Assessment of the Management and Clinical Outcomes of Patients with Non-diabetic Hyperglycaemia and Newly Diagnosed Type 2 Diabetes in Primary Care in England

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Declaration of Originality

This thesis represents my own work, with support from my supervisors Christopher Millett, Eszter Vamos, and Azeem Majeed. I received statistical advice from Kiara Chang, Victoria Cornelius, and Mansour Taghavi Azar Sharabiani.

Copyright Declaration

Abstract

Background

It is unknown whether the detection of non-diabetic hyperglycaemia before the diagnosis of Type 2 diabetes is associated with vascular disease at time or following the diagnosis of Type 2 diabetes.

Aim

I assessed the association between glycaemic testing and detection of non-diabetic hyperglycaemia before the diagnosis of Type 2 diabetes is associated and vascular disease at time or following the diagnosis of Type 2 diabetes.

Methods

I identified 159,736 individuals with newly diagnosed Type 2 diabetes from the CPRD database in England between 2004 and 2017. I used logistic regression models to compare presence of vascular disease at the time of Type 2 diabetes diagnosis by prior glycaemic status. I employed time-partitioned Cox regression models to model differences in rates of vascular disease and mortality following the diagnosis of Type 2 diabetes.

Results

Half of the study population (49.9%) had at least one vascular disease, over one-third (37.4%) had microvascular disease, and almost a quarter (23.5%) had a diagnosed macrovascular disease at the time of Type 2 diabetes diagnosis. Individuals with prior non-diabetic hyperglycaemia were more likely to have microvascular disease and coronary heart disease at time of diagnosis of Type 2 diabetes. As compared with individuals with glycaemic values within the normal range in the three years before the diagnosis of Type 2 diabetes,

those detected with non-diabetic hyperglycaemia had increased risk of microvascular disease that persisted up to 7.5 years.

Conclusions

Non-diabetic hyperglycaemia before diagnosis of Type 2 diabetes is associated with increased odds of microvascular disease and coronary heart disease in newly diagnosed Type 2 diabetes. It is also associated with increased rates of microvascular disease following the diagnosis of Type 2 diabetes. Detection of non-diabetic hyperglycaemia might represent an opportunity for a timely identification of NDH and specific clustering of NDH with other risk factors for T2D, which might prompt earlier assessment for risk factors and tailored cardiovascular risk reduction strategies during the NDH phase to reduce the burden of vascular disease.

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Abbreviations

ACEi	Angiotensin-converting-enzyme inhibitor
ADA	American Diabetes Association
AIC	Akaike's information criterion
AOR	Adjusted Odds Ratio
ARB	Angiotensin receptor blockers
AUROC	Area Under the Receiver Operating Characteristics
BIC	Bayesian information criterion
BMI	Body Mass Index
CI	Confidence Intervals
CKD	Chronic Kidney Disease
CPRD	Clinical Practice Research Datalink
CVD	Cardiovascular disease
DALYs	Disability-adjusted life years
DBP	Diastolic blood pressure
DRS	Diabetes Risk score
FPG	Fasting Plasma Glucose
HbA1c	Glycated Haemoglobin
HR	Hazard Ratio
IDF	International Diabetes Federation
IEC	International Expert Committee
IFG	Impaired Fasting Plasma glucose
IGT	Impaired Glucose Tolerance
IMD	Index of Multiple Deprivation
MET	Metabolic equivalent of task
NDH	Non-diabetic hyperglycaemia
NICE	National Institute of Health and Care Excellence
OGTT	Oral Glucose Tolerance Test
OR	Odds Ratio
ROC	Receiver Operating Characteristic
SBP	Systolic blood pressure

