65) |
| 4 risk factors on target | 0.34 (0.17; 0.51) | -12 (-16; -8) | 1.75 (1.03; 2.96) |
| 5 to 8 risk factors on target | 0.39 (0.23; 0.56) | -11 (-14; -7) | 1.62 (0.97; 2.70) |

**Supplemental Table S7. Adjusted regression coefficients for structural brain abnormalities according to the number of risk factors within target range among individuals with type 2 diabetes as compared to controls – results of additional analyses (continued)**

| | White matter hyperintensity volume (log2-transformed ml) | Total brain parenchyma volume (ml) | Presence of lacunar infarcts |
|---|---|---|---|
| | B (95%CI) | | Odds Ratio (95%CI) |
| **Additional adjustment for use of renin-angiotensin-aldosterone system inhibitors** | | | |
| *UK Biobank* | | | |
| Controls† | Reference | | |
| No to 2 risk factor on target | 0.28 (0.12; 0.44) | -5 (-10; -1) | n/a |
| 3 risk factors on target | 0.18 (0.04; 0.32) | -9 (-13; -5) | n/a |
| 4 risk factors on target | 0.08 (-0.02; 0.18) | -4 (-6; -1) | n/a |
| 5 to 7 risk factors on target | 0.01 (-0.09; 0.13) | -2 (-5; 1) | n/a |
| *The Maastricht Study* | | | |
| Controls† | Reference | | |
| No to 2 risk factors on target | 0.46 (0.23; 0.70) | -18 (-23; -13) | 1.99 (1.07; 3.73) |
| 3 risk factors on target | 0.26 (0.08; 0.44) | -10 (-15; -7) | 1.19 (0.67; 2.13) |
| 4 risk factors on target | 0.38 (0.21; 0.56) | -8 (-12; -4) | 1.26 (0.73; 2.18) |
| 5 to 7 risk factors on target | 0.26 (0.03; 0.49) | -7 (-12; -2) | 1.29 (0.60; 2.76) |
| **Additional adjustment for estimated glomerular filtration rate** | | | |
| *UK Biobank* | | | |
| Controls† | Reference | | |
| No to 2 risk factor on target | 0.35 (0.19; 0.52) | -5 (-10; -1) | n/a |
| 3 risk factors on target | 0.22 (0.08; 0.36) | -10 (-14; -6) | n/a |
| 4 risk factors on target | 0.14 (0.03; 0.24) | -4 (-7; -1) | n/a |
| 5 to 7 risk factors on target | 0.05 (-0.06; 0.17) | -1 (-4; 2) | n/a |
| *The Maastricht Study* | | | |
| Controls† | Reference | | |
| No to 2 risk factors on target | 0.56 (0.33; 0.79) | -22 (-27; -17) | 2.71 (1.49; 4.92) |
| 3 risk factors on target | 0.33 (0.15; 0.50) | -14 (-18; -10) | 1.54 (0.88; 2.69) |
| 4 risk factors on target | 0.43 (0.26; 0.60) | -10 (-14; -7) | 1.47 (0.85; 2.52) |
| 5 to 7 risk factors on target | 0.30 (0.07; 0.53) | -9 (-14; -4) | 1.48 (0.69; 3.17) |

**Supplemental Table S7. Adjusted regression coefficients for structural brain abnormalities according to the number of risk factors within target range among individuals with type 2 diabetes as compared to controls – results of additional analyses (continued)**

