Supplementary Material

Association between pre-diabetes and microvascular and macrovascular disease in newly

diagnosed type 2 diabetes

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Supplementary Figure S1. Study diagram

277,095 individuals with a diagnosis of T2D formulated between 1 Jan 2004 and 30 Sep 2017 registered with CPRD general practices in England

220,370 individuals with a diagnosis of T2D formulated between 1 Jan 2004 and 30 Sep 2017 registered with CPRD general practices in England

167,939 individuals with a diagnosis of T2D formulated between 1 Jan 2004 and 30 Sep 2017 registered with CPRD general practices in England with linkage data available

159,736 individuals with a diagnosis of T2D formulated between 1 Jan 2004 and 30 Sep 2017 registered with CPRD general practices in England with linkage data available

Abbreviations: T2D: Type 2 diabetes.

Exclude 56,720 individuals registered with English CPRD practices that did not consent to data linkage

Exclude 52,431 individuals because the date of T2D diagnosis was preceding the registration date or because the interval between registration date and date of T2D diagnosis was less than one year

Exclude 8,203 individuals because in the three years prior to the diagnosis of T2D they have been tested with glycaemic values within the diabetic range but testing has not been followed by a formal diagnosis of T2D in the following three months Supplementary Table S2. Definition of pre-diabetes and study outcomes

Detection of Pre-diabetes Microvascular dise	Laboratory diagnostic criteria: - World Health Organization/International Expert Committee: FPG 6.1-6.9 mmol/L; OGTT 7.8-11.1 mmol/L; HbA1c 42 to 47 mmol/mol (6.0-6.4%) - NICE: FPG 5.5-6.9 mmol/L; OGTT 7.8-11.1 mmol/L; HbA1c 42 to 47 mmol/mol (6.0-6.4%) - American Diabetes Association: FPG 5.6-6.9 mmol/L; OGTT 7.8-11.1 mmol/L; HbA1c 39 to 47 mmol/mol or 5.7- 6.4% Diagnostic codes for pre-diabetes, Impaired Glucose Tolerance, Impaired Glucose Metabolism, Intermediate Hyperglycaemia, and Non-diabetic Hyperglycaemia ease present at time of diagnosis of Type 2 diabetes
(diagnosed in the fiv diabetes)	ve years before and fifteen months after the diagnosis of Type 2
Diabetic	- Diagnostic codes for diabetic retinopathy (including codes
retinopathy	for photocoagulation/vitrectomy, diabetic cataract, and acquired blindness) - Results from Diabetic retinopathy screening - ICD-X (E11.3; H36.0; H28.0) - OPCS-4 (C81.1; C81.2; C81.8; C81.9; C79.1; C79.2; C74.2)
Nephropathy	 Diagnostic codes for Chronic Kidney Disease stage 3A and above (including end-stage renal disease and renal replacement therapy) If any of the following conditions is present: Microalbuminuria (albumin:creatine ratio 30-300 mg/g); Macroalbuminuria (albumin:creatine ratio ≥ 300 mg/g); Serum creatinine ≥ 3.3 mg/dL; GFR less than 60 mL/min per 1.73 m² ICD-10 (N18.3; N18.4; N18.5) OPCS-4 (M01; X40)
Macrovascular dis	ease at time of diagnosis of Type 2 diabetes
(diagnosed before o	or within the year following the diagnosis of Type 2 diabetes)
Cerebrovascular disease Stroke, Carotid Endarterectomy (CEA), Carotid artery stenting (CAS)	Stroke - Diagnostic codes for haemorrhagic and ischaemic strokes - ICD-10 (I60-I64) CEA & CAS - OPCS-4.6: L29.4; L29.5 (CEA); L31.4 (CAS)
Acute Coronary Syndrome	AMI - Diagnostic codes for acute myocardial infarction - ICD-10 (I21; I22) CAD
Acute Myocardial	

Infarction (AMI), Coronary Artery Disease (CAD), Coronary Revascularisation Procedures	 Diagnostic codes for CAD ICD-10 (I20; I25) Coronary Revascularisation Procedures OPCS-4.6: K49; K50; K75; K40-K46)
Peripheral Arterial disease	PAD - Diagnostic codes for peripheral arterial disease - ICD-10 (E11.5; I70.2/7; I70.92)
Peripheral arterial disease (PAD), non- traumatic amputation	AMPUTATION -Diagnostic codes for non-traumatic amputation -OPCS-4.6: (X09.2-5,8-9; X10.1,4,8-9; X11.1,2,8,9)

Supplementary Table S3. Characteristics of the study population in the year following the diagnosis of Type 2 diabetes stratified by whether individuals were tested and reached detection thresholds for pre-diabetes before the diagnosis of Type 2 diabetes. Results are presented using NICE and ADA criteria for the definition of pre-diabetes.

Notes: Clinical data within three years before the diagnosis of Type 2 diabetes were used to define the detection of prediabetes. For both diagnostic criteria (NICE and ADA) p-values from Chi-square and ANOVA tests, as appropriate, are reported in the last columns for comparison between the two groups defined by testing and detection of pre-diabetes. Abbreviations: FPG: fasting plasma glucose, OGTT: glucose tolerance test (2-hour after 75 g glucose load), ACEi: Angiotensin-converting-enzyme inhibitor, ARBs: Antiotensin II receptor blockers.

NICE criteria to define pre-diabetes: 5.5-6.9 mmol/L, OGTT 7.8-11.1 mmol/L, HbA1c 42 to 47 mmol/mol or 6.0-6.4%

ADA criteria to define pre-diabetes: FPG: 5.6-6.9 mmol/L, OGTT 7.8-11.1 mmol/L, HbA1c 39 to 47 mmol/mol or 5.7-6.4% ¥Chi-square test was performed to assess the unadjusted difference between groups

§ANOVA test was performed to assess the unadjusted difference between groups

ΩKruskal-Wallis test was performed to assess the unadjusted difference between groups

* Medication groups are not mutually exclusive and patients with multiple medications prescribed are counted multiple times.

