SUPPLEMENTARY DATA

Detailed protocols of the measurements performed within The Maastricht Study:

Questionnaires. As described elsewhere (15), we used web-based questionnaires to obtain information regarding smoking status (never/former/current), alcohol consumption, educational level, physical activity, diet, prior CVD and cognitive impairment. Alcohol consumption was classified as none, low (1– 7 glasses/wk for women and 1–14 glasses/wk for men) and high (> 7 glasses/wk for women and >14 glasses/wk for men). Educational level was classified as low (no education, primary education, lower vocational education), intermediate (intermediate general secondary education, intermediate vocational education, higher general secondary education), or high (higher vocational education or university). Physical activity was assessed by means of a modified version of the Champs questionnaire. Diet was assessed by a tailor-made FFQ developed by use of the National FFQ Tool. Prior CVD was defined as a history of myocardial infarction; stroke; or vascular surgery (including angioplasty) on coronary, carotid, abdominal aortic, or peripheral arteries, and prior CVA as history of cerebrovascular accident (stroke, or TIA), both based on the Rose questionnaire. Cognitive impairment was measured using the Mini-Mental State Examination (MMSE). Five participants had a MMSE score of 22 or 23 (MCI) and none had dementia Medication use was assessed in a medication interview where generic name, dose, and frequency were registered.

Laboratory assessments. Plasma glucose is measured with a standard enzymatic hexokinase reference method, and serum total cholesterol, HDL cholesterol, and triglycerides are measured with standard (enzymatic and/or colorimetric) methods by an automatic analyzer (until 9 May 2012: Beckman Synchron LX20, Beckman Coulter Inc., Brea, USA; after 9 May 2012: Cobas 6000, Roche diagnostics, Mannheim, Germany). When appropriate LDL cholesterol is calculated according to the Friedewald formula [31]. HbA1c is measured with ion-exchange high performance liquid chromatography (HPLC) (Variant tm II, Bio-Rad, Hercules, California, USA).

Physical examination. Weight and height are measured without shoes and wearing light clothing using a scale and stadiometer to the nearest 0.5 kg or 0.1 cm (Seca, Hamburg, Germany). Waist circumference is measured with a flexible plastic tape measure (Seca, Hamburg, Germany) in a duplicate midway between the lower rib margin and the iliac crest at the end of expiration, to the nearest 0.5 cm.

Blood pressure. Office blood pressure is determined three times on the right arm after a 10-minute rest period, using a non-invasive blood pressure monitor (Omron 705IT, Japan). When the difference between measurement two and three is more than 10mmHg, a fourth measurement is performed. All available measurements are used to calculate the average blood pressure. Ambulatory 24-h blood pressure (WatchBP O3, Microlife, Switzerland, respectively) is measured at the non-dominant arm, using an ambulatory device that is programmed to take blood pressure readings every 15 minutes from 8.00 – 23.00 and every 30 minutes from 23.00 – 8.00.

Additional analyses

With regard to the node degree analyses, the associations of prediabetes and type 2 diabetes, remained unchanged when substituting office systolic blood pressure for 24- hour ambulatory systolic blood pressure (24-hour ambulatory blood pressure was available in n=1888 individuals; Supplementary Table 6) or substituting BMI for waist circumference (Supplementary Table 7), or further adjustment for lifestyle factors, i.e., smoking status, alcohol use, physical activity, and diet score (data available for n=1825, Supplementary Table 8). Furthermore, in the analyses of graph measures, the association of prediabetes and type 2 diabetes remained also unchanged when substituting office systolic blood pressure for 24- hour ambulatory systolic blood pressure (24-hour ambulatory blood pressure was available in n=1888 individuals; Supplementary Table 9) or substituting BMI for waist circumference (Supplementary Table 10), or further adjustment for lifestyle factors (data available for n=1825, Supplementary Table 10).

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SUPPLEMENTARY DATA

Commentary on Supplementary Figure 2:

We want to emphasize that we depicted the normalized graph measures in the figure. These normalized graph measured show a different behavior with varying sparsity values compared to the not normalized graph measures, and are more different to interpret. However, normalization is necessary for comparisons between groups (Maslov and Sneppen, 2002). In more detail: Normalized clustering coefficient increased with sparsity, with the removal of connections at increasing sparsity, the proportion of connections between the nodes within its neighborhood divided by the number of connections that theoretically could exist between them, will decrease. However, since the clustering coefficient is normalized to a random network, for which the proportional decrease is larger, the normalized clustering coefficient thus increases at increasing sparsity (this was also found in the study of van Wijk et al. (van Wijk et al., 2010)). The normalized local efficiency is related to the normalized clustering coefficient, and will therefore show the same behavior. Since the connection-weights represent tract volumes, and since the structural connections taken into account are mostly short (intra-hemispheric) tracts with a small volume, the structural global efficiency is calculated using low connection strengths that increases with sparsity.