| | White matter hyperintensity volume (log2-transformed ml) | Total brain parenchyma volume (ml) | Presence of lacunar infarcts |
|---|---|---|---|
| | B (95%CI) | | Odds Ratio (95%CI) |
| **Controls defined as individuals without diabetes or prediabetes who had 4 risk factors on target** | | | |
| *UK Biobank* | | | |
| Controls | Reference | | |
| No to 2 risk factor on target | 0.30 (0.13; 0.46) | -6 (-11; -1) | n/a |
| 3 risk factors on target | 0.19 (0.04; 0.33) | -10 (-14; -6) | n/a |
| 4 risk factors on target | 0.10 (-0.01; 0.21) | -4 (-7; -1) | n/a |
| 5 to 7 risk factors on target | -0.01 (-0.13; 0.11) | -2 (-5; 1) | n/a |
| *The Maastricht Study* | | | |
| Controls | Reference | | |
| No to 2 risk factors on target | 0.54 (0.29; 0.80) | -19 (-25; -14) | 2.92 (1.47; 5.80) |
| 3 risk factors on target | 0.28 (0.08; 0.48) | -11 (-16; -7) | 1.67 (0.87; 3.20) |
| 4 risk factors on target | 0.38 (0.19; 0.58) | -8 (-12; -4) | 1.69 (0.90; 3.18) |
| 5 to 7 risk factors on target | 0.24 (-0.01; 0.49) | -8 (-13; -2) | 1.57 (0.68; 3.58) |
| **Controls defined as individuals without diabetes, including individuals with prediabetes in the control group** | | | |
| *UK Biobank* | | | |
| Controls | Reference | | |
| No to 2 risk factors on target | 0.35 (0.18; 0.51) | -6 (-10; -2) | n/a |
| 3 risk factors on target | 0.23 (0.09; 0.37) | -10 (-13; -6) | n/a |
| 4 risk factors on target | 0.14 (0.04; 0.24) | -4 (-7; -2) | n/a |
| 5 to 7 risk factors on target | 0.03 (-0.08; 0.15) | -2 (-5; 1) | n/a |
| *The Maastricht Study* | | | |
| Controls | Reference | | |
| No to 2 risk factors on target | 0.53 (0.20; 0.76) | -21 (-26; -16) | 2.58 (1.45; 4.57) |
| 3 risk factors on target | 0.30 (0.12; 0.47) | -13 (-16; -9) | 1.46 (0.85; 2.49) |
| 4 risk factors on target | 0.41 (0.24; 0.58) | -9 (-13; -6) | 1.49 (0.90; 2.48) |
| 5 to 7 risk factors on target | 0.27 (0.04; 0.50) | -8 (-13; -3) | 1.36 (0.65; 2.87) |

**Supplemental Table S7. Adjusted regression coefficients for structural brain abnormalities according to the number of risk factors within target range among individuals with type 2 diabetes as compared to controls – results of additional analyses (continued)**

| | White matter hyperintensity volume (log2-transformed ml) | Total brain parenchyma volume (ml) | Presence of lacunar infarcts |
|---|---|---|---|
| | B (95%CI) | | Odds Ratio (95%CI) |
| **Excluding glycated hemoglobin as a risk factor** | | | |
| *UK Biobank* | | | |
| Controls† | Reference | | |
| No to 2 risk factors on target | 0.28 (0.16; 0.40) | -7 (-10; -4) | n/a |
| 3 risk factors on target | 0.18 (0.07; 0.28) | -5 (-8; -3) | n/a |
| 4 risk factors on target | 0.09 (-0.02; 0.20) | -3 (-6; 0) | n/a |
| 5 or 6 risk factors on target | -0.05 (-0.25; 0.15) | -4 (-10; 1) | n/a |
| *The Maastricht Study* | | | |
| Controls† | Reference | | |
| No to 2 risk factors on target | 0.44 (0.27; 0.60) | -17 (-21; -14) | 1.74 (1.05; 2.87) |
| 3 risk factors on target | 0.38 (0.22; 0.53) | -11 (-14; -7) | 1.50 (0.91; 2.46) |
| 4 risk factors on target | 0.45 (0.22; 0.68) | -12 (-17; -6) | 2.36 (1.23; 4.52) |
| 5 or 6 risk factors on target | 0.17 (-0.25; 0.59) | -5 (-14; 5) | 1.27 (0.30; 5.41) |
| **Excluding body mass index as a risk factor** | | | |
| *UK Biobank* | | | |
| Controls† | Reference | | |
| No to 2 risk factors on target | 0.35 (0.19; 0.51) | -7 (-11; -3) | n/a |
| 3 risk factors on target | 0.23 (0.10; 0.36) | -8 (-11; -5) | n/a |
| 4 risk factors on target | 0.12 (0.02; 0.22) | -5 (-8; -2) | n/a |
| 5 or 6 risk factors on target | 0.05 (-0.07; 0.17) | -1 (-4; 3) | n/a |
| *The Maastricht Study* | | | |
| Controls† | Reference | | |
| No to 2 risk factors on target | 0.62 (0.41; 0.84) | -22 (-27; -17) | 2.89 (1.66; 5.07) |
| 3 risk factors on target | 0.34 (0.17; 0.51) | -14 (-18; -10) | 1.61 (0.95; 2.73) |
| 4 risk factors on target | 0.38 (0.21; 0.55) | -8 (-12; -5) | 1.21 (0.68; 2.15) |
| 5 or 6 risk factors on target | 0.20 (0.02; 0.57) | -9 (-15; -3) | 1.72 (0.72; 4.08) |