	Total	No glycaemic	NICE	DIAGNOSTIC CRITER	RIA ²	ADA DIAGNOSTIC CRITERIA ³			
		 measures recorded before the diagnosis of Type 2 diabetes 	Glycaemic values within the normal range before the diagnosis of T2D	Pre-diabetes detected before the diagnosis of T2D	p-values	Glycaemic values within the normal range before the diagnosis of T2D	Pre-diabetes detected before the diagnosis of T2D	p-values	
N	159,736	93,949	14,431	51,356		14,317	51,470		
%		58.8	9.0	32.2		9.0	32.2		
Type of glycaemic measures recorded before diagnosis of T2D (%)									
FPG			72.8	78.1		84.3	74.9		
HbA1C			41.9	54.3		30.5	57.5		
OGTT			2.0	20.6		3.0	20.3		
Multiple tests			16.0	50.9		16.9	50.5		
Time from testing to diagnosis of T2D, months; mean (SD)	33.0 (6.1)		32.7 (6.6)	33.1 (6.0)		33.1 (6.0)	33.0 (6.2)		
Female (%)	49.2	48.8	59.0	47.1	<0.001 [¥]	58.1	47.3	<0.001 [¥]	
Age, years (SD)	61.5 (14.4)	60.2 (14.8)	60.4 (15.4)	64.1 (12.7)	<0.001 [§]	60.1 (15.3)	64.2 (12.8)	<0.001 [§]	
Ethnicity (%)									
White	83	82.7	84.7	83	<0.001 [¥]	84.9	83	<0.001 [¥]	
South Asian	3.6	3.1	3.9	4.5		4.1	4.4		
Black	2.4	2.2	3.3	2.7	o oo t¥	3.2	2.7	o oo t¥	
Other	3.1	2.9	3.3	3.3	<0.001 [¥]	3.2	3.3	<0.001 [¥]	
Unknown	7.9	9.2	4.8	6.5		4.6	6.6		
Smoking status (%)									
Non-smoker	35.4	36.8	30.2	36.7	<0.001 [¥]	37	32.5	<0.001 [¥]	
Ex-smoker	51.6	43.4	51.2	47	<0.001	44.9	51.2	<0.001	
Current smoker (continued)	16.1	19.8	18.6	16.3		18.2	16.3		

	Total	No glycaemic	NICE DIAGN	IOSTIC CRITE	RIA ²	ADA DIAG	NOSTIC CRITER	IA ³
		measures recorded before the diagnosis of Type 2 diabetes	Glycaemic values within the normal range before the diagnosis of T2D	Pre-diabetes detected before the diagnosis of T2D	p-values	Glycaemic values within the normal range before the diagnosis of T2D	Pre-diabetes detected before the diagnosis of T2D	p-values
HbA1c at diagnosis, mmol/mol; mean (SD)	55.2 (20.7)	59.4 (20.8)	45.4 (17.5)	50.8 (19.7)	<0.001 [§]	46.0 (19.3)	50.1 (18.8)	<0.001 [§]
BMI, kg/m2; mean (SD)	30.30 (6.7)	30.0 (6.7)	28.9 (6.8)	31.3 (6.6)	<0.001 [§]	29.1 (6.9)	31.2 (6.6)	<0.001 [§]
SBP, mm Hg; mean (SD)	136.4 (15.9)	136.4 (16.6)	132.9 (15.9)	137.2 (14.4)	<0.001 [§]	133.0 (15.9)	137.2 (14.4)	<0.001 [§]
DBP, mm Hg; mean (SD)	79.7 (9.4)	80.1 (9.6)	78.3 (9.4)	79.4 (8.8)	<0.001 [§]	78.5 (9.4)	79.4 (8.8)	<0.001 [§]
Total cholesterol, mmol/L; mean (SD)	5.1 (1.1)	5.2 (1.1)	5.1 (1.1)	4.9 (1.1)	<0.001 [§]	5.1 (1.1)	4.9 (1.1)	<0.001 [§]
Number of chronic diseases; mean (SD)	2.7 (2.0)	2.4 (1.9)	3.2 (2.1)	3.1 (2.0)	<0.001 [§]	3.2 (2.1)	3.1 (2.0)	<0.001 [§]
Medications (%)								
Anti-hypertensive	53.8	47.5	47.2	67.1	<0.001 [¥]	48.2	66.8	<0.001 [¥]
ACEi/ARBs	39	34.1	32.6	49.9	<0.001 [¥]	33.7	49.6	<0.001 [¥]
Anti-lipid medications	49.6	44.2	38.5	62.5	<0.001 [¥]	39.6	62.1	<0.001 [¥]
Anti-diabetic*	38.4	44.7	13.8	33.9	<0.001 [¥]	15.2	33.4	<0.001 [¥]
Biguanides	34.6	39.8	11.6	31.6	<0.001 [¥]	12.9	31.2	<0.001 [¥]
Sulphonylureas	8.5	11.4	2.7	4.7	<0.001 [¥]	3.2	4.6	<0.001 [¥]
Insulin	2.7	3.5	1.8	1.4	<0.001 [¥]	2.0	1.4	<0.001 [¥]
Other	0.1	0.1	0.1	0.2	0.025^{+}	0.1	0.2	0.006^{+}
Anti-platelet	27.0	24.2	22.9	33.1	<0.001 [¥]	23.9	32.8	<0.001 [¥]
Number of primary care visits in the year before T2D diagnosis; mean (SD)	12.9 (11.7)	11.1 (10.9)	17.2 (13.8)	14.9 (11.8)	<0.001 ^Ω	16.9 (13.6)	15.0 (11.9)	<0.001 ^Ω
Index of Multiple Deprivation quintiles (%)								
1 Q - least deprived	14.1	14.6	12.7	13.5	<0.001 [¥]	12.6	13.5	<0.001 [¥]
2 Q	19.1	19.5	19.4	18.3		19.2	18.3	
3 Q	19.0	19.1	17.2	19.4	<0.001 [¥]	17.6	19.3	<0.001 [¥]
4 Q	22.3	21.1	23.4	24.2	<0.001	23.1	24.3	<0.001
5 Q - most deprived	25.6	25.8	27.3	24.6		27.4	24.6	

Supplementary Table S4. Characteristics of individuals with pre-diabetes stratified by having a diagnostic code for pre-diabetes recorded. Results are presented using WHO/IEC, NICE, and ADA criteria for the definition of pre-diabetes.

Notes: Clinical data within three years before the diagnosis of Type 2 diabetes were used to define the detection of prediabetes. For each diagnostic criteria (WHO/IEC, NICE, and ADA), p-values from Chi-square and ANOVA tests, as appropriate, are reported in the last columns for comparisons between two groups: diagnostic code recorded for pre-diabetes and pre-diabetes without a diagnostic label recorded for pre-diabetes.

