

SUPPLEMENTARY MATERIALS

Supplementary Methods

Definitions of the covariates and dementia

In the 2012 health examination, each participant completed a self-administered questionnaire, including educational background; medical history (including the time of diagnoses for diabetes); use of antihypertensive, antidiabetic, and lipid-modifying medications; smoking habits; alcohol intake; and regular exercise. A low education level was defined as ≤ 9 years of formal education. Smoking habits and alcohol intake were classified as current use or not. Regular exercise was defined as engaging in sports ≥ 3 times a week during leisure time. Blood pressure was obtained 3 times using an automated sphygmomanometer in the sitting position after resting for ≥ 5 minutes, and the mean value of the three measurements was calculated. Hypertension was defined as a systolic and diastolic blood pressure $\geq 140/90$ mmHg and/or use of antihypertensive medication. Serum total cholesterol levels were determined enzymatically, and hypercholesterolemia was defined as serum total cholesterol levels ≥ 5.69 mmol/L and/or use of lipid-modifying drugs. BMI was calculated with body weight and height, which were measured in light clothing without shoes. Cerebrovascular lesions were defined as brain infarction or hemorrhage on MRI regardless of the presence or absence of neurological symptoms. Brain infarction included lesions of ≥ 3 mm in diameter visible on both the T1-weighted image (as a hypointense lesion) and the T2-weighted image (as a hyperintense lesion) with a surrounding hyperintense rim on the FLAIR image. Brain hemorrhage was defined as any hemorrhagic lesion, including a cerebral microbleed, visible on the T2*-weighted image (as a hypointense lesion). Each scan was read by two trained stroke neurologists who were blinded to the clinical information (inter-rater agreement ratio: 74.6% for the brain infarctions, 83.7% for the brain hemorrhages). In the case of conflicting interpretations, a third stroke neurologist read the scan and

made a final decision. The diagnosis of dementia was made using the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (1). In the screening survey, we used the Mini-Mental State Examination (2) and Hasegawa's Dementia Scale-Revised (3), and secondary comprehensive investigations were conducted by psychiatrists for the subjects who were suspected to have cognitive impairment, as described previously (4).

References for the Supplementary Methods

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 3rd Ed. Revised. Washington, DC: American Psychiatric Association; 1987.
2. Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-198.
3. Katoh S, Simogaki H, Onodera A, Ueda H, Oikawa K, Ikeda K, Kosaka A, Imai Y, Hasegawa K. Development of the revised version of Hasegawa's Dementia Scale (HDS-R) (in Japanese). Jpn J Geriatr Psychiatry 1991;2:1339-1347.
4. Ohara T, Hata J, Yoshida D, Mukai N, Nagata M, Iwaki T, Kitazono T, Kanba S, Kiyohara Y, Ninomiya T. Trends in dementia prevalence, incidence, and survival rate in a Japanese community. Neurology 2017;88:1925-1932.

Supplementary Table 1. Adjusted mean values (95% CIs) of the total and regional GMV/ICV by diabetes status: a sensitivity analysis excluding 107 subjects with dementia