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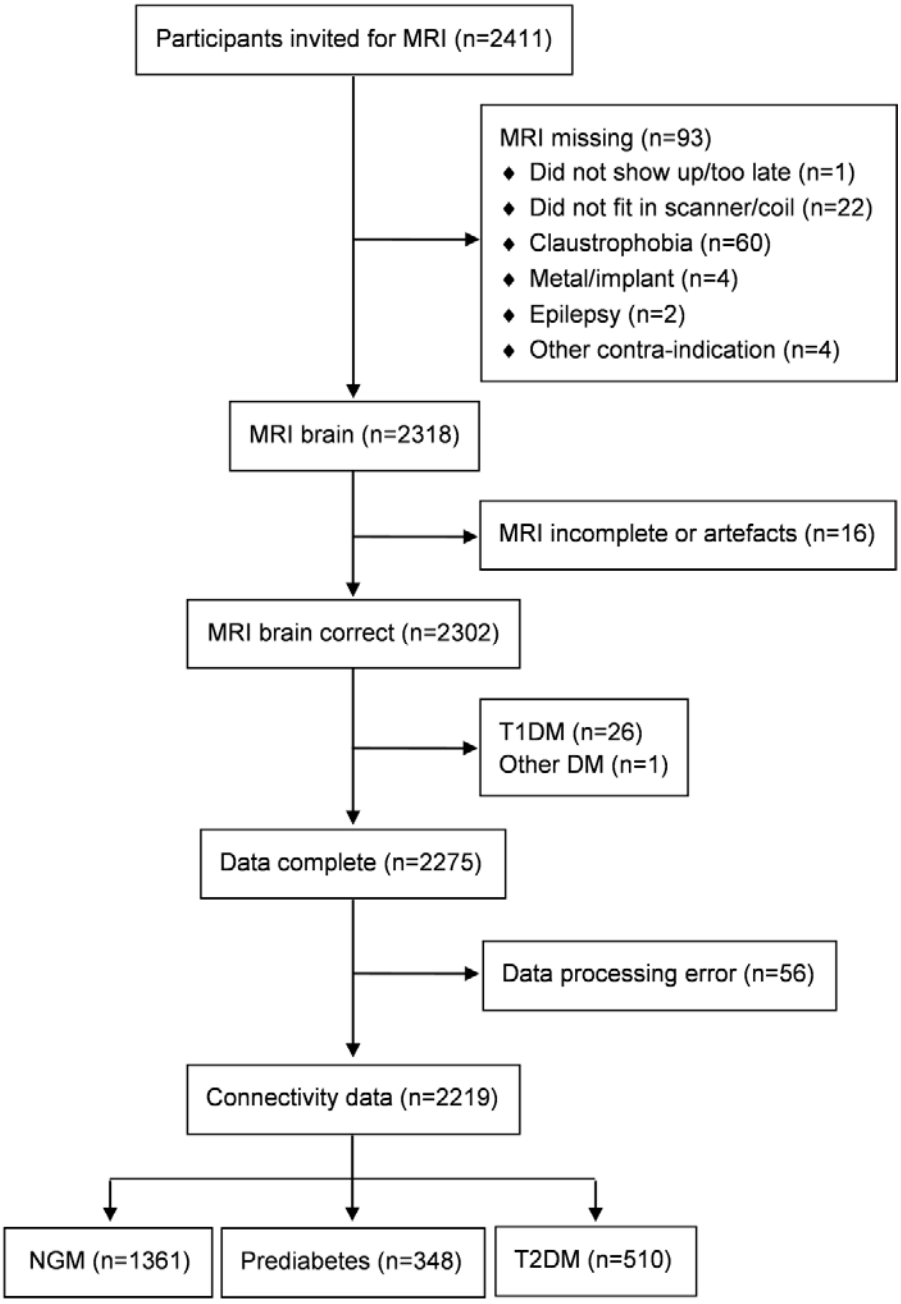
SUPPLEMENTARY DATA

Supplementary Figure 1. Flowchart of the study population. The time lag between baseline assessment and MRI was 2.3±1.3 years (mean ± standard deviation).