Abbreviations: T2D: Type 2 diabetes FPG: fasting plasma glucose, OGTT: glucose tolerance test (2-hour after 75 g glucose load), ACE: Angiotensin-converting-enzyme inhibitor, ArB: Antiotensin II receptor blockers.

WHO/IEC criteria to define pre-diabetes: FPG: 6.1-6.9 mmol/L, OGTT 7.8-11.1 mmol/L, HbA1c 42 to 47 mmol/mol or 6.0-6.4% NICE criteria to define pre-diabetes: 5.5-6.9 mmol/L, OGTT 7.8-11.1 mmol/L, HbA1c 42 to 47 mmol/mol or 6.0-6.4% ADA criteria to define pre-diabetes: FPG: 5.6-6.9 mmol/L, OGTT 7.8-11.1 mmol/L, HbA1c 39 to 47 mmol/mol or 5.7-6.4% ¥Chi-square test for the comparison of groups with and without a diagnostic label recorded for pre-diabetes §ANOVA test for the comparison of groups with and without a diagnostic label recorded for pre-diabetes ΩKruskal-Wallis test was performed to assess the unadjusted difference between groups

* Medication groups are not mutually exclusive and patients with multiple medications prescribed are counted multiple times.

	WHO/IEC D	IAGNOSTIC CRITE	ERIA ¹	NICE DIA	GNOSTIC CRITER	IA ²	ADA DIAC	GNOSTIC CRITER	IA ³
	Tested before the diagnosis of T2D	Tested before the diagnosis of T2D		Tested before the diagnosis of T2D	Tested before the diagnosis of T2D		Tested before the diagnosis of T2D	Tested before the diagnosis of T2D	
	(pre-diabetes detected without diagnostic code assigned)	(pre-diabetes detected and diagnostic code assigned)	p-values	(pre-diabetes detected without diagnostic code assigned)	(pre-diabetes detected and diagnostic code assigned)	p-values	(pre-diabetes detected without diagnostic code assigned)	(pre-diabetes detected and diagnostic code assigned)	p-values
Ν	23,459	20,426		30,930	20,426		31,044	20,426	
%	53.5	46.5		60.2	39.8		60.3	39.7	
Type of glycaemic measures recorded before diagnosis of T2D (%)									
FPG	81.2	66.5		85.8	66.5		80.40	66.50	
HbA1C	60.5	55.5		53.6	55.50		58.80	55.50	
OGTT	21.1	24.3		18.3	24.30		17.80	24.30	
Multiple tests	55.3	50.3		51.2	50.30		50.70	50.30	
Time from testing to									
diagnosis of T2D, months; mean (SD)	32.8 (6.4)	33.2 (6.8)		33.0 (6.0)	33.2 (5.8)		32.8 (6.4)	33.2 (5.8)	
Female (%)	47.1	46.3	0.086^{*}	47.6	46.3	0.004^{*}	48	46.3	<0.001 [¥]
Age, years (SD) Ethnicity (%)	64.4 (12.8)	64.2 (12.4)	0.137 [§]	64.1 (13.0)	64.2 (12.4)	0.189 [§]	64.2 (13)	64.2 (12.4)	0.667 [§]
White	82.4	83.5		82.8	83.5		82.7	83.5	
South Asian	4.8	3.8		4.9	3.8		4.8	3.8	
Black	2.7	2.6	<0.001 [¥]	2.8	2.6	<0.001 [¥]	2.8	2.6	<0.001 [¥]
Other	3.4	3.2	10.001	3.4	3.2	10.001	3.4	3.2	20.001
Unknown	6.7	7.1		6.2	7.0		6.3	7.0	
Smoking status (%)									
Non-smoker	32.6	32		16.7	15.7		32.8	32	
Ex-smoker	50.9	52.3	0.002^{*}	36.2	37.5	0.002^{*}	50.4	52.3	<0.001 [¥]
Current smoker	16.5	15.7		47.1	46.8		16.8	15.7	

(continued)

	WHO/IEC DI	AGNOSTIC CRI	TERIA ¹	NICE DIA	GNOSTIC CRITE	RIA ²	ADA DIA	GNOSTIC CRITE	RIA ³
	Tested before the diagnosis of Type 2 diabetes (pre-diabetes detected without diagnostic code assigned)	Tested before the diagnosis of Type 2 diabetes (pre-diabetes detected and diagnostic code assigned)	p-values	Tested before the diagnosis of Type 2 diabetes (pre-diabetes detected without diagnostic code assigned)	Tested before the diagnosis of Type 2 diabetes (pre-diabetes detected and diagnostic code assigned)	p-values	Tested before the diagnosis of Type 2 diabetes (pre-diabetes detected without diagnostic code assigned)	Tested before the diagnosis of Type 2 diabetes (pre-diabetes detected and diagnostic code assigned)	p-values
HbA1c at diagnosis, mmol/mol; mean (SD)	49.4 (18.3)	51.1 (19.6)	<0.001 [§]	50.8 (19.7)	50.8 (19.7)	0.001 [§]	49.7 (18.2)	51.1 (19.6)	<0.001 [§]
BMI, kg/m2; mean (SD)	31.3 (6.5)	31.4 (6.4)	0.016 [§]	31.2 (6.7)	31.4 (6.4)	<0.001 [§]	31.1 (6.6)	31.4 (6.4)	<0.001 [§]
SBP, mm Hg; mean (SD)	137.4 (14.7)	137.4 (13.9)	0.952 [§]	137.1 (14.8)	137.4 (13.9)	0.021 [§]	137.1 (14.8)	137.4 (13.9)	<0.001 [§]
DBP, mm Hg; mean (SD)	79.4 (8.9)	79.5 (4.9)	0.397 [§]	79.4 (8.9)	79.5 (8.6)	0.297 [§]	79.3 (8.9)	79.5 (8.6)	0.049 [§]
Total cholesterol, mmol/L; mean (SD)	4.9 (1.1)	4.9 (1.1)	0.027 [§]	4.9 (1.1)	4.9 (1.1.)	0.013 [§]	4.9 (1.1)	4.9 (1.1)	<0.001 [§]
Number of chronic diseases; mean (SD)	3.1 (2.0)	3.1 (2.0)	0.006^{Ω}	3.1 (2.1)	3.1 (2.0)	0.883^{Ω}	3.1 (2.1)	3.1 (2.0)	0.831 ^Ω
Medications (%)									
Anti-hypertensive ACEi/ARBs Anti-lipid medications Anti-diabetic* Biguanides Sulphonylureas Insulin Other Anti-platelet Number of primary care visits in	67.6 50 62.7 33.5 31.5 4.3 1.2 0.1 33.0	67.5 50.5 64 35.5 33.2 4.7 1.3 0.2 33.3	0.689 [*] 0.306 [*] 0.007 [*] <0.001 [*] 0.052 [*] 0.123 [*] 0.100 [*] 0.524	66.9 49.5 61.6 32.8 30.6 4.7 1.5 0.1 33.0	67.5 50.4 64 35.5 33.2 4.7 1.3 0.2 33.3	0.203 [*] 0.035 [*] <0.001 [*] <0.001 [*] 0.014 [*] 0.050 [*] 0.055 [*] 0.491	66.4 49 61 32.1 29.9 4.5 1.4 0.15 32.5	67.5 50.5 64 35.4 33.2 4.7 1.3 0.21 33.3	0.015 [*] 0.001 [*] <0.001 [*] <0.001 [*] <0.001 [*] 0.237 [*] 0.415 [*] 0.147 [*] 0.064
the year before T2D diagnosis; mean (SD) Index of Multiple Deprivation	14.3 (11.7)	15.2 (11.6)	<0.001 [§]	14.7 (12.0)	15.2 (11.6)	<0.001 [§]	14.8 (12.1)	15.2 (11.6)	0.002 [§]
quintiles (%)			· · · · ·						
1 Q - least deprived	13.1	14.4	<0.001 [¥]	13	14.4	<0.001 [¥]	13	14.4	<0.001 [¥]
2 Q	17.5	19	<0.001 [¥]	17.7	19	<0.001 [¥]	17.8	19	<0.001 [¥]