T2D	Type 2 diabetes
WHO	World Health Organization

1 The Global Burden of Type 2 Diabetes

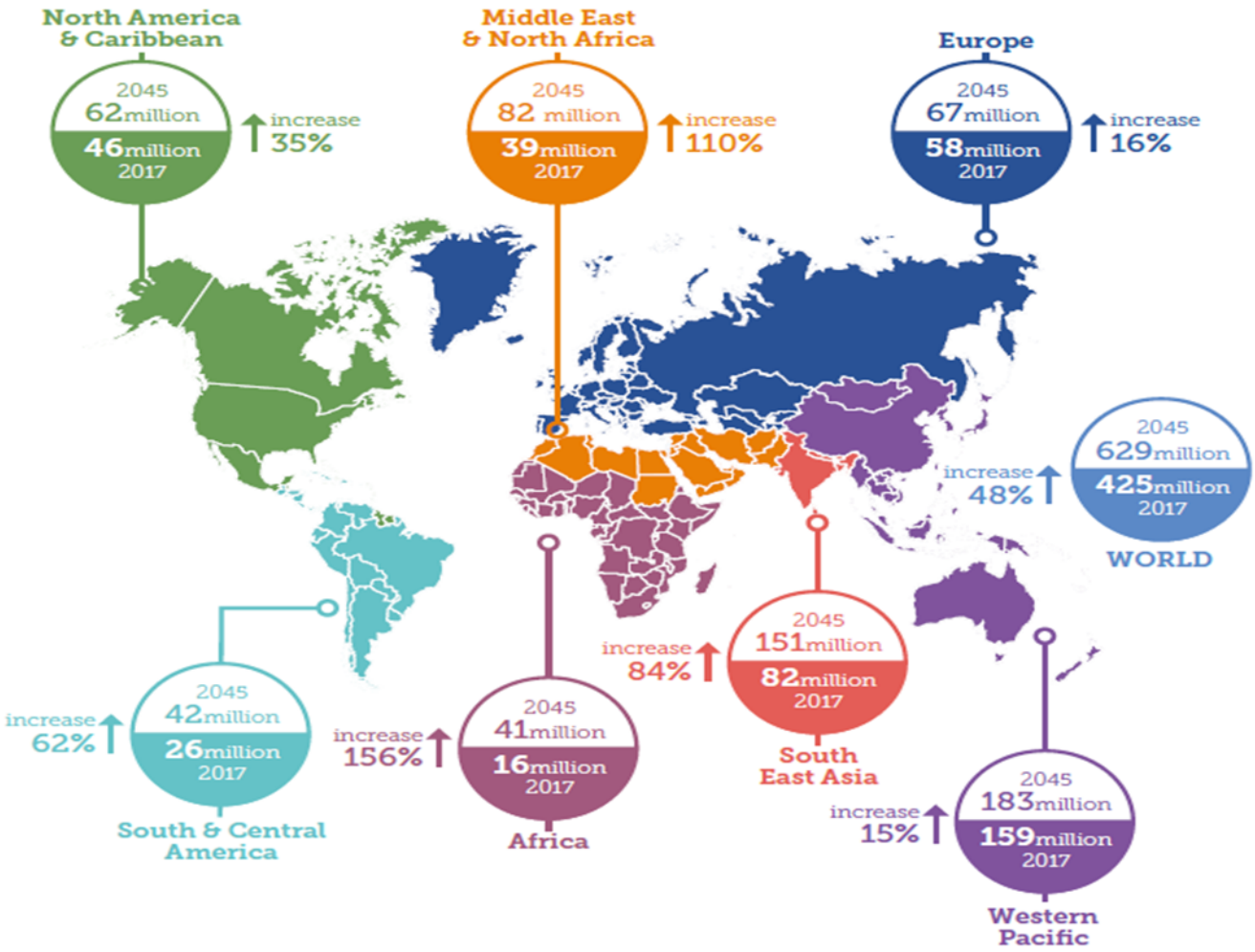
1.1 Prevalence, Projections, And Related Healthcare Costs

