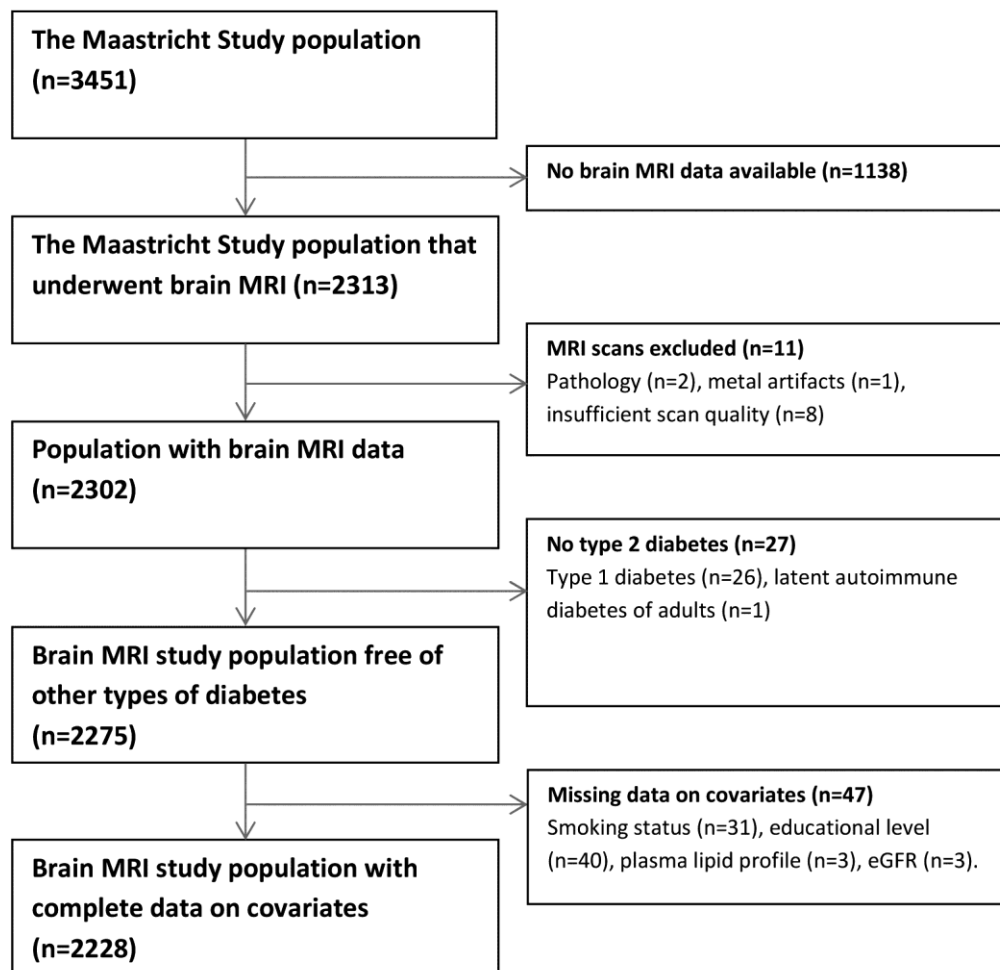SUPPLEMENTARY DATA

PREDIABETES IS ASSOCIATED WITH STRUCTURAL BRAIN ABNORMALITIES: THE MAASTRICHT STUDY

Marnix JM van Agtmaal[1,2], Alfons JHM Houben[1,2], Vera de Wit[1], Ronald MA Henry[1,2,3], Nicolaas C Schaper[1,2], Pieter C Dagnelie[1,4,5], Carla J van der Kallen[1,2], Annemarie Koster[4,6], Simone J Sep[4,7], Abraham A. Kroon[1,2], Jacobus FA Jansen[8], Paul A Hofman[8], Walter H Backes[8,9], Miranda T Schram[*,1,2,3], Coen DA Stehouwer[*,1,2]

[1]Department of Internal Medicine, [2]School for Cardiovascular Disease (CARIM), [3]Heart and Vascular Center, [4]Care and Public Health Research Institute (CAPHRI), [5]Department of Epidemiology, [6]Department of Social Medicine, [7]Department of Rehabilitation Medicine, [8]Department of Radiology & Nuclear Medicine, [9]School for Mental Health & Neuroscience; Maastricht University Medical Center (MUMC+), Maastricht, the Netherlands
* Both authors contributed equally

Supplementary Figure 1. Flowchart of the study population

SUPPLEMENTARY DATA

Supplementary Table 1. General characteristics of the study population with and without brain MRI data.