3 Q	19.7	19.2	19.5	19.2	19.4	19.2
4 Q	25.4	22.8	25.2	22.8	25.3	22.8
5 Q - most deprived	24.3	24.7	24.6	24.7	24.6	24.7

Supplementary Table S5. Glycaemic measures recorded in the three years before the diagnosis of Type 2 diabetes between 2004 and 2011 and between 2012 and 2017 in the study population

Notes: WHO/IEC, NICE, and ADA criteria were used for the detection of pre-diabetes. Results are presented for two time periods based on the date of the diagnosis of Type 2 diabetes: 2004 to 2011 and 2012 to 2017 due to changes in the national clinical guidelines in the UK introducing HbA1c as additional blood glucose testing method for the testing and detection of pre-diabetes.

WHO/IEC criteria to define pre-diabetes: FPG: 6.1-6.9 mmol/L, OGTT 7.8-11.1 mmol/L, HbA1c 42 to 47 mmol/mol or 6.0-6.4%

NICE criteria to define pre-diabetes: 5.5-6.9 mmol/L, OGTT 7.8-11.1 mmol/L, HbA1c 42 to 47 mmol/mol or 6.0-6.4%

ADA criteria to define pre-diabetes: FPG: 5.6-6.9 mmol/L, OGTT 7.8-11.1 mmol/L, HbA1c 39 to 47 mmol/mol or 5.7-6.4%

Abbreviations: T2D: Type 2 diabetes FPG: fasting plasma glucose, OGTT: glucose tolerance test (2-hour after 75 g glucose load).

		the diagnosis	of 12D			0
	[DIAGNOSTIC C	RITERIA		DIAGNOSTIC C	RITERIA
	WHO/IEC ¹	NICE ²	ADA ³	WHO/IEC ¹	NICE ²	ADA ³
Type 2 diabetes diagnosed from 2004 to 2011						
Ν	11,567	7,086	7,695	27,121	31,602	30,993
TYPE OF GLYCAEMIC MEASURES RECORDED BEFORE THE DIAGNOSIS OF TYPE 2 DIABETES (%	6)					
FPG	87.8%	80.1%	87.9%	77.7%	80.9%	78.9%
HbA1C	25.7%	29.5%	21.6%	42.5%	39.3%	41.5%
OGTT	6.4%	2.9%	4.2%	26.7%	24.6%	24.7%
Multiple tests	18.6%	11.7%	12.6%	48.7%	46.0%	46.4%
Type 2 diabetes diagnosed from 2012 to 2017						
N	10,335	7,345	6,622	16,764	19,754	20,477
TYPE OF GLYCAEMIC MEASURES RECORDED BEFORE THE DIAGNOSIS OF TYPE 2 DIABETES (%	6)					
FPG	75.6%	65.7%	80.1%	69.0%	73.7%	68.7%
HbA1C	52.6%	53.8%	40.8%	83.4%	78.3%	81.7%
OGTT	2.4%	1.2%	1.5%	15.9%	14.3%	13.7%
Multiple tests	29.4%	20.2%	21.9%	59.9%	58.7%	56.8%
Type 2 diabetes diagnosed from 2004 to 2017						
Ν	21,902	14,431	14,317	43,885	51,356	51,470
TYPE OF GLYCAEMIC MEASURES RECORDED BEFORE THE DIAGNOSIS OF TYPE 2 DIABETES (%	6)					
FPG	82.1%	72.8%	84.3%	74.4%	78.1%	74.9%
HbA1C	38.4%	41.9%	30.5%	58.2%	54.3%	57.5%

Glycaemic values within the normal range before the diagnosis of T2D

Pre-diabetes detected before the diagnosis of T2D

Multiple tests 23.7% 16.0%	16.9%	53.0%	50.9%	50.5%

Supplementary Figure S6. Prevalence of microvascular (retinopathy and nephropathy) and macrovascular (acute coronary syndrome, cerebrovascular, and peripheral arterial disease) disease present at time of the diagnosis of Type 2 diabetes according to pre-diabetes status in the three years before the diagnosis of Type 2 diabetes.