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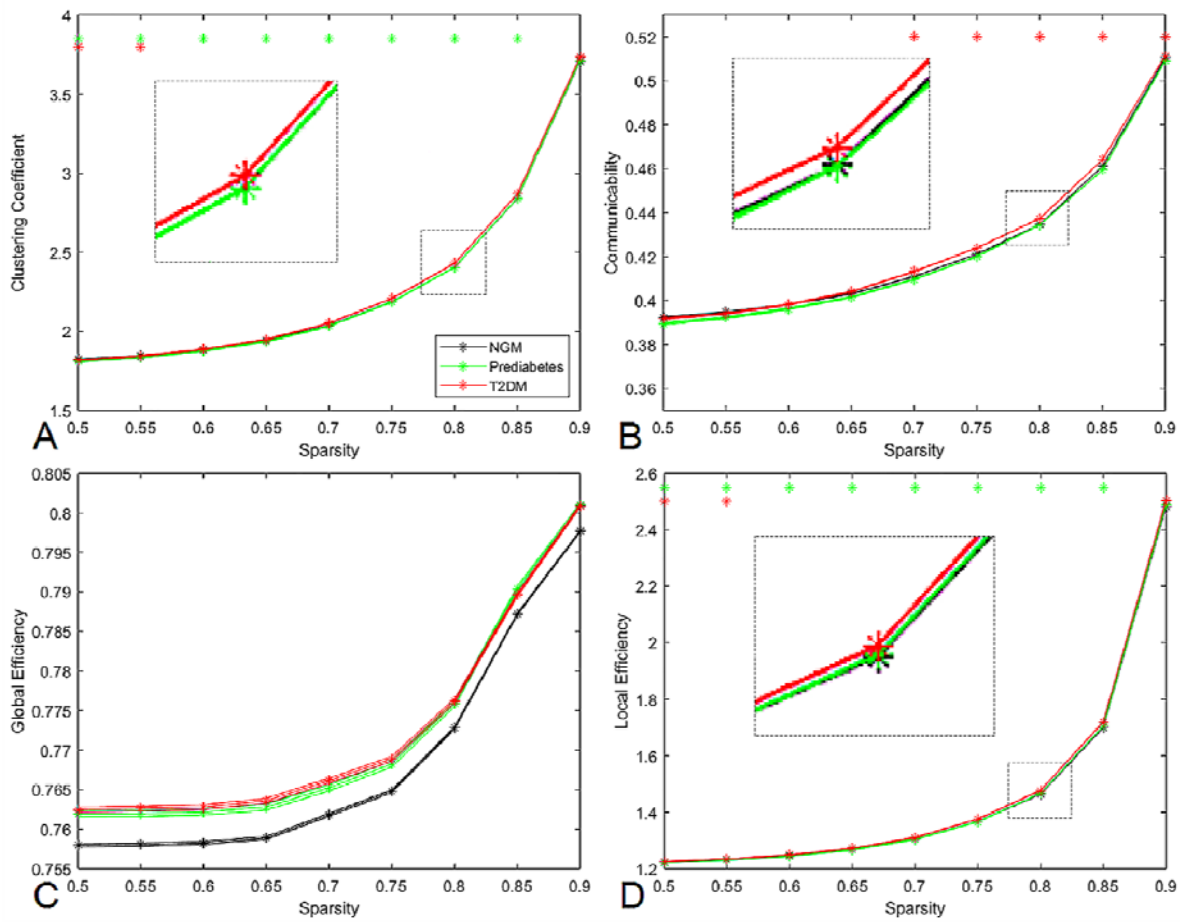
SUPPLEMENTARY DATA

Supplementary Figure 2. Normalized graph measures over a range a sparsity values for participants with type 2 diabetes, prediabetes, and NGM. SEM = standard error of mean.✶= sparsity values analyzed. All graph measures were normalized to random networks (see additional comment in the Supplementary Material on page 3). * = p-value<0.05, red for type 2 diabetes compared to NGM and green for prediabetes compared to NGM. (**A**) Clustering coefficient. (**B**) Communicability. (**C**) Global efficiency, and (**D**) Local efficiency.



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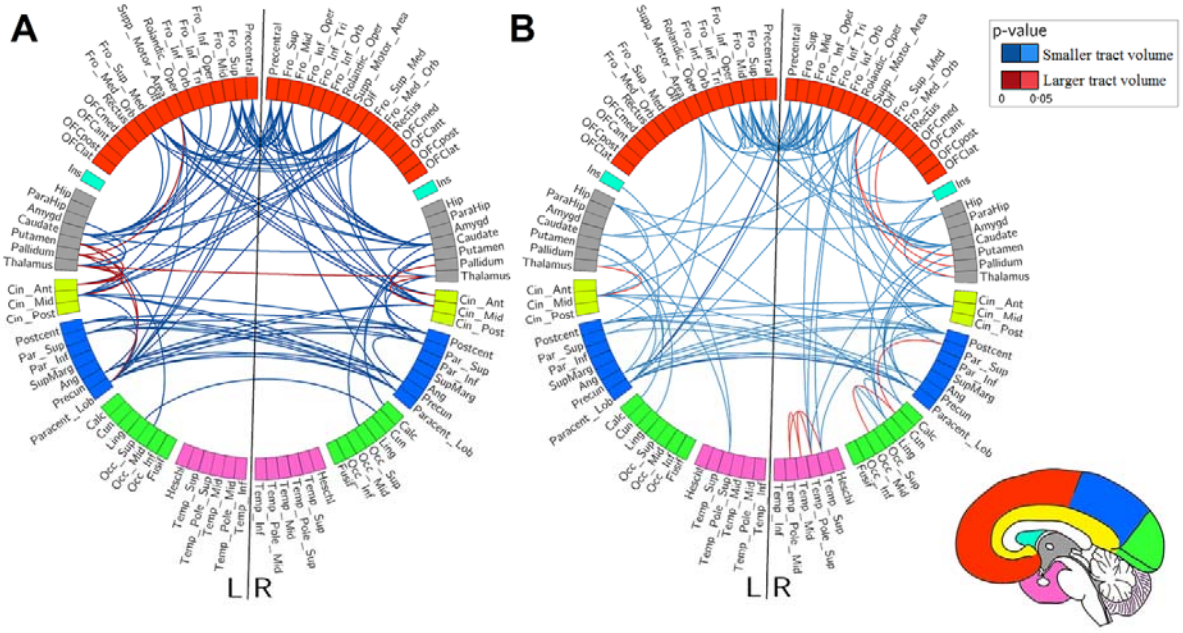
SUPPLEMENTARY DATA