Characteristic	Study population (n=2228)	No brain MRI data available (n=1138)	*P* value
Demographics			
Age (years)	59.1 ± 8.2	61.0 ± 8.1	<0.001
Sex (% female)	48.3	48.9	0.81
Glucose metabolism			
Type 2 diabetes (%)	22.8	39.1	<0.001
Fasting glucose (mmol/l)	5.7 ± 1.1	6.0 ± 1.2	<0.001
2h post-load glucose (mmol/l)	7.5 ± 4.0	8.8 ± 4.6	<0.001
HbA1c (perc)	5.7 ± 0.6	6.1 ± 1.0	<0.001
HbA1c (mmol/mol)	40.0 ± 8.8	43.4 ± 11.6	<0.001
Cardiovascular risk factors			
Body mass index (kg/m^2)	26.4 ± 4.0	27.5 ± 4.6	<0.001
Systolic BP (mmHg)	133.3 ± 17.0	137.3 ± 19.7	0.01
Diastolic BP (mmHg)	76.1 ± 9.8	76.5 ± 10.0	0.37
Hypertension (%)	52.0	64.7	<0.001
Total-to-HDL cholesterol	3.7 ± 1.2	3.7 ± 1.1	0.11
Triglycerides (mmol/l)	1.4 ± 0.8	1.5 ± 0.9	<0.001
eGFR (ml/min/1.73m^2)	89.1 ± 13.9	81.0 ± 16.3	0.08
History of CVD (%)	11.9	26.5	<0.001
Medication use			
Antihypertensive medication (%)	34.7	49.8	<0.001
Lipid-modifying medication (%)	30.1	46.5	<0.001
Life style factors			
Smoking, never/former/current (%)	37.3 / 51.1 / 11.6	29.3 / 52.9 / 17.8	<0.001
Educational level, low/medium/high (%)	30.0 / 29.1 / 40.9	40.7 / 26.3 / 32.9	<0.001

Data are presented as means ± standard deviation or percentage and stratified for availability of MRI data.
HbA1c indicates hemoglobin A1c; BP, blood pressure; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease.

SUPPLEMENTARY DATA

Supplementary Table 2. Multivariable adjusted differences in structural brain abnormalities (in % intracranial volume) among individuals with normal glucose metabolism, prediabetes and type 2 diabetes.

Characteristic	Prediabetes β (95%CI)	Type 2 diabetes β (95%CI)	*P* for trend
White matter volume (% intracranial volume)			
Model 1	-0.24 (-0.47 to -0.00)	-0.43 (-0.64 to -0.21)	<0.001
Model 2	-0.29 (-0.53 to -0.05)	-0.49 (-0.72 to -0.27)	<0.001
Gray matter volume (% intracranial volume)			
Model 1	-0.05 (-0.28 to 0.18)	-0.60 (-0.80 to -0.40)	0.004
Model 2	0.00 (-0.23 to 0.23)	-0.47 (-0.68 to -0.25)	0.052
Cerebrospinal fluid (% intracranial volume)			
Model 1	0.26 (0.00 to 0.52)	0.96 (0.73 to 1.20)	<0.001
Model 2	0.26 (-0.01 to 0.52)	12.5 (0.64 to 1.15)	<0.001

Regression coefficients (β) indicate the mean difference (95% CI) in white matter hyperintensity, deep cortical hyperintensity and periventricular white matter hyperintensity volumes (in log10-transformed ml) or white matter, gray matter, and cerebrospinal fluid volumes (in % intracranial volume) of participants with prediabetes and type 2 diabetes, as compared to normal glucose metabolism.

CI indicates confidence interval

Model 1: adjusted for age, sex, intracranial volume, and time between baseline and MRI measurements **Model 2:** Model 1 additionally adjusted for body mass index, smoking status, total-to-high-density lipoprotein-cholesterol ratio, office systolic blood pressure, estimated glomerular filtration rate, and educational level.

SUPPLEMENTARY DATA

Supplementary Table 3. Multivariable adjusted associations of HbA1c, fasting glucose and 2-hour post-load glucose levels with structural brain abnormalities (in % intracranial volume).

Model	HbA1c stβ (95%CI)	*P* value	Fasting glucose stβ (95%CI)	*P* value	2h post-load glucose* stβ (95%CI)	*P* value
White matter volume (% intracranial volume)						
Model 1	-0.06 (-0.10 to -0.02)	0.002	-0.07 (-0.12 to -0.03)	<0.001	-0.10 (-0.14 to -0.06)	<0.001
Model 2	-0.06 (-0.11 to -0.02)	0.005	-0.08 (-0.12 to -0.03)	0.001	-0.11 (-0.15 to -0.06)	<0.001
Gray matter volume (% intracranial volume)						
Model 1	-0.06 (-0.10 to -0.03)	0.001	-0.06 (-0.09 to -0.02)	0.004	-0.02 (-0.05 to 0.02)	0.399
Model 2	-0.05 (-0.09 to -0.01)	0.012	-0.04 (-0.08 to 0.00)	0.037	-0.01 (-0.05 to 0.03)	0.548
Cerebrospinal fluid (% intracranial volume)						
Model 1	0.10 (0.06 to 0.13)	<0.001	0.10 (0.06 to 0.14)	<0.001	0.09 (0.05 to 0.12)	<0.001
Model 2	0.09 (0.05 to 0.12)	<0.001	0.09 (0.05 to 0.13)	<0.001	0.09 (0.05 to 0.12)	<0.001