Notes: A microvascular complication was considered being present at time of Type 2 diabetes diagnosis if the complication was diagnosed between five years before and fifteen months after the diagnosis of Type 2 diabetes. A macrovascular complication was considered being present at time of Type 2 diabetes diagnosis if the complication was diagnosed any time before the diagnosis and during the year following the diagnosis of Type 2 diabetes. 1) WHO/IEC criteria: FPG: 6.1-6.9 mmol/L, OGTT 7.8-11.1 mmol/L, HbA1c 42 to 47 mmol/mol or 6.0-6.4%; 2) NICE criteria: 5.5-6.9 mmol/L, OGTT 7.8-11.1 mmol/L, HbA1c 42 to 47 mmol/mol or 6.0-6.4%; 3) ADA criteria: FPG: 5.6-6.9 mmol/L, OGTT 7.8-11.1 mmol/L, HbA1c 39 to 47 mmol/mol or 5.7-6.4%.

Microvascular disease Macrovascular disease Retinopathy Nephropathy Cerebrovascular disease Acute coronary syndrome 30 40 24.3 24.2 24.2 21 30 19 2 20 25.2 22.924.2 22.9 24 23.8 23.8 23.7 22.9 20.7 19.5 19 19 19 19 20 13 10 6.5 6.8 6.6 6.7 6.6 5.2 5.2 5.2 5.2 6.9 10 0 0 WHO/IEC NICE WHO/IEC NICE WHO/IEC NICE ADA ADA ADA WHO/IEC NICE ADA Any microvascular disease Both microvascular diseases Peripheral arterial disease Any macrovascular disease 42.4 29.8 30 29.9 41.7 41.5 30 26.9 40 36 24 9 27. 30 27. 20 20 9 10 4.7 3.7 4.6 4.5 3.7 4.7 4.6 3.7 4.7 3.9 5.2 6.4 5.2 6.3 5.2 6.2 0 0 WHO/IEC NICE ADA WHO/IEC NICE ADA WHO/IEC NICE WHO/IEC NICE ADA ADA Tested before the diagnosis of Type 2 diabetes (normal glycaemic values) No glycaemic measures recorded before the diagnosis of Type 2 diabetes Tested before the diagnosis of Type 2 diabetes (pre-diabetes detected)

Supplementary Figure S7. Prevalence of microvascular (retinopathy and nephropathy) and macrovascular (acute coronary syndrome, cerebrovascular, and peripheral arterial disease) disease present at time of the diagnosis of Type 2 diabetes according to pre-diabetes status in the three years before the diagnosis of Type 2 diabetes. Individuals with pre-diabetes were further classified into two groups based on whether a diagnostic code for pre-diabetes was recorded in their health records at time of pre-diabetes detection.

Notes: A microvascular complication was defined as being present at time of Type 2 diabetes diagnosis if the complication was diagnosed between five years before and fifteen months after the diagnosis of Type 2 diabetes. A macrovascular complication was defined as being present at time of Type 2 diabetes diagnosis if the complication was diagnosed any time before the diagnosis and during the year of diagnosis of Type 2 diabetes. 1) WHO/IEC criteria: FPG: 6.1-6.9 mmol/L, OGTT 7.8-11.1 mmol/L, HbA1c 42 to 47 mmol/mol or 6.0-6.4%;

2) NICE criteria: 5.5-6.9 mmol/L, OGTT 7.8-11.1 mmol/L, HbA1c 42 to 47 mmol/mol or 6.0-6.4%;

3) ADA criteria: FPG: 5.6-6.9 mmol/L, OGTT 7.8-11.1 mmol/L, HbA1c 39 to 47 mmol/mol or 5.7-6.4%.

Microvascular disease Macrovascular disease Retinopathy Nephropathy Acute coronary syndrome Cerebrovascular disease 30 40 ^{24.5}23.9 24.4 23.9 ^{24.4}23.9 30 22.9^{23.7}24.9 24.9 22.9^{23.4} 20 24.2 25.2 24.9 24.3 23.2 ²⁴ 23.2 22 0 20 10 10 0 0 WHO/IEC NICE ADA WHO/IEC NICE ADA WHO/IEC NICE ADA WHO/IEC NICE ADA Any microvascular disease Both microvascular diseases Peripheral arterial disease Any macrovascular disease 42.9 41.8 30.4 30.3 41.641.8 41.3 41.8 30 40 30 20 20 10 10 6.3 6.3 5.2 5.2 6.1 6.3 4.6 4.6 4.5 4.7 4.6 4.6 4.7 4.6 5.2 3.9 6.5 6.3 0 0 WHO/IEC NICE ADA ADA WHO/IEC NICE ADA WHO/IEC NICE ADA WHO/IEC NICE Tested before the diagnosis of Type 2 diabetes (normal glycaemic values) No glycaemic measures recorded before the diagnosis of Type 2 diabetes Tested before the diagnosis of Type 2 diabetes (pre-diabetes detected without diagnostic code assigned) Tested before the diagnosis of Type 2 diabetes (pre-diabetes detected and diagnostic code assigned)

Supplementary Figure S8. Association between glycaemic testing and detection of pre-diabetes and presence of microvascular disease at the time of diagnosis of Type 2 diabetes

Notes: Adjusted Odds Ratios (AOR) and 95% confidence intervals (95% CI) have been estimated employing multivariable logistic regression models adjusted for age, sex, ethnicity (White, South Asian, Black, Other, Unknown), smoking status (non-smoker, ex-smoker, smoker), total cholesterol, systolic and diastolic blood pressure, number of co-existing chronic conditions, number of primary care visits in the previous year, general practice index of multiple deprivation, and year of diagnosis of Type 2 diabetes. Abbreviations: T2D: Type 2 diabetes.