Supplementary Figure 3. Schematic representation of connections between the atlas regions which had a significantly different tract volume for (**A**) higher age, and (**B**) in type 2 diabetes compared to NGM. Blue lines indicate connections with significantly lower tract volumes (unstandardized β<0), and red lines with significantly higher tract volumes (unstandardized β>0). For the comparison of type 2 diabetes with normal aging only the 100 connections with the lowest p-values (all p-values were <0.05) were visualized. Darker blue or red lines indicate lower p-values.



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SUPPLEMENTARY DATA

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

Characteristic	Study population (n=2219)	No brain MRI data available (n=1232)	P value
Demographics			
Age (years)	59.3±8.2	60.6±8.3	<0.001
Sex, male (%)	51.5	51.3	0.905
Education level (%), Low/Middle/High	30.2/29.0/40.7	39.7/26.8/33.5	<0.001
Glucose metabolism			
Type 2 diabetes (%)	23.0	37.7	<0.001
Fasting blood glucose (mmol/l)	5.9±1.5	6.5±2.2	<0.001
2h post-load glucose (mmol/l)	7.5±4.0	8.8±4.6	<0.001
HbA_{1c} (%)	5.8±0.8	6.2±1.1	<0.001
HbA_{1c} (mmol/mol)	40.0±8.9	43.9±12.0	<0.001
Diabetes duration* (years)	6.9±7.2	7.3±1.1	0.449
Cardiovascular risk factors			
BMI (kg/m^2)	26.6±4.2	27.9±5.1	<0.001
Waist circumference (cm)	94.5±12.8	98.5±15.1	<0.001
Office systolic blood pressure (mmHg)	133±17	137±20	<0.001
Office diastolic blood pressure (mmHg)	76±10	76±10	0.320
Hypertension, yes (%)	52.1	61.0	<0.001
Total cholesterol (mmol/L)	5.3±1.1	5.0±1.2	<0.001
HDL cholesterol (mmol/L)	1.6±0.5	1.5±0.5	<0.001
LDL cholesterol (mmol/L)	3.2±1.0	2.9±1.0	<0.001
Triglyceride levels (mmol/L)	1.4±0.8	1.5±0.9	<0.001
Total cholesterol-to-HDL-ratio	3.7±1.2	3.7±1.2	0.283
History of cardiovascular disease, yes (%)	12.1	25.1	<0.001
Medication use			
Insulin use, yes (%)*	19.6	33.8	<0.001
Antihypertensive medication, yes (%)	34.9	49.2	<0.001
Lipid-modifying medication, yes (%)	30.7	47.0	<0.001
Lifestyle factors			
Alcohol consumption (%), None/Low/High	17.1/55.9/27.9	21.3/54.6/24.1	0.003
Smoking status (%), Never/Former/Current	37.4/50.8/11.8	29.3/53.1/17.7	<0.001
Cognitive score			
MMSE total score	29.0±1.2	28.7±1.4	<0.001

Data are presented as means ± standard deviation or percentage, and stratified for availability of MRI data. HbA1c indicates hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MMSE, Mini-Mental State Examination. *Available in type 2 diabetes individuals.

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SUPPLEMENTARY DATA

Supplementary Table 2. Associations of prediabetes and type 2 diabetes with node degree.

	Prediabetes	Type 2 diabetes	P_{trend}
Node degree	standardized β (95% CI)	standardized β (95% CI)	
Unthresholded network			
Model 1	-0.044 (-0.164, 0.076)	**-0.111 (-0.220, -0.002)**	0.047
Model 2	-0.060 (-0.183, 0.063)	**-0.151 (-0.280, -0.022)**	0.022
NGM-based network			
Model 1	-0.066 (-0.181, 0.048)	**-0.296 (-0.400, -0.191)**	<0.001
Model 2	-0.055 (-0.172, 0.062)	**-0.256 (-0.379, -0.133)**	<0.001
Type 2 diabetes-based network			
Model 1	-0.055 (-0.174, 0.064)	**-0.135 (-0.243, -0.027)**	0.015
Model 2	-0.071 (-0.193, 0.050)	**-0.168 (-0.296, -0.040)**	0.010

Associations of prediabetes and type 2 diabetes with node degree, with NGM as reference. Regression coefficients and 95% CI indicate the mean difference in node degree of participants with prediabetes or type 2 diabetes compared with NGM. Model 1: Adjusted for age, sex, education, and MRI date. Model 2: Model 1 + additionally adjusted for BMI, office systolic blood pressure, total cholesterol-to-HDL-ratio, antihypertensive medication, lipid-lowering medication, history of cardiovascular disease. Bold values = p<0.05.