Point estimates (standardized betas) and 95% Cis indicate the mean difference in white matter hyperintensity, deep cortical hyperintensity and periventricular white matter hyperintensity volumes (in log10-transformed ml) per SD increase in HbA1c, fasting glucose, or 2h post-load glucose levels.
CI indicates confidence interval; HbA1c, hemoglobin A1c; SD, standard deviation, stβ, standardized beta.
Model 1: adjustment for age, sex, intracranial volume, and time between baseline and MRI measurements
Model 2: Model 1 additionally adjusted for body mass index, smoking status, total-to-high-density lipoprotein-cholesterol ratio, office systolic blood pressure, estimated glomerular filtration rate, and educational level.

SUPPLEMENTARY DATA

Supplementary Table 4. Multivariable adjusted differences in structural brain abnormalities in individuals with normal glucose metabolism, prediabetes and type 2 diabetes, adjusted for 24h systolic blood pressure.

Characteristic	Prediabetes OR (95% CI)	Type 2 diabetes OR (95% CI)	P for trend
Markers of cerebral small vessel disease			
Lacunar infarctions (yes/no), OR (95% CI)			
Model 1	1.80 (1.08 to 3.00)	1.85 (1.17 to 2.91)	0.006
Model 2	1.80 (1.07 to 3.02)	1.82 (1.10 to 3.00)	0.014
Model 3	1.69 (1.00 to 2.86)	1.49 (0.87 to 2.54)	0.115
Total white matter hyperintensity volume (log-ml), β (95% CI)			
Model 1	0.11 (0.03 to 0.18)	0.21 (0.15 to 0.28)	<0.001
Model 2	0.10 (0.03 to 0.18)	0.20 (0.13 to 0.28)	<0.001
Model 3	0.09 (0.01 to 0.17)	0.14 (0.07 to 0.22)	<0.001
Deep cortical white matter hyperintensity volume (log-ml), β (95% CI)			
Model 1	0.10 (0.02 to 0.19)	0.16 (0.09 to 0.24)	<0.001
Model 2	0.10 (0.01 to 0.18)	0.15 (0.07 to 0.23)	<0.001
Model 3	0.08 (-0.01 to 0.16)	0.08 (-0.01 to 0.17)	0.040
Periventricular white matter hyperintensity volume (log-ml), β (95% CI)			
Model 1	0.10 (0.02 to 0.17)	0.21 (0.15 to 0.27)	<0.001
Model 2	0.09 (0.02 to 0.16)	0.20 (0.13 to 0.27)	<0.001
Model 3	0.08 (0.01 to 0.15)	0.15 (0.08 to 0.23)	<0.001
Cerebral microbleeds (yes/no), OR (95% CI)			
Model 1	0.93 (0.61 to 1.39)	1.09 (0.77 to 1.54)	0.686
Model 2	0.92 (0.60 to 1.39)	1.05 (0.72 to 1.53)	0.869
Model 3	0.93 (0.61 to 1.42)	1.10 (0.73 to 1.66)	0.725
Brain volumes			
White matter volume (ml), β (95% CI)			
Model 1	-2.4 (-6.0 to 1.1)	-6.2 (-9.3 to -3.0)	<0.001
Model 2	-3.3 (-6.9 to 0.3)	-7.5 (-10.9 to -4.1)	<0.001
Model 3	-3.3 (-6.9 to 0.3)	-7.4 (-11.1 to -3.8)	<0.001
Gray matter volume (ml), β (95% CI)			
Model 1	-0.6 (-4.1 to 2.8)	-7.1 (-10.2 to -4.0)	<0.001
Model 2	-0.1 (-3.6 to 3.4)	-5.5 (-8.8 to -2.2)	0.002
Model 3	0.7 (-2.8 to 4.2)	-3.2 (-6.8 to 0.3)	0.123
Cerebrospinal fluid (ml), β (95% CI)			
Model 1	2.6 (-1.4 to 6.5)	12.5 (9.0 to 16.0)	<0.001
Model 2	2.8 (-1.2 to 6.8)	12.2 (8.4 to 16.0)	<0.001
Model 3	2.2 (-1.8 to 6.2)	10.2 (6.1 to 14.3)	<0.001

Associations between prediabetes and type 2 diabetes with structural brain abnormalities in the study population. Odds ratios with 95% CI represent the risk of the presence of lacunar infarctions or cerebral microbleeds, and regression coefficients indicate the mean difference with 95% CI in total white matter hyperintensity, deep cortical hyperintensity, and periventricular white matter hyperintensity volumes (in log10-transformed ml) or white matter, gray matter, and cerebrospinal fluid volumes (in ml) of participants with prediabetes or type 2 diabetes, as compared to normal glucose metabolism.

OR indicates odds ratio; CI, confidence interval

Model 1: adjusted for age, sex, and time between baseline and MRI measurements

Model 2: Model 1 additionally adjusted for body mass index, smoking status, total-to-high-density lipoprotein-cholesterol ratio, 24h systolic blood pressure*, estimated glomerular filtration rate, and educational level.