Outcome and diagnostic criteria	Testing before the diagnosis of T2D		AOR (95% CI)
Retinopathy	Tested before the diagnosis of T2D (normal glycaemic values) as ref		
WHO/IEC	No results of blood glucose tests available before the diagnosis of T2D	→	1.50 (1.44, 1.57)
	Tested before the diagnosis of T2D (pre-diabetes detected)		1.76 (1.69, 1.85)
NICE	No results of blood glucose tests available before the diagnosis of T2D		1.83 (1.73, 1.93)
	Tested before the diagnosis of T2D (pre-diabetes detected)		2.07 (1.95, 2.19)
ADA	No results of blood glucose tests available before the diagnosis of T2D		1.80 (1.70, 1.90)
	Tested before the diagnosis of T2D (pre-diabetes detected)		2.04 (1.93, 2.16)
Nephropathy	Tested before the diagnosis of T2D (normal glycaemic values) as ref		
WHO/IEC	No results of blood glucose tests available before the diagnosis of T2D	←	1.04 (1.00, 1.08)
	Tested before the diagnosis of T2D (pre-diabetes detected)	◆	1.14 (1.10, 1.19)
NICE	No results of blood glucose tests available before the diagnosis of T2D	+	1.12 (1.06, 1.17)
	Tested before the diagnosis of T2D (pre-diabetes detected)	▲	1.23 (1.17, 1.29)
ADA	No results of blood glucose tests available before the diagnosis of T2D	*	1.09 (1.04, 1.15)
	Tested before the diagnosis of T2D (pre-diabetes detected)	+	1.20 (1.14, 1.26)
Any microvascular disease	Tested before the diagnosis of T2D (normal glycaemic values) as ref		
WHO/IEC	No results of blood glucose tests available before the diagnosis of T2D	•	1.26 (1.22, 1.31)
	Tested before the diagnosis of T2D (pre-diabetes detected)		1.47 (1.42, 1.52)
NICE	No results of blood glucose tests available before the diagnosis of T2D	*	1.43 (1.37, 1.49)
	Tested before the diagnosis of T2D (pre-diabetes detected)	-	1.62 (1.55, 1.69)
ADA	No results of blood glucose tests available before the diagnosis of T2D	▲	1.42 (1.36, 1.48)
	Tested before the diagnosis of T2D (pre-diabetes detected)	→ I	1.62 (1.55, 1.69)
Both microvascular diseases	Tested before the diagnosis of T2D (normal glycaemic values) as ref		
WHO/IEC	No results of blood glucose tests available before the diagnosis of T2D		1.35 (1.25, 1.46)
	Tested before the diagnosis of T2D (pre-diabetes detected)		1.53 (1.41, 1.65)
NICE	No results of blood glucose tests available before the diagnosis of T2D	│ _←	1.68 (1.52, 1.86)
	Tested before the diagnosis of T2D (pre-diabetes detected)		1.86 (1.68, 2.06)
ADA	No results of blood glucose tests available before the diagnosis of T2D	│ <u> </u>	1.54 (1.40, 1.70)
	Tested before the diagnosis of T2D (pre-diabetes detected)		• 1.69 (1.53, 1.87)
		0.80	2.20

Supplementary Figure S9. Association between glycaemic testing and detection of pre-diabetes and presence of macrovascular disease at the time of diagnosis of Type 2 diabetes

Notes: Adjusted Odds Ratios (AOR) and 95% confidence intervals (95% CI) have been estimated employing multivariable logistic regression models adjusted for age, sex, ethnicity (White, South Asian, Black, Other, Unknown), smoking status (non-smoker, ex-smoker, smoker), total cholesterol, systolic and diastolic blood pressure, number of co-existing chronic conditions, number of primary care visits in the previous year, general practice index of multiple deprivation, and year of diagnosis of Type 2 diabetes. Abbreviations: T2D: Type 2 diabetes.

Outcome and diagnostic criteria	Testing before the diagnosis of T2D		AOR (95% CI)
Acute coronary syndrome	Tested before the diagnosis of T2D (normal glycaemic values) as ref		
WHO/IEC	No results of blood glucose tests available before the diagnosis of T2D	+	0.73 (0.70, 0.7
	Tested before the diagnosis of T2D (pre-diabetes detected)	-+	1.07 (1.03, 1.1)
NICE	No results of blood glucose tests available before the diagnosis of T2D	-	0.80 (0.76, 0.8
	Tested before the diagnosis of T2D (pre-diabetes detected)		1.18 (1.12, 1.2
ADA	No results of blood glucose tests available before the diagnosis of T2D	→	0.79 (0.75, 0.8
	Tested before the diagnosis of T2D (pre-diabetes detected)		1.17 (1.11, 1.23
Cerebrovascular disease	Tested before the diagnosis of T2D (normal glycaemic values) as ref		
WHO/IEC	No results of blood glucose tests available before the diagnosis of T2D		0.91 (0.85, 0.9
	Tested before the diagnosis of T2D (pre-diabetes detected)	→	0.88 (0.82, 0.94
NICE	No results of blood glucose tests available before the diagnosis of T2D	_ • _	0.89 (0.83, 0.9
	Tested before the diagnosis of T2D (pre-diabetes detected)	- -	0.88 (0.81, 0.95
ADA	No results of blood glucose tests available before the diagnosis of T2D	_ -	0.90 (0.83, 0.9
	Tested before the diagnosis of T2D (pre-diabetes detected)	_ -	0.88 (0.81, 0.9
Peripheral arterial disease	Tested before the diagnosis of T2D (normal glycaemic values) as ref		
WHO/IEC	No results of blood glucose tests available before the diagnosis of T2D	- -	0.90 (0.84, 0.9
	Tested before the diagnosis of T2D (pre-diabetes detected)	- -	0.88 (0.81, 0.9
NICE	No results of blood glucose tests available before the diagnosis of T2D	_ +	0.90 (0.82, 0.99
	Tested before the diagnosis of T2D (pre-diabetes detected)	- - -	0.89 (0.82, 0.9
ADA	No results of blood glucose tests available before the diagnosis of T2D	_ _	0.90 (0.82, 0.9
	Tested before the diagnosis of T2D (pre-diabetes detected)	_ -	0.89 (0.81, 0.9
Any macrovascular disease	Tested before the diagnosis of T2D (normal glycaemic values) as ref		
WHO/IEC	No results of blood glucose tests available before the diagnosis of T2D	+	0.77 (0.74, 0.80
	Tested before the diagnosis of T2D (pre-diabetes detected)	†	1.00 (0.96, 1.04
NICE	No results of blood glucose tests available before the diagnosis of T2D	←	0.82 (0.78, 0.8
	Tested before the diagnosis of T2D (pre-diabetes detected)	-+	1.08 (1.03, 1.13
ADA	No results of blood glucose tests available before the diagnosis of T2D	→	0.82 (0.78, 0.86
	Tested before the diagnosis of T2D (pre-diabetes detected)		1.08 (1.03, 1.14
		 0.60	1.30

Supplementary Figure S10. Association between glycaemic testing and detection of pre-diabetes and the presence of microvascular disease at the time of diagnosis of Type 2 diabetes.

Notes: Adjusted Odds Ratios (AOR) and 95% confidence intervals (95% CI) have been estimated employing multivariable logistic regression models adjusted for age, sex, ethnicity (White, South Asian, Black, Other, Unknown), smoking status (non-smoker, ex-smoker, smoker), total cholesterol, systolic and diastolic blood pressure, number of co-existing chronic conditions, number of primary care visits in the previous year, general practice index of multiple deprivation, and year of diagnosis of Type 2 diabetes. Abbreviations: T2D: Type 2 diabetes.