	Model 1	Model 2
Total GMV/ICV (%)		
No diabetes	39.0 (38.8-39.2)	39.0 (38.8-39.2)
Diabetes	38.4 (38.0-38.7)	38.5 (38.2-38.8)
P value	<0.001	0.006
Frontal GMV/ICV (%)		
No diabetes	9.94 (9.89-10.00)	9.94 (9.89-9.99)
Diabetes	9.79 (9.69-9.89)	9.83 (9.73-9.93)
P value	0.007	0.053
Temporal GMV/ICV (%)		
No diabetes	7.28 (7.24-7.32)	7.27 (7.23-7.31)
Diabetes	7.11 (7.04-7.19)	7.14 (7.06-7.21)
P value	<0.001	0.003
Parietal GMV/ICV (%)		
No diabetes	6.15 (6.12-6.18)	6.15 (6.11-6.18)
Diabetes	6.10 (6.04-6.15)	6.12 (6.05-6.18)
P value	0.10	0.37
Occipital GMV/ICV (%)		
No diabetes	4.60 (4.57-4.63)	4.60 (4.57-4.62)
Diabetes	4.56 (4.52-4.61)	4.58 (4.53-4.62)
P value	0.18	0.47
Insular GMV/ICV (%)		
No diabetes	0.868 (0.862-0.874)	0.868 (0.862-0.874)
Diabetes	0.856 (0.845-0.867)	0.856 (0.845-0.867)
P value	0.0504	0.06
Cingulate GMV/ICV (%)		
No diabetes	1.79 (1.78-1.79)	1.79 (1.78-1.79)
Diabetes	1.78 (1.77-1.80)	1.79 (1.78-1.80)
P value	0.84	0.61
Deep GMV/ICV (%)		
No diabetes	1.31 (1.29-1.32)	1.31 (1.29-1.32)
Diabetes	1.25 (1.22-1.28)	1.25 (1.22-1.28)
P value	0.001	0.002
Cerebellar GMV/ICV (%)		
No diabetes	5.93 (5.88-5.97)	5.92 (5.87-5.97)
Diabetes	5.76 (5.67-5.84)	5.78 (5.69-5.87)
P value	<0.001	0.006

Abbreviations: GMV, gray matter volume; ICV, intracranial volume.

Model 1: Adjusted for age and sex.

Model 2: Adjusted for covariates in Model 1 plus low education, hypertension, serum total cholesterol, BMI, smoking habits, alcohol intake, regular exercise, and cerebrovascular lesions on magnetic resonance imaging.

Supplementary Table 2. Mean values (95% CIs) of the total and regional GMV/ICV ratios by diabetes status: a sensitivity analysis based on a 1:1 propensity score matching

	No diabetes (n=269)	Diabetes (n=269)	<i>P</i> value
Total GMV/ICV (%)	38.6 (38.2-39.0)	37.7 (37.3-38.2)	0.006
Frontal GMV/ICV (%)	9.87 (9.75-10.00)	9.61 (9.48-9.75)	0.004
Temporal GMV/ICV (%)	7.16 (7.07-7.26)	7.00 (6.89-7.10)	0.02
Parietal GMV/ICV (%)	6.10 (6.03-6.17)	6.01 (5.94-6.08)	0.051
Occipital GMV/ICV (%)	4.58 (4.53-4.63)	4.53 (4.48-4.58)	0.15
Insular GMV/ICV (%)	0.853 (0.840-0.866)	0.837 (0.823-0.852)	0.13
Cingulate GMV/ICV (%)	1.77 (1.76-1.79)	1.76 (1.74-1.78)	0.33
Deep GMV/ICV (%)	1.29 (1.26-1.32)	1.21 (1.17-1.24)	0.001
Cerebellar GMV/ICV (%)	5.80 (5.71-5.89)	5.66 (5.57-5.75)	0.03

Abbreviations: GMV, gray matter volume; ICV, intracranial volume.

Supplementary Table 3. Multivariable-adjusted mean values (95% CIs) of the total and regional GMV/ICV according to the duration of diabetes