**Supplemental Table S7. Adjusted regression coefficients for structural brain abnormalities according to the number of risk factors within target range among individuals with type 2 diabetes as compared to controls – results of additional analyses (continued)**

| | White matter hyperintensity volume (log2-transformed ml) | Total brain parenchyma volume (ml) | Presence of lacunes |
|---|---|---|---|
| | B (95%CI) | | Odds Ratio (95%CI) |
| **Excluding physical activity as a risk factor** | | | |
| *UK Biobank* | | | |
| Controls† | Reference | | |
| No to 2 risk factors on target | 0.31 (0.18; 0.43) | -7 (-11; -4) | n/a |
| 3 risk factors on target | 0.16 (0.06; 0.26) | -7 (-10; -5) | n/a |
| 4 risk factors on target | 0.08 (-0.03; 0.20) | 0 (-3; 3) | n/a |
| 5 or 6 risk factors on target | -0.03 (-0.24; 0.18) | -3 (-9; 2) | n/a |
| *The Maastricht Study* | | | |
| Controls† | Reference | | |
| No to 2 risk factors on target | 0.42 (0.25; 0.59) | -17 (-21; -13) | 2.01 (1.22; 3.32) |
| 3 risk factors on target | 0.42 (0.26; 0.57) | -11 (-15; -8) | 1.61 (0.99; 2.62) |
| 4 risk factors on target | 0.35 (0.13; 0.56) | -11 (-16; -6) | 1.62 (0.83; 3.15) |
| 5 or 6 risk factors on target | 0.38 (-0.09; 0.84) | -8 (-19; 2) | 0.69 (0.09; 5.18) |

All analyses adjusted for age, sex, education and time between baseline examination and MRI examination. Analyses with brain volumes were additionally adjusted for total intracranial volume.

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, ≥20 and <25 kg/m$^2$), smoking (being a nonsmoker), albuminuria (absence of micro- or macroalbuminuria), physical activity (cutoff value, ≥150 minutes per week moderate-to-vigorous physical activity) and dietary habits (optimal as defined by the 5-item healthy diet score of the American Heart Association(2)).

* Duration of diabetes was centralized around the grand mean (the mean duration among all individuals) for individuals with type 2 diabetes, and set to 0 years for controls; † Controls were defined as individuals without diabetes or prediabetes; ‡ Data not available in UK Biobank.

CI, confidence interval; n/a, not applicable; LDL, low-density lipoprotein; MRI, Magnetic Resonance Imaging.