Model 3: Model 2 additionally adjusted for the use of blood pressure-lowering and lipid-modifying medication

SUPPLEMENTARY DATA

* Note that 24h ambulatory blood pressure was available in n=1984 (1229 individuals with normal glucose metabolism, 303 with prediabetes, and 452 with type 2 diabetes).

SUPPLEMENTARY DATA

Supplementary Table 5. Multivariable adjusted associations, including 24h systolic blood pressure, of HbA1c, fasting glucose, and 2-hour post-load glucose levels with structural brain abnormalities.

Model	HbA1c	P value	Fasting glucose	P value	2h post-load glucose	P value
Markers of cerebral small vessel disease						
Lacunar infarctions (yes/no), OR (95% CI)						
Model 1	1.30 (1.11 to 1.53)	0.001	1.25 (1.06 to 1.48)	0.010	1.24 (1.04 to 1.47)	0.016
Model 2	1.29 (1.08 to 1.54)	0.005	1.25 (1.03 to 1.50)	0.021	1.26 (1.05 to 1.51)	0.015
Model 3	1.21 (1.00 to 1.47)	0.048	1.17 (0.96 to 1.43)	0.119	1.17 (0.96 to 1.42)	0.123
Total white matter hyperintensity volume (log-ml), β (95% CI)						
Model 1	0.10 (0.06 to 0.14)	<0.001	0.12 (0.08 to 0.16)	<0.001	0.11 (0.07 to 0.15)	<0.001
Model 2	0.08 (0.04 to 0.13)	<0.001	0.11 (0.07 to 0.15)	<0.001	0.10 (0.06 to 0.14)	<0.001
Model 3	0.05 (0.00 to 0.09)	0.037	0.08 (0.04 to 0.13)	0.001	0.07 (0.03 to 0.12)	0.001
Deep cortical white matter hyperintensity volume (log-ml), β (95% CI)						
Model 1	0.06 (0.02 to 0.10)	<0.001	0.08 (0.04 to 0.12)	<0.001	0.06 (0.02 to 0.10)	0.007
Model 2	0.04 (0.00 to 0.08)	0.075	0.07 (0.03 to 0.12)	0.002	0.05 (0.01 to 0.10)	0.016
Model 3	0.00 (-0.05 to 0.05)	0.946	0.04 (-0.01 to 0.09)	0.116	0.02 (-0.03 to 0.06)	0.480
Periventricular white matter hyperintensity volume (log-ml), β (95% CI)						
Model 1	0.11 (0.07 to 0.15)	<0.001	0.13 (0.09 to 0.18)	<0.001	0.12 (0.08 to 0.16)	<0.001
Model 2	0.10 (0.05 to 0.14)	<0.001	0.13 (0.08 to 0.17)	<0.001	0.12 (0.08 to 0.16)	<0.001
Model 3	0.07 (0.02 to 0.11)	0.003	0.10 (0.05 to 0.15)	<0.001	0.10 (0.05 to 0.14)	<0.001
Cerebral microbleeds (yes/no), OR (95% CI)						
Model 1	1.06 (0.92 to 1.23)	0.401	1.05 (0.90 to 1.22)	0.531	0.99 (0.86 to 1.15)	0.889
Model 2	1.05 (0.90 to 1.22)	0.546	1.04 (0.88 to 1.22)	0.674	0.99 (0.85 to 1.16)	0.929
Model 3	1.07 (0.91 to 1.26)	0.437	1.05 (0.89 to 1.25)	0.558	1.00 (0.85 to 1.18)	0.969
Brain volumes						
White matter volume (ml), β (95% CI)						
Model 1	-0.02 (-0.04 to 0.00)	0.080	-0.03 (-0.05 to -0.01)	0.016	-0.04 (-0.06 to -0.01)	0.002
Model 2	-0.03 (-0.05 to 0.00)	0.033	-0.04 (-0.06 to -0.01)	0.004	-0.04 (-0.07 to -0.02)	<0.001
Model 3	-0.02 (-0.04 to 0.01)	0.110	-0.03 (-0.06 to -0.01)	0.014	-0.04 (-0.07 to -0.02)	0.001
Gray matter volume (ml), β (95% CI)						
Model 1	-0.05 (-0.07 to -0.03)	<0.001	-0.04 (-0.06 to -0.02)	<0.001	-0.03 (-0.05 to -0.01)	0.014
Model 2	-0.04 (-0.06 to -0.01)	0.002	-0.03 (-0.06 to -0.01)	0.006	-0.02 (-0.04 to 0.00)	0.064
Model 3	-0.02 (-0.05 to 0.00)	0.054	-0.02 (-0.04 to 0.01)	0.132	-0.01 (-0.03 to 0.02)	0.561
Cerebrospinal fluid (ml), β (95% CI)						
Model 1	0.08 (0.05 to 0.11)	<0.001	0.08 (0.05 to 0.11)	<0.001	0.07 (0.04 to 0.10)	<0.001
Model 2	0.07 (0.04 to 0.10)	<0.001	0.08 (0.05 to 0.11)	<0.001	0.07 (0.04 to 0.11)	<0.001
Model 3	0.05 (0.02 to 0.08)	0.004	0.06 (0.03 to 0.09)	0.001	0.06 (0.03 to 0.09)	0.001