Diabetes is considered one of the largest global health emergencies due to its rising prevalence, economic burden posed on healthcare systems, and disproportionate impact on health. It has been estimated that 425 million individuals in the world have diabetes (8.8% of the adult population aged 20-79 years), with the figure projected to further increase to 629 million by 2045 (48% increase as compared with the 2017 estimate; Figure 1), mostly due to population growth and ageing (1-3). Type 2 diabetes (T2D) accounts for over 90% of all diabetes cases (4, 5). The highest age-adjusted prevalence of diabetes (including all types) in the adult population, equal to 11.0% and corresponding to 46 million of individuals with the condition, is estimated in the North America and Caribbean region. The prevalence in the European region is ranked second last (6.8%), followed by the African region (estimated prevalence 4.4%). Diabetes prevalence is estimated to be 0.7% higher in men than in women (9.1% and 8.4%, respectively, considering the adult population aged 20-79 years) (1). Prevalence and trajectories also vary between ethnic groups, with South Asians and Black ethnic groups having the greatest risk of developing diabetes at younger age and progressing faster (6-8). Approximately 50% of diabetes cases are undiagnosed, although proportion of undiagnosed cases varies profoundly between regions, with Africa having the highest proportion of undiagnosed cases (69.2%) and Europe being the second lowest region with 37.9% of total cases (1). Diabetes has been ranked as the seventh leading cause of death among both sexes and sixth among women (9). It has been estimated that approximately 4 million individuals died in 2017 due to diabetes and its complications (1). The number of deaths attributable to diabetes is also larger in women than in men (2.1 million in women and 1.8 million in men). In Europe almost 480,000 deaths in individuals

aged 20-79 years in 2017 were attributed to diabetes (9% of all cases), 32.9% of them occurred in individuals 60 years and younger, corresponding to 160,000 cases (1).

Healthcare expenditure on diabetes was estimated to be 850 billion US dollars worldwide in 2017. It has more than doubled in the past ten years and projected to increase by a further 100 billion by 2045, due to increases in prevalence, improvements in care, and life expectancy gains (1). Despite the relatively lower prevalence, the European region has the second highest total healthcare expenditure associated with diabetes care (181 billion of US dollars in 2017), corresponding to 9.1% of the total healthcare budget (1).

Figure 1. Number of individuals with diabetes in 2017 worldwide and projections for 2045



Source: IDF Diabetes Atlas 8th edition (1)

1.1.1 The burden of diabetes in England

In England alone, over 3.0 million people or 6.7% of the adult population had diagnosed diabetes in 2017, which correspond to a 166% increase (over 1.2 million adults) on 2005 figures (10). It has been estimated that around 940,000 adults have undiagnosed diabetes, increasing the overall prevalence to approximately 3.8 million people living with the condition (diagnosed and undiagnosed) (11). An estimated 9.6% of the adult male population have diabetes (both diagnosed and undiagnosed), while the prevalence for the

female population is lower at 7.6%. In South Asian and Black ethnic groups the prevalence is almost doubled than in the White population (15.2% and 8.0%, respectively)(11). The number of individuals affected by the condition is expected to further increase in the next 20 years, with 4.9 millions of individuals or 9.7% of population England expected to be living with diabetes by 2035. Prevalence of diabetes raises rapidly with increasing of age, currently ranging from 2% in adults aged 16-44 years to 23.8% in those aged 75 years and over (11). T2D accounts for the majority of the cases (90%) and its treatment accounts for almost 9% of the annual NHS budget, corresponding to £8.8 million a year (12).

1.2 Risk Factors for the Development of Type 2 Diabetes

Due to the high prevalence and associated healthcare costs, many countries have implemented national policies to reduce the burden of T2D. Considering that the aim of this doctor thesis is to assess the management of individuals at increased risk of T2D in primary care in England, from now on I will specifically focus on the epidemiology and policy implications specifically related to T2D.

The development of T2D results from an interaction between genetic, behavioural and environmental factors, which determine insulin resistance and β-cell dysfunction (13-15). Previous literature has consistently identified increasing age, sex, and ethnicity as non-modifiable risk factors associated with T2D (13, 14, 16). Among modifiable risk factors, increased body weight is the strongest risk factors for the development of T2D (13, 17). Other risk factors include unhealthy dietary patterns (e.g. consumption of processed meat, high intake of sugar-sweetened beverages) (18-21), behavioural factors such as smoking, drinking, and sedentary lifestyle (13), exposure to pollutants such as PM_{10} and NO_2 (22), and

lower socio-economic status (23). Clinical characteristics also associated with increased risk of T2D include history of preterm birth, menarche at later age, gestational diabetes, metabolic syndrome, and hypertension (13, 24-27).