**Supplemental Table S8. Associations between individual risk factors and incident dementia, domain-specific cognitive performance and structural brain abnormalities among individuals with type 2 diabetes**

| | Incident dementia | Domain-specific cognitive performance outcomes | | | Structural brain abnormalities | | |
|---|---|---|---|---|---|---|---|
| Risk factor | | Processing speed (SD) | Memory (SD) | Executive function (SD) | White matter hyperintensity (log2-transformed ml) | Total brain parenchyma volume (ml) | Presence of Lacunes |
| | Hazard ratio (95% CI) | B (95%CI) | | | B (95%CI) | | Odds ratio (95% CI) |
| *UK Biobank* | | | | | | | |
| Glycated hemoglobin level, <53 mmol/mol (<7%) | 0.87 (0.62; 1.21) | 0.09 (0.04; 0.13) | -0.03 (-0.07; 0.01) | n/a | -0.12 (-0.26; 0.02) | 5 (1; 9) | n/a |
| Systolic blood pressure <130 mmHg and diastolic blood pressure <80 mmHg | 0.93 (0.58; 1.48) | -0.07 (-0.12; -0.02) | -0.04 (-0.09; 0.02) | n/a | -0.18 (-0.35; 0.00) | 1 (-4; 6) | n/a |
| Body mass index, ≥20 kg/m2 and <25 kg/m2 | 1.44 (0.87; 2.37) | -0.09 (-0.16; -0.02) | 0.00 (-0.06; 0.07) | n/a | -0.11 (-0.32; 0.10) | -3 (-9; 3) | n/a |
| Being a nonsmoker | 1.09 (0.87; 2.37) | 0.04 (-0.03; 0.10) | -0.05 (-0.11; 0.01) | n/a | -0.10 (-0.38; 0.19) | 4 (-4; 13) | n/a |
| Absence of micro- or macroalbuminuria | 0.63 (0.45; 0.88) | 0.07 (0.03; 0.11) | 0.03 (-0.01; 0.07) | n/a | -0.10 (-0.24; 0.03) | 5 (1; 9) | n/a |
| Physical activity, ≥150 minutes/week moderate-to-vigorous activity | 0.61 (0.44; 0.85) | 0.01 (-0.03; 0.06) | -0.04 (-0.08; 0.00) | n/a | -0.08 (-0.22; 0.06) | -3 (-7; 1) | n/a |
| Dietary habits at optimal level as defined by 5-item healthy diet score of the American Heart Association(2) | 0.81 (0.58; 1.13) | 0.05 (0.00; 0.09) | -0.01 (-0.05; 0.03) | n/a | 0.02 (-0.12; 0.15) | 3 (-1; 7) | n/a |

**Supplemental Table S8. Associations between individual risk factors and incident dementia, domain-specific cognitive performance and structural brain abnormalities among individuals with type 2 diabetes (continued)**