	No diabetes (n=917)	Newly diagnosed diabetes (n=82)	Duration of known diabetes			<i>P</i> for trend
			≤9 years (n=63)	10-16 years (n=59)	≥17 years (n=62)	
Total GMV/ICV (%)	38.5 (38.4-38.7)	38.0 (37.4-38.6)	38.6 (38.0-39.3)	37.9 (37.2-38.6)	37.5 (36.8-38.2)*	0.003
Frontal GMV/ICV (%)	9.82 (9.77-9.88)	9.65 (9.47-9.83)	9.86 (9.65-10.07)	9.68 (9.46-9.89)	9.59 (9.38-9.80)	0.03
Temporal GMV/ICV (%)	7.15 (7.11-7.20)	7.08 (6.93-7.22)	7.15 (6.99-7.32)	6.91 (6.74-7.08)*	6.96 (6.79-7.12)	0.003
Parietal GMV/ICV (%)	6.10 (6.07-6.14)	6.06 (5.95-6.17)	6.11 (5.99-6.24)	6.04 (5.91-6.17)	6.03 (5.90-6.15)	0.18
Occipital GMV/ICV (%)	4.57 (4.55-4.60)	4.52 (4.44-4.60)	4.56 (4.46-4.65)	4.63 (4.53-4.72)	4.48 (4.38-4.58)	0.37
Insular GMV/ICV (%)	0.856 (0.849-0.862)	0.841 (0.820-0.863)	0.866 (0.842-0.891)	0.844 (0.819-0.869)	0.814 (0.789-0.838)*	0.008
Cingulate GMV/ICV (%)	1.77 (1.76-1.78)	1.78 (1.75-1.80)	1.79 (1.76-1.82)	1.76 (1.73-1.80)	1.76 (1.73-1.79)	0.59
Deep GMV/ICV (%)	1.28 (1.26-1.30)	1.22 (1.17-1.28)	1.27 (1.21-1.28)	1.22 (1.16-1.28)	1.17 (1.11-1.23)*	<0.001
Cerebellar GMV/ICV (%)	5.85 (5.80-5.89)	5.72 (5.57-5.87)	5.87 (5.70-6.05)	5.65 (5.47-5.83)	5.62 (5.44-5.79)	0.005

Abbreviations: GMV, gray matter volume; ICV, intracranial volume.

Adjusted for age, sex, low education, hypertension, serum total cholesterol, BMI, smoking habits, alcohol intake, regular exercise, and cerebrovascular lesions on magnetic resonance imaging.

Six subjects with missing values of the duration of known diabetes were excluded from the analysis.

**P*<0.05 vs. no diabetes group.

Supplementary Table 4. Multivariable-adjusted mean values (95% CIs) of the total and regional GMV/ICV ratios according to the time of diabetes diagnosis

	No diabetes (n=623)	Late-life diabetes (n=135)	Midlife diabetes (n=58)	P for trend
Total GMV/ICV ratio (%)	38.4 (38.1-38.6)	38.0 (37.6-38.5)	37.2 (36.4-37.9)*	0.003
Frontal GMV/ICV ratio (%)	9.77 (9.70-9.84)	9.68 (9.53-9.82)	9.42 (9.19-9.65)*	0.004
Temporal GMV/ICV ratio (%)	7.10 (7.05-7.16)	7.05 (6.93-7.17)	6.83 (6.65-7.01)*	0.008
Parietal GMV/ICV ratio (%)	6.08 (6.04-6.12)	6.04 (5.95-6.13)	6.03 (5.89-6.16)	0.35
Occipital GMV/ICV ratio (%)	4.56 (4.53-4.60)	4.54 (4.48-4.61)	4.45 (4.35-4.55)	0.06
Insular GMV/ICV ratio (%)	0.853 (0.845-0.861)	0.852 (0.835-0.869)	0.809 (0.783-0.835)*†	0.01
Cingulate GMV/ICV ratio (%)	1.77 (1.76-1.78)	1.78 (1.76-1.80)	1.73 (1.70-1.77)	0.28
Deep GMV/ICV (%)	1.27 (1.25-1.29)	1.25 (1.21-1.29)	1.15 (1.08-1.21) *†	0.001
Cerebellar GMV/ICV ratio (%)	5.82 (5.76-5.87)	5.72 (5.60-5.84)	5.63 (5.44-5.81)	0.03

Abbreviations: GMV, gray matter volume; ICV, intracranial volume.

Adjusted for age, sex, education status, hypertension, total cholesterol, BMI, smoking habit, alcohol intake, regular exercise, and cerebrovascular lesions on magnetic resonance imaging.