1.2.1 Adiposity levels

According to the World Health Organization obesity is on the rise worldwide. It estimated that in 2016 more than 1.9 billion adults aged 18 years and older were at least overweight (BMI ≥ 25.0 kg/m^2) and over 650 million were obese (defined as BMI ≥ 30.0 kg/m^2) (28). A recent study estimated that in 2016 15.7% of the female adult population and 11.6% of the male adult population were obese worldwide. The mean BMI levels in 2016 were estimated to be 24.8 kg/m^2 in women and 24.5 kg/m^2 in men worldwide, which in both cases constitutes a remarkable increase from the estimated 22.1 kg/m^2 in women and 21.7 kg/m^2 in men in 1975 (29). In the UK in 2016 the proportion of the adult population who is obese was greater than the worldwide average, and equal to 15.7% in women and 11.6% in men. By 2025 it is projected to further increase and exceed the 35% in both sexes (35.6% in women and 35.4% in men). Accordingly, the mean BMI levels in women and men in the UK in 2016 were estimated to be 24.8 and 24.5 kg/m^2, respectively, which in both cases corresponds to more than 2 kg/m^2 increase from the 1975 estimates (22.1 kg/m^2 in women and 21.7 in men kg/m^2)(29).

The rise of obesity is one of the main causes of the T2D pandemic. As compared with normal weight individuals, those who are obese and overweight have a 7-fold and 3-fold increased risk of developing T2D, respectively (30). When further categorising obesity into 'metabolically healthy/unhealthy' (with metabolically unhealthy obesity defined by the presence of at least two of the following metabolic risk factors: hypertension, HbA1c>6.0%,

systemic inflammation, adverse high-density-lipoprotein cholesterol, and adverse triglycerides (31)), the risk of developing T2D for 'metabolically healthy' obese was still more than 4-fold increased, as compared with healthy normal-weight adults (32). Similarly, a recent meta-analysis estimated that as compared with no weight gain, a 5-kg/m^2 BMI increase in the early adulthood (18-24 years old) was associated with 3.1 increased risk of T2D, while the risk associated with late weight gain (5-kg/m^2 BMI increase for those ≥ 25 years old) was equal to 2.1 (33)

1.2.2 Behavioural factors

Among behavioural risk factors smoking is one of the strongest factors associated with the risk of T2D (13, 34). A recent meta-analysis estimated that as compared with non-smokers, the risk of T2D was 37% greater for current smokers and 14% greater for former smokers. Among smokers a dose-response relationship was found, with the relative risk ranging from 21% in light smokers to 57% in heavy smokers (34). No gender-related differences in this association were found (35). Similarly, the association did not seem to change in relation to the ethnicity as studies selectively focusing on European or Japanese populations had similar results (35, 36).

The relationship between alcohol consumption and T2D is still not entirely clear (37, 38). The U-shaped relationship between alcohol consumption and risk of T2D found in both sexes in a meta-analysis by Baliunas et al was only partially confirmed by a more recent meta-analysis, which found the risk of T2D in moderate drinkers to be reduced only in women and non-Asian populations (37, 38). On the contrary, the effect of alcohol consumption becomes deleterious at just 60 g/day for men and 50g/day for women (37).

Previous literature found a strong inverse relationship between physical activity and risk of T2D (39, 40). There is good evidence suggesting that this relationship is not linear. For instance, Smith et all in a recent meta-analysis found a risk reduction of 26%, 36%, 53% in development of T2D for individuals who achieved 11.25 metabolic equivalent of task (MET) h/week, 22.5 MET h/week, and 60 MET h/week, respectively, as compared with those who were inactive (40).