- WHO/IEC criteria to define pre-diabetes: FPG: 6.1-6.9 mmol/L, OGTT 7.8-11.1 mmol/L, HbA1c 42 to 47 mmol/mol or 6.0-6.4%
- 2. NICE criteria to define pre-diabetes: 5.5-6.9 mmol/L, OGTT 7.8-11.1 mmol/L, HbA1c 42 to 47 mmol/mol or 6.0-6.4%
- 3. ADA criteria to define pre-diabetes: FPG: 5.6-6.9 mmol/L, OGTT 7.8-11.1 mmol/L, HbA1c 39 to 47 mmol/mol or 5.7-6.4%

Outcome and diagnostic criteria	Testing before the diagnosis of T2D		AOR (95% CI)	Outcome and diagnostic criteria	Testing before the diagnosis of T2D		AOR (95% CI)
Retinopathy	Tested before the diagnosis of T2D (normal glycaemic values) as ref			Any microvascular disease	Tested before the diagnosis of T2D (normal glycaemic values) as ref		
WHO/IEC	No results of blood glucose tests available before the diagnosis of T2D	*	1.50 (1.44, 1.57)	WHO/IEC	No results of blood glucose tests available before the diagnosis of T2D	+	1.26 (1.22, 1.31)
	Tested before the diagnosis of T2D (pre-diabetes detected without diagnostic code assigned)	-	1.78 (1.69, 1.87)		Tested before the diagnosis of T2D (pre-diabetes detected without diagnostic code assigned)	+	1.51 (1.45, 1.57)
	Tested before the diagnosis of T2D (pre-diabetes detected and diagnostic code assigned)	+	1.75 (1.66, 1.84)		Tested before the diagnosis of T2D (pre-diabetes detected and diagnostic code assigned)	+	1.43 (1.37, 1.49)
NICE	No results of blood glucose tests available before the diagnosis of T2D	-	1.83 (1.73, 1.93)	NICE	No results of blood glucose tests available before the diagnosis of T2D	+	1.43 (1.37, 1.49)
	Tested before the diagnosis of T2D (pre-diabetes detected without diagnostic code assigned)		2.02 (1.91, 2.15)		Tested before the diagnosis of T2D (pre-diabetes detected without diagnostic code assigned)	+	1.63 (1.56, 1.70)
	Tested before the diagnosis of T2D (pre-diabetes detected and diagnostic code assigned)	-	2.13 (2.00, 2.27)		Tested before the diagnosis of T2D (pre-diabetes detected and diagnostic code assigned)	-	1.61 (1.54, 1.69)
ADA	No results of blood glucose tests available before the diagnosis of T2D	-	1.80 (1.70, 1.90)	ADA	No results of blood glucose tests available before the diagnosis of T2D	+	1.42 (1.36, 1.48)
	Tested before the diagnosis of T2D (pre-diabetes detected without diagnostic code assigned)	-	2.00 (1.89, 2.12)		Tested before the diagnosis of T2D (pre-diabetes detected without diagnostic code assigned)	★	1.62 (1.55, 1.70)
	Tested before the diagnosis of T2D (pre-diabetes detected and diagnostic code assigned)		2.10 (1.97, 2.23)		Tested before the diagnosis of T2D (pre-diabetes detected and diagnostic code assigned)	→	1.61 (1.53, 1.69)
Nephropathy	Tested before the diagnosis of T2D (normal glycaemic values) as ref			Both microvascular diseases	Tested before the diagnosis of T2D (normal glycaemic values) as ref		
WHO/IEC	No results of blood glucose tests available before the diagnosis of T2D	•	1.04 (1.00, 1.08)	WHO/IEC	No results of blood glucose tests available before the diagnosis of T2D	→	1.35 (1.25, 1.46)
	Tested before the diagnosis of T2D (pre-diabetes detected without diagnostic code assigned)		1.19 (1.13, 1.24)		Tested before the diagnosis of T2D (pre-diabetes detected without diagnostic code assigned)	_ → _	1.56 (1.43, 1.71)
	Tested before the diagnosis of T2D (pre-diabetes detected and diagnostic code assigned)	*	1.09 (1.04, 1.15)		Tested before the diagnosis of T2D (pre-diabetes detected and diagnostic code assigned)		1.48 (1.35, 1.62)
NICE	No results of blood glucose tests available before the diagnosis of T2D	*	1.12 (1.06, 1.17)	NICE	No results of blood glucose tests available before the diagnosis of T2D		1.68 (1.52, 1.86)
	Tested before the diagnosis of T2D (pre-diabetes detected without diagnostic code assigned)	+	1.27 (1.20, 1.33)		Tested before the diagnosis of T2D (pre-diabetes detected without diagnostic code assigned)		1.87 (1.68, 2.09)
	Tested before the diagnosis of T2D (pre-diabetes detected and diagnostic code assigned)	+	1.18 (1.12, 1.25)		Tested before the diagnosis of T2D (pre-diabetes detected and diagnostic code assigned)	│	1.84 (1.64, 2.06)
ADA	No results of blood glucose tests available before the diagnosis of T2D	+	1.09 (1.04, 1.15)	ADA	No results of blood glucose tests available before the diagnosis of T2D	_ _	1.54 (1.40, 1.70)
	Tested before the diagnosis of T2D (pre-diabetes detected without diagnostic code assigned)	+	1.23 (1.17, 1.29)		Tested before the diagnosis of T2D (pre-diabetes detected without diagnostic code assigned)		1.69 (1.52, 1.88)
	Tested before the diagnosis of T2D (pre-diabetes detected and diagnostic code assigned)	+	1.16 (1.09, 1.22)		Tested before the diagnosis of T2D (pre-diabetes detected and diagnostic code assigned)		1.69 (1.51, 1.88)
	 0.8	D	2.30		 0.80	·	2.10

Supplementary Figure S11. Association between testing and detection of pre-diabetes and presence of macrovascular disease at the time of diagnosis of Type 2 diabetes. For individuals with pre-diabetes detected a further stratification has been considered according to whether a corresponding diagnostic code was assigned at time of pre-diabetes detection.