*P<0.05 vs. no diabetes group, †P<0.05 vs. late-life diabetes group.

Supplementary Table 5. Decreased gray matter regions in the subjects with diabetes compared to those without diabetes.

Anatomic region	Peak MNI coordinates			Cluster size (voxels)	Peak <i>t</i> value
	X	Y	Z		
B thalami, R caudate	-18	-31	-0	6486	5.05
R superior temporal gyrus, R middle temporal gyrus	56	-19	-8	1208	4.93
R middle frontal gyrus	27	54	7	1027	4.88
R cerebellum exterior	12	-82	-51	3340	4.28
L planum tempolare, L superior temporal gyrus, L parietal operculum	-57	-36	16	1177	4.10
L inferior temporal gyrus	-51	-9	-33	1104	3.95

Abbreviations: MNI, Montreal Neurological Institute; L, left; R, right; B, bilateral.

Supplementary Table 6. Gray matter regions that were negatively correlated with 2-hour postload glucose levels

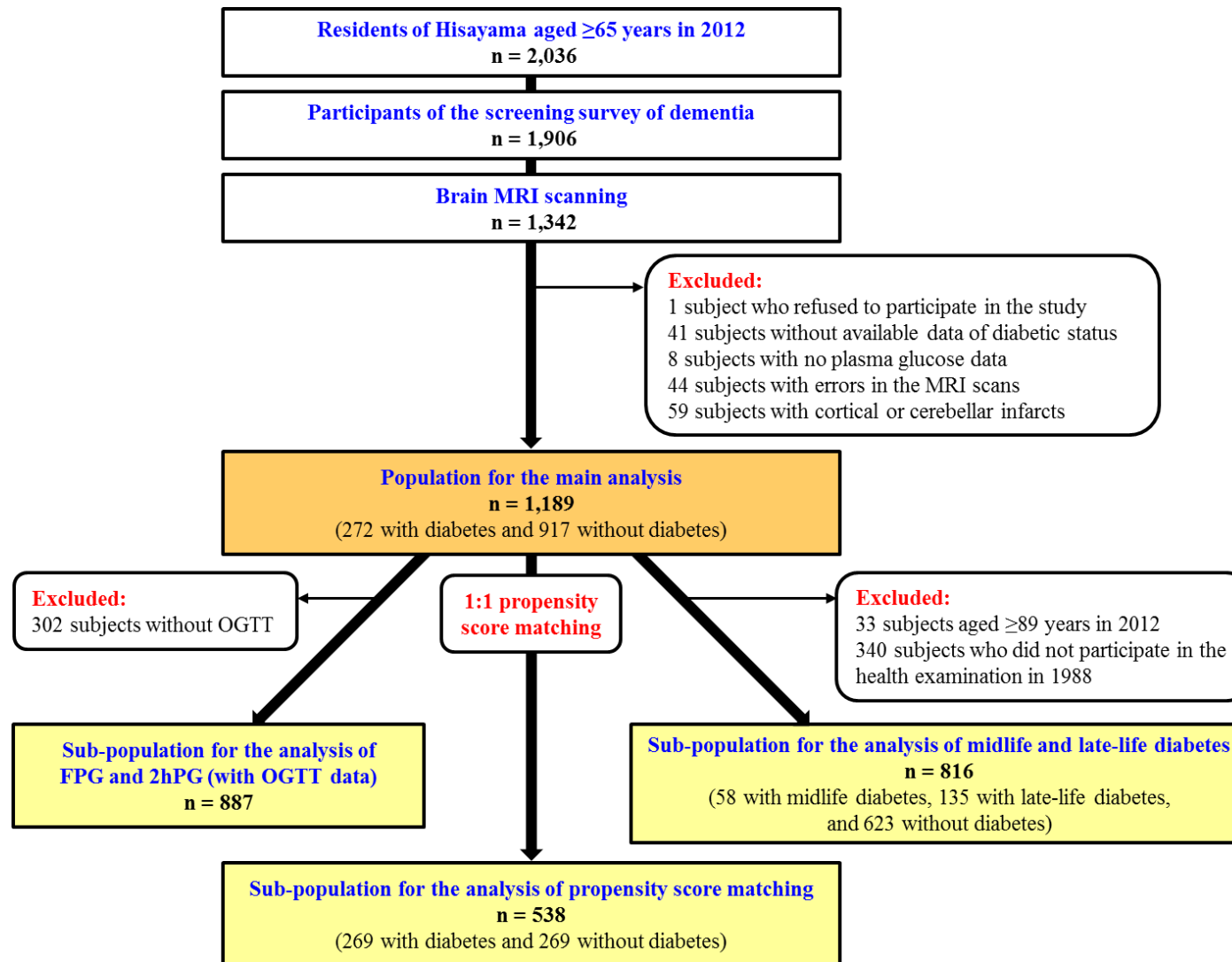
Anatomic region	Peak MNI coordinates			Cluster size (voxels)	Peak <i>t</i> value
	X	Y	Z		
R thalamus	15	-16	13	899	5.27
L middle temporal gyrus, L inferior temporal gyrus, L anterior insula, L temporal pole, L putamen, L planum tempolare, L posterior insula	-57	-12	-29	5576	5.12
R anterior insula	44	11	-14	921	4.93
R middle temporal gyrus, R superior temporal gyrus, R inferior temporal gyrus, R temporal pole	54	-21	-3	2732	4.60
L parietal operculum, L planum tempolare, L transverse temporal gyrus	-59	-33	18	1281	4.49
R opecular part of the inferior frontal gyrus	54	15	24	887	4.47