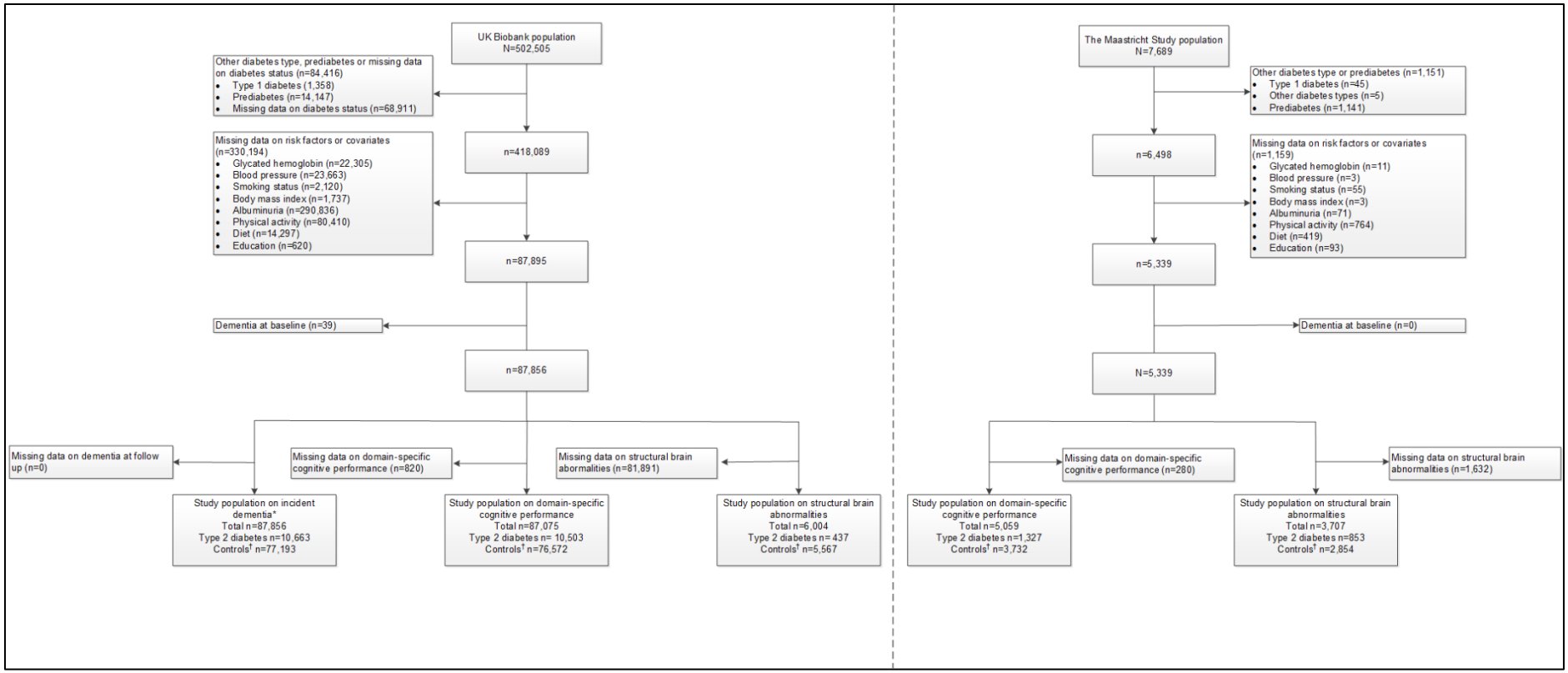
| | Incident dementia | Domain-specific cognitive performance outcomes | | | Structural brain abnormalities | | |
|---|---|---|---|---|---|---|---|
| Risk factor | | Processing speed (SD) | Memory (SD) | Executive function (SD) | White matter hyperintensity (log2-transformed ml) | Total brain parenchyma volume (ml) | Presence of Lacunes |
| | Hazard ratio (95% CI) | B (95%CI) | | | B (95%CI) | | Odds ratio (95% CI) |
| *The Maastricht Study* | | | | | | | |
| Glycated hemoglobin level, <53 mmol/mol (<7%) | n/a | 0.10 (0.02; 0.18) | 0.04 (-0.14; 0.06) | 0.05 (-0.04; 0.13) | -0.01 (-0.23; 0.21) | 4 (-1; 8) | 0.52 (0.30; 0.91) |
| Systolic blood pressure <130 mmHg and diastolic blood pressure <80 mmHg | n/a | -0.09 (-0.17; 0.00) | -0.04 (-0.15; 0.08) | 0.05 (-0.04; 0.15) | 0.02 (-0.23; 0.26) | -1 (-7; 4) | 1.34 (0.69; 2.62) |
| Body mass index, ≥20 kg/m2 and <25 kg/m2 | n/a | -0.02 (-0.12; 0.08) | -0.19 (-0.32; -0.06) | -0.06 (-0.18; 0.05) | 0.19 (-0.08; 0.47) | -2 (-8; 4) | 1.26 (0.63; 2.50) |
| Being a nonsmoker | n/a | 0.09 (-0.02; 0.19) | 0.15 (0.02; 0.29) | 0.16 (0.04; 0.27) | -0.08 (-0.39; 0.23) | 1 (-6; 7) | 0.69 (0.30; 1.59) |
| Absence of micro- or macroalbuminuria | n/a | 0.13 (0.03; 0.22) | -0.01 (-0.13; 0.11) | 0.08 (-0.03; 0.18) | -0.48 (-0.75; -0.22) | 6 (1; 12) | 0.50 (0.27; 0.91) |
| Physical activity, ≥150 minutes/week moderate-to-vigorous activity | n/a | -0.02 (-0.16; 0.12) | 0.04 (-0.05; 0.14) | 0.10 (0.02; 0.19) | -0.14 (-0.25; 0.07) | 8 (3; 12) | 0.83 (0.47; 1.46) |
| Dietary habits at optimal level as defined by 5-item healthy diet score of the American Heart Association(2) | n/a | -0.02 (-0.16; -0.03) | -0.01 (-0.19; 0.17) | 0.02 (-0.14; 0.18) | 0.24 (-0.16; 0.63) | -1 (-9; 8) | 2.70 (1.21; 6.05) |