Associations between continuous measures of glycemia with structural brain abnormalities in the study population. Odds ratios with 95% CI represent the risk of the presence of lacunar infarctions or cerebral microbleeds, and standardized betas and 95% CIs indicate the mean difference in white matter hyperintensity, deep cortical hyperintensity and periventricular white matter hyperintensity volumes (in log10-transformed ml) or white matter, gray matter, and cerebrospinal fluid volumes (in ml), per SD increase in HbA1c, fasting plasma glucose, or 2h post-load glucose.

CI indicates confidence interval; HbA1c, hemoglobin A1c; SD, standard deviation, stβ, standardized beta.

Model 1: adjustment for age, sex, intracranial volume, and time between baseline and MRI measurements

Model 2: Model 1 additionally adjusted for body mass index, smoking status, total-to-high-density lipoprotein-cholesterol ratio, 24h systolic blood pressure[#], estimated glomerular filtration rate, and educational level.

Model 3: Model 2 additionally adjusted for the use of blood pressure-lowering and lipid-modifying medication

SUPPLEMENTARY DATA

Note that 24h ambulatory blood pressure was available in n=1984 (1229 individuals with normal glucose metabolism, 303 with prediabetes, and 452 with type 2 diabetes).

SUPPLEMENTARY DATA

Supplementary Table 6. Multivariable adjusted differences in structural brain abnormalities among individuals with normal glucose metabolism, prediabetes and type 2 diabetes, additionally adjusted for eGFR< 60 mL/min/1.73m^2 and urinary albumin excretion > 30 mg/24 hours.

Characteristic	Prediabetes OR (95% CI)	Type 2 diabetes OR (95% CI)	*P* for trend
Markers of cerebral small vessel disease			
Lacunar infarctions (yes/no), OR (95% CI)			
Model 1	1.65 (0.99 to 2.75)	1.79 (1.14 to 2.81)	0.010
Model 2	1.62 (0.97 to 2.73)	1.73 (1.05 to 2.83)	0.026
Model 3	1.62 (0.97 to 2.73)	1.74 (1.05 to 2.88)	0.025
Total white matter hyperintensity volume (log-ml), β (95% CI)			
Model 1	0.09 (0.01 to 0.16)	0.22 (0.16 to 0.29)	<0.001
Model 2	0.08 (0.01 to 0.16)	0.21 (0.13 to 0.28)	<0.001
Model 3	0.08 (0.01 to 0.16)	0.19 (0.12 to 0.26)	<0.001
Deep cortical white matter hyperintensity volume (log-ml), β (95% CI)			
Model 1	0.09 (0.01 to 0.17)	0.17 (0.10 to 0.25)	<0.001
Model 2	0.08 (0.00 to 0.16)	0.16 (0.08 to 0.24)	<0.001
Model 3	0.08 (0.00 to 0.16)	0.14 (0.06 to 0.22)	0.001
Periventricular white matter hyperintensity volume (log-ml), β (95% CI)			
Model 1	0.08 (0.01 to 0.14)	0.21 (0.15 to 0.28)	<0.001
Model 2	0.07 (0.00 to 0.14)	0.20 (0.13 to 0.27)	<0.001
Model 3	0.07 (0.00 to 0.14)	0.18 (0.12 to 0.25)	<0.001
Cerebral microbleeds (yes/no), OR (95% CI)			
Model 1	0.86 (0.58 to 1.28)	1.16 (0.83 to 1.28)	0.471
Model 2	0.87 (0.58 to 1.30)	1.16 (0.81 to 1.67)	0.511
Model 3	0.87 (0.58 to 1.30)	1.13 (0.78 to 1.64)	0.616
Brain volumes			
White matter volume (ml), β (95% CI)			
Model 1	-3.4 (-6.8 to -0.1)	-6.1 (-9.2 to -3.1)	<0.001
Model 2	-4.3 (-7.6 to -0.8)	-7.7 (-11.0 to -4.4)	<0.001
Model 3	-4.2 (-7.6 to -0.8)	-6.7 (-10.1 to -3.4)	<0.001
Gray matter volume (ml), β (95% CI)			
Model 1	-1.1 (-4.4 to 2.3)	-8.0 (-11.0 to -4.9)	<0.001
Model 2	-0.4 (-3.8 to 2.9)	-6.0 (-9.2 to -2.7)	0.001
Model 3	-0.4 (-3.8 to 2.9)	-5.5 (-8.8 to -2.3)	0.002
Cerebrospinal fluid (ml), β (95% CI)			
Model 1	4.1 (0.2 to 7.9)	13.2 (9.7 to 16.7)	<0.001
Model 2	4.2 (0.3 to 8.0)	12.7 (9.0 to 16.4)	<0.001
Model 3	4.1 (0.3 to 8.0)	11.4 (7.7 to 15.2)	<0.001