1.2.3 Family History and Genetic factors

There is also a large and convincing body of evidence suggesting that T2D has a strong genetic basis (41). Family history of diabetes is considered as strong risk factor for the development of T2D (42-44). Evidence from the Framingham Offspring Study suggested that the lifetime risk of developing T2D among offspring was 3.5 fold higher for those with a single diabetic parent, and 6-fold higher for those with both parents having diabetes, as compared with offspring without parental diabetes. Additionally, the first-degree family history of T2D is associated with a 2-fold increased risk of developing T2D (42, 45). Findings from the Framingham Offspring Study have been confirmed by other cohort studies (46). 70% of monozygotic twins have a concordant T2D status, which, however, lowers to 20-30% if twins are dizygotic (47). However, despite the isolation of a number of genetic variants increasing the risk of developing T2D their identification in routine clinical practice adds little information as compared with the assessment of well-established clinical and environmental risk factors (41).

1.3 Type 2 Diabetes Complications

Optimal management of T2D is essential to avoid diabetes-related complications, which are often associated with poorer quality of life, increased risk of hospital admission and

mortality (1, 48). This section will discuss the evidence linking T2D to the development of both macrovascular and microvascular disease.

1.3.1 Type 2 Diabetes and Cardiovascular Disease

Cardiovascular disease (CVD) is one of the leading cause of morbidity and mortality worldwide (49, 50). It has been estimated that in 2015 in Europe there were 11.3 million of new cases of CVD, 5.4 million among males and 5.8 million among females, and CVD was responsible for the loss of more than 64 million disability-adjusted life years (DALYs) (51). Approximately 3.9 million of deaths were caused by CVD in Europe, which remains the leading cause of death for both men and women (52). Considering specific CVD, ischemic heart disease is the leading cause of death in England (accounting for the 14.1% of the total deaths), while stroke is the third cause (7.4%) and together they account for the 10% of the total DALYs lost due to chronic conditions (53). Diabetes is considered as one of the strongest risk factors for CVD, as it confers approximately a two-fold excess risk for coronary heart disease and stroke, with the risk being even greater in groups otherwise considered at lower risk of vascular disease e.g. women, younger ages, with low blood-pressure, and non-smoker (54). In a recent systematic review, which included data on 4,549,481 individuals with T2D, Einarson and colleagues estimated the overall prevalence of CVD to be 32.2% in those with T2D (55). The study estimated that the most prevalent CVD in individuals with T2D was coronary artery disease (21.2%) and the lowest was stroke (7.6%). Prevalence of CVD was higher in men with T2D then women. It has also been estimated that CVD is responsible for about half of all deaths in T2D (55). In high-income countries diabetes might have been responsible for about 10% of the fatal CVD events in the last decade (54).

1.3.2 Type 2 Diabetes and Microvascular Complications

In individuals with T2D poor glycaemic controls causes microvascular damage of the small blood vessels that can lead to microvascular complications (48). These microvascular complications typically include diabetic retinopathy, nephropathy, and neuropathy.

1.3.2.1 Diabetic retinopathy

The most common microvascular complications in individuals with T2D is diabetic retinopathy (1), which is divided in two main categories: non-proliferative retinopathy and proliferative retinopathy. The first is characterised by small haemorrhages in the middle layers of the retina, the second is considered as a progression of the first type and is characterised by new blood vessels forming on the surface of the retina, with and without vitreous haemorrhage. It has been estimated that in individuals affected by diabetes the prevalence of diabetic retinopathy is 35%, while the prevalence of proliferative retinopathy is around 7% (56). It has also been estimated that retinopathy is the leading cause of vision loss in adult population aged 20 to 65 years (57, 58). The risk of developing retinopathy differs by gender, ethnic group, and deprivation worldwide (59-61). A US study estimated that among individuals with T2D, the prevalence of diabetic retinopathy was 36% higher in Blacks and 84% higher in Mexican Americans, as compared with the White population (62). A Swedish study estimated that diabetic retinopathy was responsible for 10 million of euros in healthcare expenditure, with similar estimates from other European countries (1).