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Supplementary Table 3. Associations of HbA_{1c}, fasting glucose, and 2-h post-load glucose levels with node degree.

	HbA_{1c}	*P*	Fasting glucose	*P*	2-h post-load glucose*	*P*
Node degree	**stdβ (95% CI)**		**stdβ (95% CI)**		**stdβ (95% CI)**	
Unthresholded network						
Model 1	**-0.013 (-0.026, 0.000)**	**0.043**	**-0.085 (-0.162, -0.009)**	**0.029**	**-0.031 (-0.060, -0.003)**	**0.033**
Model 2	**-0.016 (-0.030, -0.002)**	**0.029**	**-0.108 (-0.194, -0.022**	**0.014**	**-0.043 (-0.075, -0.010)**	**0.009**
NGM-based network						
Model 1	**-0.003 (-0.004, -0.002)**	**<0.001**	**-0.017 (-0.023, -0.010)**	**<0.001**	**-0.005 (-0.008, -0.003)**	**<0.001**
Model 2	**-0.003 (-0.004, -0.001)**	**<0.001**	**-0.013 (-0.020, -0.007)**	**<0.001**	**-0.005 (-0.007, -0.002)**	**<0.001**

Associations between continuous measures of glycaemia with node degree. Regression coefficients and 95% CI indicate the mean difference in node degree. Model 1: Adjusted for age, sex, education, and MRI date. Model 2: Model 1 + additionally adjusted for BMI, office systolic blood pressure, total cholesterol-to-HDL-ratio, antihypertensive medication, lipid-lowering medication, history of cardiovascular disease. *2h post-load glucose values were available in n=2098. Bold values = p<0.05.

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Supplementary Table 4. Associations of HbA_{1c}, fasting glucose, and 2-h post-load glucose levels with graph network measures at a sparsity value of 0.8.

	HbA_{1c}	*P*	Fasting glucose	*P*	2-h post-load glucose*	*P*
Normalized graph measures	**stdβ (95% CI)**		**stdβ (95% CI)**		**stdβ (95% CI)**	
Clustering coefficient						
Model 1	-0.020 (-0.055, 0.015)	0.255	-0.021 (-0.056, 0.015)	0.250	-0.004 (-0.040, 0.032)	0.815
Model 2	-0.004 (-0.044, 0.035)	0.823	-0.002 (-0.042, 0.037)	0.915	0.015 (-0.025, 0.055)	0.466
Global efficiency						
Model 1	-0.035 (-0.080, 0.009)	0.121	**-0.052 (-0.097, -0.008)**	**0.022**	-0.015 (-0.060, 0.030)	0.512
Model 2	-0.030 (-0.080, 0.021)	0.248	-0.049 (-0.099, 0.001)	0.054	-0.006 (-0.056, 0.045)	0.821
Local efficiency						
Model 1	**-0.029 (-0.058, -0.001)**	**0.046**	**-0.030 (-0.059, -0.001)**	**0.042**	-0.012 (-0.042, 0.017)	0.423
Model 2	-0.013 (-0.046, 0.019)	0.425	-0.011 (-0.043, 0.021)	0.506	0.007 (-0.026, 0.040)	0.662
Communicability						
Model 1	0.043 (-0.001, 0.087)	0.053	**0.051 (0.007, 0.095)**	**0.023**	**0.051 (0.006, 0.095)**	**0.026**
Model 2	0.042 (-0.007, 0.092)	0.094	**0.054 (0.005, 0.103)**	**0.032**	**0.053 (0.003, 0.103)**	**0.039**

Associations between continuous measures of hyperglycemia with graph measures (based on most sparse type 2 diabetes-based group network). Regression coefficients and 95% CI indicate the mean difference in clustering coefficient, global efficiency, local efficiency, and communicability. Model 1: Adjusted for age, sex, education, node degree, and MRI date. Model 2: Model 1 + additionally adjusted for BMI, office systolic blood pressure, total cholesterol-to-HDL-ratio, antihypertensive medication, lipid-lowering medication, history of cardiovascular disease. *2h post-load glucose values were available in n=2098. Bold values = p<0.05.

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SUPPLEMENTARY DATA

Supplementary Table 5. Relative change for (pre)diabetes and age in node degree.