All analyses adjusted for age, sex, education and the other individual risk factors. Analyses with structural brain abnormalities were additionally adjusted for time between baseline examination and MRI examination, and analyses with brain volumes were additionally adjusted for total intracranial volume.
SD, standard deviation; CI, confidence interval; n/a, not applicable; MRI, Magnetic Resonance Imaging.

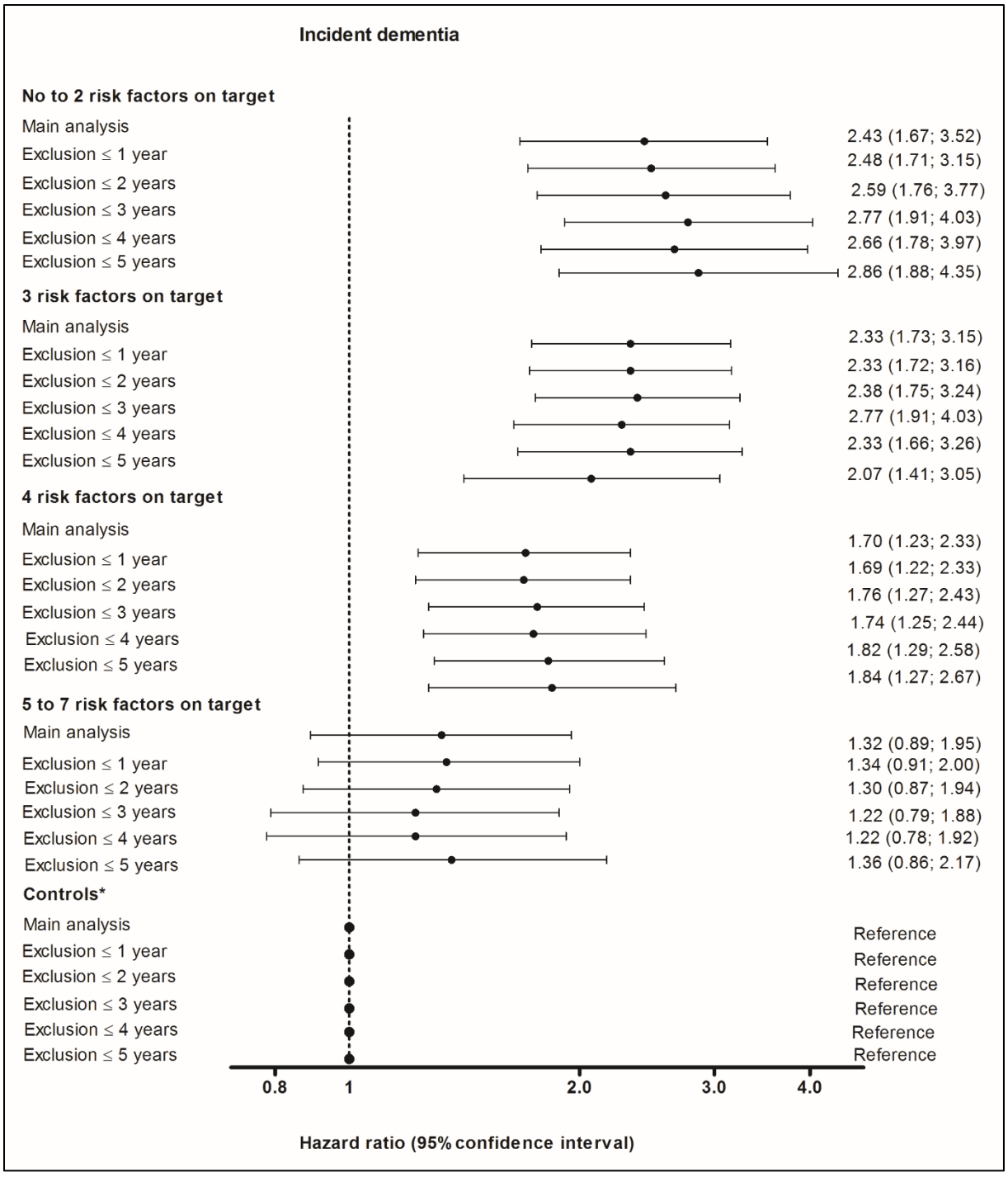
**Supplemental Table S9. Associations between incident dementia, domain-specific cognitive performance and structural brain abnormalities and the number of risk factors within target range on a continuous scale among individuals with type 2 diabetes**