Associations between prediabetes and type 2 diabetes with structural brain abnormalities in the study population. Odds ratios with 95% CI represent the risk of the presence of lacunar infarctions or cerebral microbleeds, and regression coefficients indicate the mean difference with 95% CI in total white matter hyperintensity, deep cortical hyperintensity, and periventricular white matter hyperintensity volumes (in log10-transformed ml) or white matter, gray matter, and cerebrospinal fluid volumes (in ml) of participants with prediabetes or type 2 diabetes, as compared to normal glucose metabolism.

OR indicates odds ratio; CI indicates confidence interval

Model 1: adjusted for age, sex, and time between baseline and MRI measurements

Model 2: Model 1 additionally adjusted for body mass index, smoking status, total-to-high-density lipoprotein-cholesterol ratio, office systolic blood pressure, estimated glomerular filtration rate, and educational level.

SUPPLEMENTARY DATA

Model 3: Model 2 additionally adjusted for eGFR < 60 mL/min/1.73m^2 and urinary albumin excretion > 30 mg/24 hours*

* Note that urinary albumin excretion values were available in n=2060

SUPPLEMENTARY DATA

Supplementary Table 7. Multivariable adjusted associations of HbA1c, fasting glucose and 2-hour post-load glucose levels with structural brain abnormalities, additionally adjusted for eGFR<60 mL/min/1.73m^2 and urinary albumin excretion > 30 mg/24 hours.

Model	HbA1c	*P* value	Fasting glucose	*P* value	2h post-load glucose	*P* value
Markers of cerebral small vessel disease						
Lacunar infarctions (yes/no), OR (95% CI)						
Model 1	1.32 (1.13 to 1.53)	<0.001	1.26 (1.07 to 1.47)	0.004	1.22 (1.02 to 1.45)	0.027
Model 2	1.31 (1.11 to 1.54)	0.002	1.24 (1.05 to 1.48)	0.014	1.24 (1.03 to 1.50)	0.022
Model 3	1.31 (1.11 to 1.56)	0.002	1.25 (1.05 to 1.50)	0.014	1.26 (1.05 to 1.52)	0.016
Total white matter hyperintensity volume (log-ml), β (95% CI)						
Model 1	0.10 (0.06 to 0.14)	<0.001	0.11 (0.08 to 0.15)	<0.001	0.11 (0.07 to 0.15)	<0.001
Model 2	0.08 (0.04 to 0.13)	<0.001	0.10 (0.06 to 0.15)	<0.001	0.11 (0.07 to 0.15)	<0.001
Model 3	0.07 (0.03 to 0.12)	0.001	0.09 (0.05 to 0.14)	<0.001	0.10 (0.06 to 0.14)	<0.001
Deep cortical white matter hyperintensity volume (log-ml), β (95% CI)						
Model 1	0.06 (0.02 to 0.11)	0.002	0.08 (0.04 to 0.12)	<0.001	0.07 (0.03 to 0.11)	0.001
Model 2	0.05 (0.01 to 0.09)	0.019	0.07 (0.03 to 0.12)	0.001	0.06 (0.02 to 0.10)	0.006
Model 3	0.04 (-0.01 to 0.08)	0.091	0.06 (0.01 to 0.10)	0.010	0.05 (0.01 to 0.10)	0.021
Periventricular white matter hyperintensity volume (log-ml), β (95% CI)						
Model 1	0.11 (0.07 to 0.15)	<0.001	0.12 (0.09 to 0.16)	<0.001	0.13 (0.09 to 0.17)	<0.001
Model 2	0.09 (0.05 to 0.14)	<0.001	0.12 (0.07 to 0.16)	<0.001	0.12 (0.08 to 0.16)	<0.001
Model 3	0.09 (0.04 to 0.13)	<0.001	0.11 (0.06 to 0.15)	<0.001	0.11 (0.07 to 0.16)	<0.001
Cerebral microbleeds (yes/no), OR (95% CI)						
Model 1	1.05 (0.92 to 1.20)	0.492	1.05 (0.92 to 1.21)	0.460	0.97 (0.84 to 1.13)	0.717
Model 2	1.05 (0.90 to 1.21)	0.543	1.05 (0.91 to 1.22)	0.490	0.98 (0.84 to 1.14)	0.804
Model 3	1.03 (0.89 to 1.20)	0.661	1.04 (0.89 to 1.21)	0.619	0.98 (0.84 to 1.14)	0.777
Brain volumes						
White matter volume (ml), β (95% CI)						
Model 1	-0.02 (-0.04 to 0.00)	0.121	-0.02 (-0.04 to 0.00)	0.060	-0.04 (-0.06 to -0.01)	0.002
Model 2	-0.02 (-0.04 to 0.00)	0.054	-0.03 (-0.05 to 0.00)	0.020	-0.04 (-0.07 to -0.02)	<0.001
Model 3	-0.02 (-0.04 to 0.01)	0.177	-0.02 (-0.04 to 0.00)	0.099	-0.04 (-0.06 to -0.02)	0.001
Gray matter volume (ml), β (95% CI)						
Model 1	-0.06 (-0.08 to -0.04)	<0.001	-0.05 (-0.07 to -0.03)	<0.001	-0.03 (-0.05 to -0.01)	0.016
Model 2	-0.04 (-0.07 to -0.02)	<0.001	-0.04 (-0.06 to -0.02)	<0.001	-0.02 (-0.04 to 0.00)	0.068
Model 3	-0.04 (-0.06 to -0.02)	<0.001	-0.04 (-0.06 to 0.01)	0.002	-0.02 (-0.04 to 0.00)	0.097
Cerebrospinal fluid (ml), β (95% CI)						
Model 1	0.08 (0.05 to 0.11)	<0.001	0.08 (0.05 to 0.11)	<0.001	0.07 (0.04 to 0.10)	<0.001
Model 2	0.07 (0.04 to 0.11)	<0.001	0.08 (0.04 to 0.11)	<0.001	0.07 (0.04 to 0.10)	<0.001
Model 3	0.06 (0.03 to 0.09)	<0.001	0.06 (0.03 to 0.10)	<0.001	0.07 (0.04 to 0.10)	<0.001