		Node degree*	
		standardized β (95%)	**p-value**
Model 1†	*Prediabetes*	-0.024 (-0.065, 0.017)	0.258
	Type 2 diabetes	-0.134 (-0.181, -0.086)	**<0.001**
	Age	-0.236 (-0.279, -0.194)	**<0.001**
	$\frac{\beta_{Prediabetes}}{\beta_{Age}} \cdot \frac{SD_{Age}}{SD_{Prediabetes}}$	**2.3 years**	
	$\frac{\beta_{Type2diabetes}}{\beta_{Age}} \cdot \frac{SD_{Age}}{SD_{Type2diabetes}}$	**10.4 years**	
Model 2‡	*Prediabetes*	-0.020 (-0.061, 0.022)	0.357
	Type 2 diabetes	-0.116 (-0.171, -0.060)	**<0.001**
	Age	-0.219 (-0.264, -0.174)	**<0.001**
	$\frac{\beta_{Prediabetes}}{\beta_{Age}} \cdot \frac{SD_{Age}}{SD_{Prediabetes}}$	**2.1 years**	
	$\frac{\beta_{Type2diabetes}}{\beta_{Age}} \cdot \frac{SD_{Age}}{SD_{Type2diabetes}}$	**9.7 years**	

*Node degree for entire dataset (n=2219), calculated in NGM-based standard network. †Additionally adjusted for sex, education, and MRI date. ‡Model 1 + additionally adjusted for BMI, office systolic blood pressure, total-cholesterol-to-HDL-ratio, antihypertensive medication, lipid-lowering medication, history of cardiovascular disease. Bold values = p<0.05.

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Supplementary Table 6: Associations of prediabetes and type 2 diabetes with node degree, with replacement of office by 24-h systolic ambulatory blood pressure in regression models.

	Prediabetes	Type 2 diabetes	P_{trend}
Node degree	standardized β (95% CI)	standardized β (95% CI)	
Unthresholded network			
Model 1	-0.058 (-0.189, 0.072)	**-0.169 (-0.287, -0.051)**	0.005
Model 2	-0.078 (-0.211, 0.055)	**-0.234 (-0.371, -0.097)**	0.001
NGM-based network			
Model 1	-0.068 (-0.194, 0.058)	**-0.279 (-0.393, -0.166)**	<0.001
Model 2	-0.063 (-0.192, 0.065)	**-0.259 (-0.392, -0.127)**	<0.001
Type 2 diabetes-based network			
Model 1	-0.057 (-0.189, 0.074)	**-0.150 (-0.269, -0.032)**	0.013
Model 2	-0.077 (-0.211, 0.057)	**-0.201 (-0.340, -0.063)**	0.004

Associations of prediabetes and type 2 diabetes with node degree, with NGM as reference. Regression coefficients and 95% CI indicate the mean difference in node degree of participants with prediabetes or type 2 diabetes compared with NGM. Model 1: Adjusted for age, sex, education, and MRI date. Model 2: Model 1 + additionally adjusted for BMI, 24-h systolic ambulatory blood pressure, total cholesterol-to-HDL-ratio, antihypertensive medication, lipid-lowering medication, history of cardiovascular disease. Data were available in n=1888 individuals (type 2 diabetes/prediabetes/NGM, 437/293/1158, respectively). Bold values = p<0.05.

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SUPPLEMENTARY DATA

Supplementary Table 7. Associations of prediabetes and type 2 diabetes with node degree, with replacement of BMI by waist circumference in regression models.

	Prediabetes	Type 2 diabetes	P_{trend}
Node degree	standardized β (95% CI)	standardized β (95% CI)	
Unthresholded network			
Model 1	-0.043 (-0.163, 0.077)	**-0.111 (-0.220, -0.002)**	0.047
Model 2	-0.054 (-0.177, 0.069)	**-0.139 (-0.270, -0.009)**	0.037
NGM-based network			
Model 1	-0.066 (-0.181, 0.049)	**-0.296 (-0.400, -0.191)**	<0.001
Model 2	-0.055 (-0.172, 0.062)	**-0.256 (-0.380, -0.131)**	<0.001
Type 2 diabetes-based network			
Model 1	-0.054 (-0.173, 0.065)	**-0.135 (-0.243, -0.027)**	0.015
Model 2	-0.070 (-0.192, 0.052)	**-0.168 (-0.295, -0.037)**	0.012

Associations of prediabetes and type 2 diabetes with node degree, with NGM as reference. Regression coefficients and 95% CI indicate the mean difference in node degree of participants with prediabetes or type 2 diabetes compared with NGM. Model 1: Adjusted for age, sex, education, and MRI date. Model 2: Model 1 + additionally adjusted for waist circumference, office systolic blood pressure, total cholesterol-to-HDL-ratio, antihypertensive medication, lipid-lowering medication, history of cardiovascular disease. Data were available in n=2218 individuals (type 2 diabetes/prediabetes/NGM, 510/348/1360, respectively). Bold values = p<0.05.

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Supplementary Table 8. Associations of prediabetes and type 2 diabetes with node degree, additionally adjusted for lifestyle factors.