Abbreviations: MNI, Montreal Neurological Institute; L, left; R, right.

Supplementary Table 7. Decreased regional cortical thickness in the subjects with diabetes compared to those without diabetes

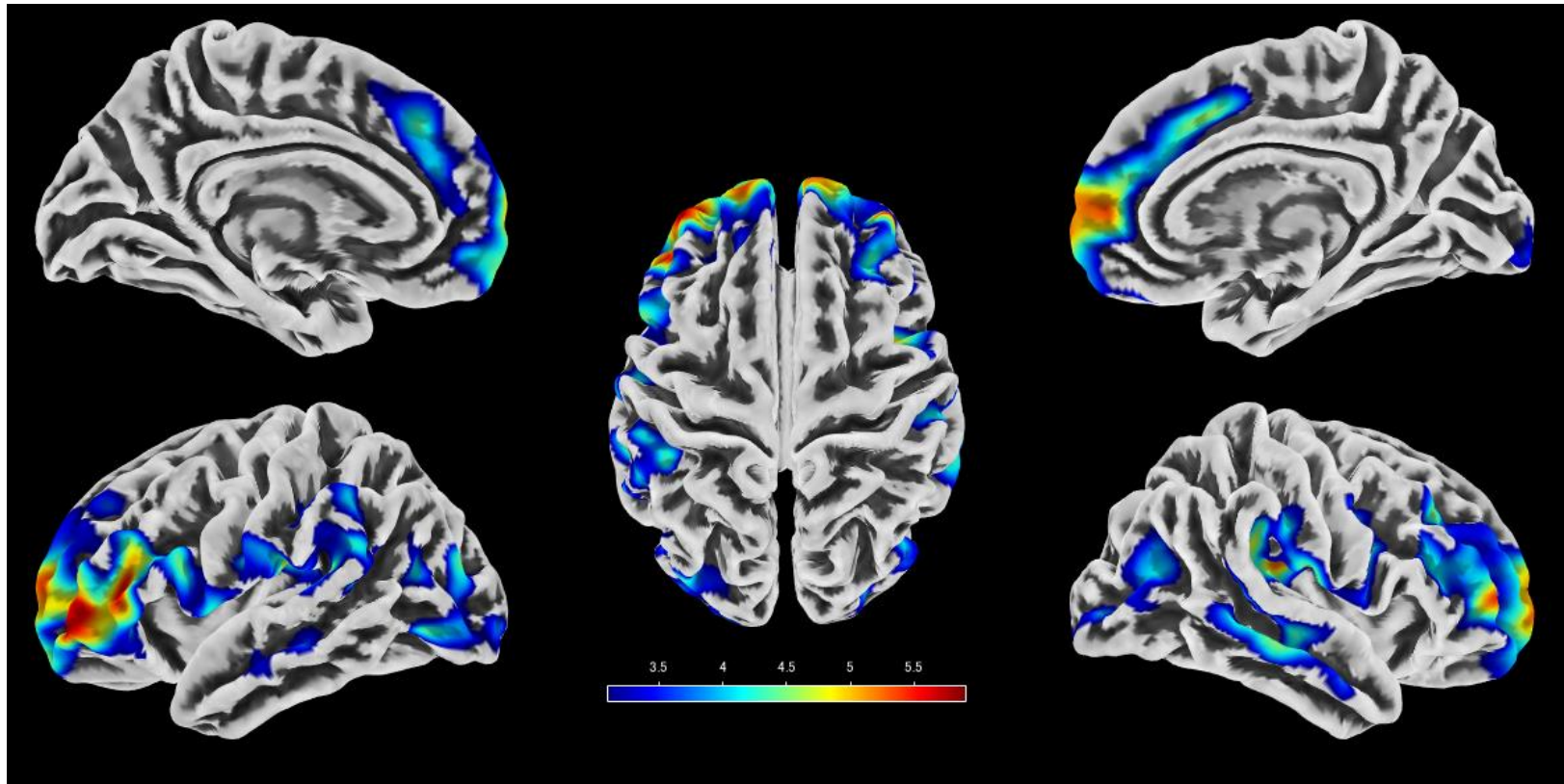
Anatomic region	Peak MNI coordinates			Cluster size (vertices)	Peak <i>t</i> value
	X	Y	Z		
L rostral middle frontal gyrus, L pars opercularis, L pars triangularis, L superior frontal gyrus	-37	55	-4	2510	5.91
R rostral middle frontal gyrus, R superior frontal gyrus	40	53	6	2234	5.48
R supramarginal gyrus, R precentral gyrus, R postcentral gyrus, R insula	34	-27	19	1796	5.33
L supramarginal gyrus, L postcentral gyrus, L superior temporal gyrus, L insula	-53	-37	13	1453	5.22
R middle temporal gyrus, R superior temporal gyrus	67	-27	-11	742	4.53
L lateral occipital gyrus, L inferior parietal gyrus	-44	-74	-6	486	4.42
L superior frontal gyrus	-7	35	38	338	4.38
L supramarginal gyrus	-45	-40	42	388	4.35
L inferior parietal gyrus	-41	-69	17	145	4.18
R inferior parietal gyrus	45	-72	15	288	4.16
R lateral occipital gyrus	31	-91	-0	135	3.88
L middle temporal gyrus	-59	-53	4	146	3.84
L middle temporal gyrus	-59	-30	-11	242	3.76

Abbreviations: MNI, Montreal Neurological Institute; L, left; R, right.



Supplementary Figure 1. Study participants in the main analysis (n = 1,189) and the sub-populations for the analysis of FPG and 2hPG (n = 887), the analysis of midlife and late-life diabetes (n = 816), and the analysis of propensity score matching (n = 538).

Abbreviations: OGTT, oral glucose tolerance test; FPG, fasting plasma glucose; 2hPG, 2-hour postload glucose.



Supplementary Figure 2. Decreased regional cortical thickness in the subjects with diabetes compared to those without diabetes