Associations between continuous measures of glycemia with structural brain abnormalities in the study population. Odds ratios with 95% CI represent the risk of the presence of lacunar infarctions or cerebral microbleeds, and standardized betas and 95% CIs indicate the mean difference in white matter hyperintensity, deep cortical hyperintensity and periventricular white matter hyperintensity volumes (in log10-transformed ml) or white matter, gray matter, and cerebrospinal fluid volumes (in ml), per SD increase in HbA1c, fasting plasma glucose, or 2h post-load glucose.
OR indicates odds ratio; CI, confidence interval; HbA1c, hemoglobin A1c.
Model 1: adjustment for age, sex, intracranial volume, and time between baseline and MRI measurements
Model 2: Model 1 additionally adjusted for body mass index, smoking status, total-to-high-density lipoprotein-cholesterol ratio, 24h systolic blood pressure*, estimated glomerular filtration rate, and educational level.

SUPPLEMENTARY DATA

Model 3: Model 2 additionally adjusted for eGFR < 60 mL/min/1.73m^2 and urinary albumin excretion > 30 mg/24 hours*

* Note that urinary albumin excretion values were available in n=2107

SUPPLEMENTARY DATA

Supplementary Table 8. Multivariable adjusted differences in structural brain abnormalities among individuals with normal glucose metabolism (HbA1c <5.7%), prediabetes (HbA1c 5.7 to <6.5%), and type 2 diabetes (HbA1c≥6.5%), based on ADA criteria (5).

Characteristic	Prediabetes OR (95% CI)	Type 2 diabetes OR (95% CI)	P for trend
Markers of cerebral small vessel disease			
Lacunar infarctions (yes/no), OR (95% CI)			
Model 1	1.27 (0.82 to 1.96)	1.71 (1.07 to 2.74)	0.026
Model 2	1.23 (0.79 to 1.91)	1.64 (0.99 to 2.72)	0.059
Total white matter hyperintensity volume (log-ml), β (95% CI)			
Model 1	0.11 (0.05 to 0.17)	0.24 (0.17 to 0.32)	<0.001
Model 2	0.10 (0.04 to 0.16)	0.22 (0.15 to 0.30)	<0.001
Deep cortical white matter hyperintensity volume (log-ml), β (95% CI)			
Model 1	0.08 (0.02 to 0.15)	0.17 (0.09 to 0.25)	<0.001
Model 2	0.08 (0.01 to 0.14)	0.15 (0.06 to 0.23)	<0.001
Periventricular white matter hyperintensity volume (log-ml), β (95% CI)			
Model 1	0.10 (0.04 to 0.15)	0.25 (0.18 to 0.32)	<0.001
Model 2	0.09 (0.04 to 0.15)	0.23 (0.16 to 0.30)	<0.001
Cerebral microbleeds (yes/no), OR (95% CI)			
Model 1	0.88 (0.64 to 1.20)	1.04 (0.73 to 1.50)	0.984
Model 2	0.87 (0.63 to 1.19)	1.01 (0.68 to 1.48)	0.830
Brain volumes			
White matter volume (ml) , β (95% CI)			
Model 1	1.4 (-1.3 to 4.1)	-5.6 (-9.0 to -2.3)	0.012
Model 2	1.1 (-1.6 to -3.9)	-5.6 (-9.0 to -2.3)	0.007
Gray matter volume (ml) , β (95% CI)			
Model 1	-1.7 (-4.4 to 0.9)	-7.2 (-10.5 to -3.9)	<0.001
Model 2	-1.2 (-3.8 to 1.5)	-4.9 (-8.4 to -1.2)	0.009
Cerebrospinal fluid (ml) , β (95% CI)			
Model 1	0.0 (-3.0 to 3.1)	11.9 (8.2 to 15.7)	<0.001
Model 2	-0.3 (-3.4 to 2.7)	10.3 (6.3 to 14.3)	<0.001