	Prediabetes	Type 2 diabetes	P_{trend}
Node degree	standardized β (95% CI)	standardized β (95% CI)	
Unthresholded network			
Model 1	-0.009 (-0.139, 0.120)	**-0.126 (-0.246, -0.006)**	0.054
Model 2	-0.030 (-0.162, 0.103)	**-0.179 (-0.321, -0.037)**	0.020
Model 3	-0.027 (-0.160, 0.106)	**-0.174 (-0.318, -0.031)**	0.026
NGM-based network			
Model 1	-0.066 (-0.188, 0.055)	**-0.320 (-0.433, -0.207)**	<0.001
Model 2	-0.047 (-0.171, 0.078)	**-0.264 (-0.397, -0.130)**	<0.001
Model 3	-0.041 (-0.165, 0.084)	**-0.253 (-0.388, -0.118)**	0.001
Type 2 diabetes-based network			
Model 1	-0.035 (-0.163, 0.093)	**-0.168 (-0.287, -0.049)**	0.008
Model 2	-0.048 (-0.179, 0.083)	**-0.188 (-0.329, -0.047)**	0.012
Model 3	-0.044 (-0.175, 0.087)	**-0.176 (-0.318, -0.034)**	0.020

Associations of prediabetes and type 2 diabetes with node degree, with NGM as reference. Regression coefficients and 95% CI indicate the mean difference in node degree of participants with prediabetes or type 2 diabetes compared with NGM. Model 1: Adjusted for age, sex, education, and MRI date. Model 2: Model 1 + additionally adjusted for BMI, office systolic blood pressure, total cholesterol-to-HDL-ratio, antihypertensive medication, lipid-lowering medication, history of cardiovascular disease. Model 3: Model 2 + additionally adjusted for smoking status, alcohol use, physical activity and diet score. Bold values = p<0.05. Physical activity and diet score data were available in n=1825 individuals (388/294/1143 for type 2 diabetes/prediabetes/NGM, respectively).

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SUPPLEMENTARY DATA

Supplementary Table 9. Associations of prediabetes and type 2 diabetes with graph network measures at a sparsity value of 0.8, with replacement of office by 24-h systolic ambulatory blood pressure in regression models.

	Prediabetes*	P	Type 2 diabetes†	P
Normalized graph measures, β (95% CI)				
Clustering coefficient				
Model 1	**-0.110 (-0.210, -0.009)**	**0.032**	-0.036 (-0.128, 0.056)	0.448
Model 2	-0.085 (-0.188, 0.017)	0.103	0.024 (-0.083, 0.131)	0.665
Global efficiency				
Model 1	0.015 (-0.117, 0.147)	0.820	-0.071 (-0.188, 0.046)	0.235
Model 2	0.028 (-0.107, 0.163)	0.683	-0.021 (-0.158, 0.116)	0.762
Local efficiency				
Model 1	**-0.093 (-0.175, -0.011)**	**0.027**	-0.050 (-0.126, 0.025)	0.191
Model 2	-0.073 (-0.157, 0.011)	0.087	0.012 (-0.076, 0.099)	0.794
Communicability				
Model 1	0.032 (-0.097, 0.162)	0.622	**0.165 (0.048, 0.282)**	**0.006**
Model 2	0.047 (-0.086, 0.179)	0.490	**0.173 (0.037, 0.310)**	**0.013**

*Prediabetes-based standard network. †Type 2 diabetes-based standard network. Associations of prediabetes and type 2 diabetes with graph measures. Regression coefficients and 95% CI indicate the mean difference in clustering coefficient, global efficiency, local efficiency, and communicability of participants with prediabetes or type 2 diabetes compared with NGM. Model 1: Adjusted for age, sex, education, node degree, and MRI date. Model 2: Model 1 + additionally adjusted for BMI, 24-h systolic ambulatory blood pressure, total cholesterol-to-HDL-ratio, antihypertensive medication, lipid-lowering medication, history of cardiovascular disease. Data were available in n=1888 individuals (type 2 diabetes/prediabetes/NGM, 437/293/1158, respectively). Bold values = p<0.05.

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SUPPLEMENTARY DATA

Supplementary Table 10. Associations of prediabetes and type 2 diabetes with graph network measures at a sparsity value of 0.8, with replacement of BMI by waist circumference in regression models.

	Prediabetes*	P	Type 2 diabetes†	P
Normalized graph measures, β (95% CI)				
Clustering coefficient				
Model 1	**-0.092 (-0.185, 0.000)**	**0.050**	-0.025(-0.112, 0.061)	0.562
Model 2	-0.067 (-0.162, 0.028)	0.168	0.035 (-0.067, 0.137)	0.500
Global efficiency				
Model 1	0.030 (-0.091, 0.151)	0.624	-0.069 (-0.178, 0.040)	0.212
Model 2	0.049 (-0.076, 0.173)	0.445	-0.014 (-0.144, 0.116)	0.836
Local efficiency				
Model 1	**-0.082 (-0.157, -0.006)**	**0.034**	-0.045 (-0.116, 0.025)	0.208
Model 2	-0.057 (-0.135, 0.020)	0.148	0.022 (-0.062, 0.105)	0.615
Communicability				
Model 1	0.029 (-0.090, 0.147)	0.475	**0.146 (0.039, 0.253)**	**0.008**
Model 2	0.035 (-0.087, 0.157)	0.577	**0.154 (0.026, 0.282)**	**0.018**

*Prediabetes-based standard network. †Type 2 diabetes-based standard network. Associations of prediabetes and type 2 diabetes with graph measures. Regression coefficients and 95% CI indicate the mean difference in clustering coefficient, global efficiency, local efficiency, and communicability of participants with prediabetes or type 2 diabetes compared with NGM. Model 1: Adjusted for age, sex, education, node degree, and MRI date. Model 2: Model 1 + additionally adjusted for waist circumference, office systolic blood pressure, total cholesterol-to-HDL-ratio, antihypertensive medication, lipid-lowering medication, history of cardiovascular disease. Data were available in n=2218 individuals (type 2 diabetes/prediabetes/NGM, 510/348/1360, respectively). Bold values = p<0.05.