| | Incident dementia | Domain-specific cognitive performance outcomes | | | Structural brain abnormalities | | |
|---|---|---|---|---|---|---|---|
| | | Processing speed (SD) | Memory (SD) | Executive function (SD) | White matter hyperintensity (log2-transformed ml) | Total brain parenchyma volume (ml) | Presence of Lacunes |
| | Hazard ratio (95% CI) | B (95%CI) | | | B (95%CI) | | Odds ratio (95% CI) |
| *UK Biobank* | | | | | | | |
| Each additional risk factor on target (range 0-7) | 0.80 (0.70; 0.91) | 0.03 (0.01; 0.05) | -0.02 (-0.03; 0.00) | n/a | -0.09 (-0.14; -0.04) | 2 (0; 3) | n/a |
| *The Maastricht Study* | | | | | | | |
| Each additional risk factor on target (range 0-7) | n/a | 0.04 (0.01; 0.07) | -0.01 (-0.05; 0.03) | 0.06 (0.02; 0.09) | -0.07 (-0.16; 0.02) | 3 (1; 5) | 0.86 (0.68; 1.09) |

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, ≥20 and <25 kg/m$^2$), smoking (being a nonsmoker), albuminuria (absence of micro- or macroalbuminuria), physical activity (cutoff value, ≥150 minutes per week moderate-to-vigorous physical activity) and dietary habits (optimal as defined by the 5-item healthy diet -score of the American Heart Association(2)). All analyses adjusted for age, sex and education. Analyses with structural brain abnormalities were additionally adjusted for time between baseline examination and MRI examination, and analyses with brain volumes were additionally adjusted for total intracranial volume.
SD, standard deviation; CI, confidence interval; n/a, not applicable; MRI, Magnetic Resonance Imaging.




**Supplemental Figure S1. Flow chart derivation of the study populations.**
Missing data not mutually exclusive. * Data not available in the Maastricht Study; † Controls were defined as individuals without diabetes or prediabetes.




**Supplemental Figure S2. UK Biobank: adjusted hazard ratios for incident dementia according to the number of risk factors within target range among individuals with type 2 diabetes as compared to controls, with consecutive exclusion of the first five years of follow-up.**
Results show the excess risk of dementia among participants with type 2 diabetes according to the number of risk factors within target range as compared to controls. 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, ≥20 and <25 kg/m$^2$), smoking (being a nonsmoker), albuminuria (absence of micro- or macroalbuminuria), physical activity (cutoff value, ≥150 minutes/per week moderate-to-vigorous physical activity) and dietary habits (optimal as defined by the 5-item healthy diet score of the American Heart Association(2)).
* Controls were defined as individuals without diabetes or prediabetes.

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