Associations between prediabetes and type 2 diabetes with structural brain abnormalities in the study population. Odds ratios with 95% CI represent the risk of the presence of lacunar infarctions or cerebral microbleeds, and regression coefficients indicate the mean difference with 95% CI in total white matter hyperintensity, deep cortical hyperintensity, and periventricular white matter hyperintensity volumes (in log10-transformed ml) or white matter, gray matter, and cerebrospinal fluid volumes (in ml) of participants with prediabetes or type 2 diabetes, as compared to normal glucose metabolism.
OR indicates odds ratio; CI, confidence interval
Model 1: adjusted for age, sex, and time between baseline and MRI measurements
Model 2: Model 1 additionally adjusted for body mass index, smoking status, total-to-high-density lipoprotein-cholesterol ratio, office systolic blood pressure, estimated glomerular filtration rate, and educational level.

SUPPLEMENTARY DATA

Supplementary Table 9. Multivariable adjusted differences in structural brain abnormalities in individuals with normal glucose metabolism, prediabetes and type 2 diabetes, excluding participants with a lagtime > 1 year (n=1333).

Characteristic	Prediabetes OR (95% CI)	Type 2 diabetes OR (95% CI)	*P* for trend
Markers of cerebral small vessel disease			
Lacunar infarctions (yes/no), OR (95% CI)			
Model 1	1.71 (0.80 to 3.65)	1.25 (0.63 to 2.47)	0.468
Model 2	1.56 (0.72 to 3.39)	1.07 (0.51 to 2.26)	0.807
Total white matter hyperintensity volume (log-ml), β (95% CI)			
Model 1	0.05 (-0.06 to 0.17)	0.27 (0.17 to 0.36)	<0.001
Model 2	0.05 (-0.07 to 0.16)	0.25 (0.14 to 0.35)	<0.001
Deep cortical white matter hyperintensity volume (log-ml), β (95% CI)			
Model 1	0.05 (-0.07 to 0.18)	0.22 (0.11 to 0.33)	<0.001
Model 2	0.04 (-0.08 to 0.17)	0.19 (0.08 to 0.31)	0.001
Periventricular white matter hyperintensity volume (log-ml), β (95% CI)			
Model 1	0.05 (-0.06 to 0.16)	0.26 (0.17 to 0.35)	<0.001
Model 2	0.04 (-0.07 to 0.15)	0.24 (0.14 to 0.34)	<0.001
Cerebral microbleeds (yes/no), OR (95% CI)			
Model 1	1.06 (0.57 to 2.00)	1.33 (0.81 to 2.18)	0.276
Model 2	1.17 (0.62 to 2.18)	1.55 (0.90 to 2.65)	0.119
Brain volumes			
White matter volume (ml), β (95% CI)			
Model 1	-5.6 (-10.8 to -0.3)	-7.3 (-11.8 to -2.9)	0.001
Model 2	-6.3 (-11.6 to -1.0)	-8.7 (-13.5 to -3.9)	<0.001
Gray matter volume (ml), β (95% CI)			
Model 1	0.1 (-4.8 to 5.0)	-9.3 (-13.4 to -5.1)	<0.001
Model 2	1.3 (-3.6 to 6.3)	-6.5 (-11.0 to -2.1)	0.006
Cerebrospinal fluid (ml), β (95% CI)			
Model 1	5.3 (-0.4 to 11.0)	15.8 (11.0 to 20.8)	<0.001
Model 2	4.9 (-0.9 to 10.6)	14.4 (9.2 to 19.6)	<0.001

Associations between prediabetes and type 2 diabetes with structural brain abnormalities in the study population. Odds ratios with 95% CI represent the risk of the presence of lacunar infarctions or cerebral microbleeds, and regression coefficients indicate the mean difference with 95% CI in total white matter hyperintensity, deep cortical hyperintensity, and periventricular white matter hyperintensity volumes (in log10-transformed ml) or white matter, gray matter, and cerebrospinal fluid volumes (in ml) of participants with prediabetes or type 2 diabetes, as compared to normal glucose metabolism.

OR indicates odds ratio; CI, confidence interval

Model 1: adjusted for age, sex, and time between baseline and MRI measurements

Model 2: Model 1 additionally adjusted for body mass index, smoking status, total-to-high-density lipoprotein-cholesterol ratio, 24h systolic blood pressure*, estimated glomerular filtration rate, and educational level.

SUPPLEMENTARY DATA

Supplementary Figure 2. Scatterplots with regression lines on the associations of HbA1c, fasting glucose and 2-hour post-load glucose levels with white matter abnormalities.