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SUPPLEMENTARY DATA

Supplementary Table 11. Associations of prediabetes and type 2 diabetes with graph network measures at a sparsity value of 0.8, additionally adjusted for lifestyle factors.

	Prediabetes*	P	Type 2 diabetes†	P
Normalized graph measures, β (95% CI)				
Clustering coefficient				
Model 1	-0.077 (-0.177, 0.023)	0.130	-0.014 (-0.109, 0.081)	0.771
Model 2	-0.047 (-0.150, 0.056)	0.371	0.046 (-0.066, 0.158)	0.425
Model 3	-0.049 (-0.152, 0.054)	0.349	0.034 (-0.079, 0.146)	0.560
Global efficiency				
Model 1	0.023 (-0.107, 0.152)	0.733	-0.042 (-0.161, 0.077)	0.490
Model 2	0.021 (-0.113, 0.155)	0.755	-0.014 (-0.155, 0.128)	0.847
Model 3	0.023 (-0.111, 0.157)	0.737	-0.015 (-0.157, 0.128)	0.839
Local efficiency				
Model 1	-0.072 (-0.154, 0.009)	0.083	-0.039 (-0.117, 0.039)	0.326
Model 2	-0.048 (-0.132, 0.036)	0.259	0.017 (-0.075, 0.109)	0.712
Model 3	-0.049 (-0.133, 0.035)	0.252	0.010 (-0.082, 0.103)	0.828
Communicability				
Model 1	0.082 (-0.046, 0.211)	0.208	**0.171 (0.052, 0.290)**	**0.005**
Model 2	0.103 (-0.030, 0.235)	0.128	**0.199 (0.059, 0.340)**	**0.005**
Model 3	0.097 (-0.036, 0.229)	0.154	**0.184 (0.042, 0.326)**	**0.011**

*Prediabetes-based standard network. †Type 2 diabetes-based standard network. Associations of prediabetes and type 2 diabetes with graph measures. Regression coefficients and 95% CI indicate the mean difference in clustering coefficient, global efficiency, local efficiency, and communicability of participants with prediabetes or type 2 diabetes compared with NGM. Model 1: Adjusted for age, sex, education, node degree, and MRI date. Model 2: Model 1 + additionally adjusted for BMI, office systolic blood pressure, total cholesterol-to-HDL-ratio, antihypertensive medication, lipid-lowering medication, history of cardiovascular disease. Model 3: Model 2 + additionally adjusted for smoking status, alcohol use, physical activity, and diet score. Bold values = p<0.05. Physical activity and diet score data were available in n=1825 individuals (388/294/1143 for type 2 diabetes/prediabetes/NGM, respectively).

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SUPPLEMENTARY DATA

Supplementary Table 12. Additional clinical characteristics of participants according to glucose metabolism status.

Characteristic	NGM (n = 1361)	Prediabetes (n = 348)	Type 2 diabetes (n = 510)	P_{trend}
Cardiovascular risk factors				
24-h ambulatory systolic BP (mmHg)[*]	118±11	121±12	123±11	<0.001
24-h ambulatory diastolic BP (mmHg)[*]	75±7	76±7	74±7	0.114
Total cholesterol (mmol/L)	5.6±1.0	5.5±1.1	4.5±1.0	<0.001
HDL cholesterol (mmol/L)	1.7±0.5	1.5±0.4	1.3±0.4	<0.001
LDL cholesterol (mmol/L)	3.4±0.9	3.3±1.0	2.4±0.9	<0.001
Triglyceride levels (mmol/L)	1.2±0.7	1.6±1.0	1.7±1.0	<0.001
Lifestyle factors				
Physical activity (hours/week)[†]	15.2±8.1	14.4±7.7	12.1±7.1	<0.001
Diet (Greek Mediterranean diet score, 1-9)[‡]	4.6±1.7	4.5±1.7	4.1±1.6	<0.001

Data are presented as means ± standard deviation or percentage, and stratified for glucose metabolism status: normal glucose metabolism (NGM), prediabetes, and type 2 diabetes. P-values indicate trend analysis over glucose metabolism status. BP indicates blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein. [*]24-h ambulatory blood pressure data was available in n=1888. [†]Physical activity data was available in n=1969. [‡]Diet score was available in n=2104. Detailed protocols of the general measurements are presented in the supplementary material.

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