Notes: Adjusted Odds Ratios (AOR) and 95% confidence intervals (95% CI) have been estimated employing multivariable logistic regression models adjusted for age, sex, ethnicity (White, South Asian, Black, Other, Unknown), smoking status (non-smoker, ex-smoker, smoker), total cholesterol, systolic and diastolic blood pressure, number of co-existing chronic conditions, number of primary care visits in the previous year, general practice index of multideprivation, and year of diagnosis of Type 2 diabetes. Abbreviations: T2D: Type 2 diabetes.

WHO/IEC criteria to define pre-diabetes: FPG: 6.1-6.9 mmol/L, OGTT 7.8-11.1 mmol/L, HbA1c 42 to 47 mmol/mol or 6.0-6.4% NICE criteria to define pre-diabetes: 5.5-6.9 mmol/L, OGTT 7.8-11.1 mmol/L, HbA1c 42 to 47 mmol/mol or 6.0-6.4% ADA criteria to define pre-diabetes: FPG: 5.6-6.9 mmol/L, OGTT 7.8-11.1 mmol/L, HbA1c 39 to 47 mmol/mol or 5.7-6.4%

Outcome and diagnostic criteria	Testing before the diagnosis of T2D			AOR (95% CI)	Outcome and diagnostic criteria	Testing before the diagnosis of T2D			AOR (95% CI)
Acute coronary syndrome	Tested before the diagnosis of T2D (normal glycaemic values) as ref				Peripheral arterial disease	Tested before the diagnosis of T2D (normal glycaemic values) as ref			
WHO/IEC	No results of blood glucose tests available before the diagnosis of T2D	+		0.73 (0.70, 0.77)	WHO/IEC	No results of blood glucose tests available before the diagnosis of T2D			0.90 (0.84, 0.98)
	Tested before the diagnosis of T2D (pre-diabetes detected without diagnostic code assigned)		-	1.10 (1.05, 1.16)		Tested before the diagnosis of T2D (pre-diabetes detected without diagnostic code assigned)	_ +	6	0.89 (0.81, 0.97)
	Tested before the diagnosis of T2D (pre-diabetes detected and diagnostic code assigned)		 ∙-	1.04 (0.99, 1.10)		Tested before the diagnosis of T2D (pre-diabetes detected and diagnostic code assigned)	-+		0.88 (0.80, 0.96)
NICE	No results of blood glucose tests available before the diagnosis of T2D			0.80 (0.76, 0.84)	NICE	No results of blood glucose tests available before the diagnosis of T2D		-	0.90 (0.82, 0.99)
	Tested before the diagnosis of T2D (pre-diabetes detected without diagnostic code assigned)		→	1.21 (1.14, 1.28)		Tested before the diagnosis of T2D (pre-diabetes detected without diagnostic code assigned)	-+	-	0.91 (0.82, 1.00)
	Tested before the diagnosis of T2D (pre-diabetes detected and diagnostic code assigned)		-	1.13 (1.07, 1.20)		Tested before the diagnosis of T2D (pre-diabetes detected and diagnostic code assigned)	_ 		0.87 (0.79, 0.97)
ADA	No results of blood glucose tests available before the diagnosis of T2D	-		0.79 (0.75, 0.83)	ADA	No results of blood glucose tests available before the diagnosis of T2D	_ 	-	0.90 (0.82, 0.98)
	Tested before the diagnosis of T2D (pre-diabetes detected without diagnostic code assigned)		→	1.20 (1.13, 1.26)		Tested before the diagnosis of T2D (pre-diabetes detected without diagnostic code assigned)	+	-	0.90 (0.82, 1.00)
	Tested before the diagnosis of T2D (pre-diabetes detected and diagnostic code assigned)		-	1.12 (1.06, 1.19)		Tested before the diagnosis of T2D (pre-diabetes detected and diagnostic code assigned)			0.87 (0.78, 0.97)
Cerebrovascular disease	Tested before the diagnosis of T2D (normal glycaemic values) as ref				Any macrovascular disease	Tested before the diagnosis of T2D (normal glycaemic values) as ref			
WHO/IEC	No results of blood glucose tests available before the diagnosis of T2D	-	c	0.91 (0.85, 0.97)	WHO/IEC	No results of blood glucose tests available before the diagnosis of T2D	+		0.77 (0.74, 0.80)
	Tested before the diagnosis of T2D (pre-diabetes detected without diagnostic code assigned)		4	0.93 (0.86, 1.01)		Tested before the diagnosis of T2D (pre-diabetes detected without diagnostic code assigned)		+	1.04 (0.99, 1.09)
	Tested before the diagnosis of T2D (pre-diabetes detected and diagnostic code assigned)	-		0.81 (0.75, 0.88)		Tested before the diagnosis of T2D (pre-diabetes detected and diagnostic code assigned)		+	0.96 (0.92, 1.01)
NICE	No results of blood glucose tests available before the diagnosis of T2D	-		0.89 (0.83, 0.96)	NICE	No results of blood glucose tests available before the diagnosis of T2D			0.82 (0.78, 0.86)
	Tested before the diagnosis of T2D (pre-diabetes detected without diagnostic code assigned)		4	0.93 (0.85, 1.00)		Tested before the diagnosis of T2D (pre-diabetes detected without diagnostic code assigned)		-	1.12 (1.06, 1.18)
	Tested before the diagnosis of T2D (pre-diabetes detected and diagnostic code assigned)	-		0.80 (0.73, 0.88)		Tested before the diagnosis of T2D (pre-diabetes detected and diagnostic code assigned)	,	↓	1.02 (0.97, 1.08)
ADA	No results of blood glucose tests available before the diagnosis of T2D	_		0.89 (0.83, 0.97)	ADA	No results of blood glucose tests available before the diagnosis of T2D	-		0.82 (0.78, 0.86)
	Tested before the diagnosis of T2D (pre-diabetes detected without diagnostic code assigned)		4	0.93 (0.85, 1.01)		Tested before the diagnosis of T2D (pre-diabetes detected without diagnostic code assigned)			1.12 (1.06, 1.18)
	Tested before the diagnosis of T2D (pre-diabetes detected and diagnostic code assigned)	-		0.80 (0.73, 0.88)		Tested before the diagnosis of T2D (pre-diabetes detected and diagnostic code assigned)		- ≁	1.03 (0.97, 1.08)
·		l 0.60	1.	I .30	·		I 0.60	1.2	20