In the UK it has been estimated that the prevalence of diabetic retinopathy is 28.3% in individuals with T2D, with the risk of severe retinopathy being 25% higher in South Asians, as compared with White population (63). The study found that the prevalence of

retinopathy in individuals with T2D remained constant between 2004 and 2014, while the screening for retinopathy increased. In the UK a diabetic eye screening programme is currently in place, which offers a free eye screening for individuals with diabetes aged 12 or over (64). Furthermore, the Quality and Outcomes Framework as specific process of care for patients with T2D established a diabetic retinopathy screening every 12 months (10).

1.3.2.2 Diabetic nephropathy

Diabetic nephropathy is the leading case of chronic kidney disease worldwide (65). Hyperglycaemia and hypertension are considered among the strongest risk factors, with the first considered as initiation and the second as progression factor (65). The metabolic changes caused by T2D can lead to processes such as glomerular hypertrophy, glomerulosclerosis, as well as tubulointerstitial inflammation and fibrosis, which can cause diabetic retinopathy (65). Around 7% of individuals with T2D might have already developed microalbuminuria at the time of diabetes diagnosis (66). Furthermore, individuals with diabetes have a 50% increased risk of developing chronic kidney disease, with almost 20% of them who will have a stage 3 or higher (67). Similarly, the prevalence of end-stage renal disease is 10 times higher in individuals who have diabetes (68). A study from the US estimated mean annual costs of USD 4,573 for individuals who have diabetic nephropathy.

In the UK it has been estimated that around 20% of individuals who have diabetes will develop diabetic nephropathy (69). The Quality and Outcomes Framework established a screening for proteinuria or microalbuminuria every 15 months as specific process of care for patients with T2D (10).

1.3.2.3 Diabetic neuropathy

Diabetic neuropathy is a heterogeneous group of diabetes-related complications characterised by nerve damage. According to the American Diabetes Association, the diagnosis of diabetic neuropathy is a diagnosis of exclusion as it might be diagnosed in individuals who have diabetes who present relevant symptoms after exclusion of other causes (70). In individuals with T2D factors associated with the nerve damage are hyperglycaemia, dyslipidaemia, impaired insulin signalling, and metabolic syndrome (70, 71). Estimates of prevalence of diabetic neuropathy in individuals with diabetes present a high degree of variation, ranging from 15% to 66% (72). Amputation, which is a complication of diabetic neuropathy, is estimated to be 10 to 20 times more likely in individuals who have diabetes (73). Foot complication is considered as one of the most costly diabetes-related complication. It has been estimated that the cost of care for individuals with diabetes who have foot ulcer is 5.4 times higher in the year of the first episode, as compared with those who have diabetes without foot ulcer (74).

A study by Vamos and Millett et al estimated that incidence of diabetes-related amputations in 2008 was 25.0 per 10,000 individuals with diabetes. For individuals with diabetes the relative risk of undergoing low extremity amputation was 21.2 higher in 2008, as compared with those without diabetes (75).

1.4 Inequalities in the Identification and Management of Type 2 Diabetes

Not only is the prevalence of T2D higher among those in the socially and economically most disadvantaged groups (23), but according to a recent meta-analysis social deprivation has

also been associated with worse management and subsequently worse intermediate outcomes (76). Despite the heterogeneity of the included studies, which were mostly conducted in Europe and the US, individuals in the lower socio-economic groups had process measures for T2D (e.g. HbA1c, blood pressure, smoking status, BMI, etc.) less frequently recorded. Furthermore, lower socio-economic status (SES) was also associated with poorer glycaemic control and increased risk of diabetes-related complications (76). Similarly, there is evidence that also links younger age with poorer recording and worse process indicators in individuals with T2D (77).

Gender inequalities have been widely documented in the diagnosis, management and clinical outcomes of T2D. Whilst the absolute CVD risk is higher among men, diabetes confers a greater excess risk among women compared with men (78). Women with T2D have also a higher risk of CVD hospitalization and higher all-cause mortality as compared with men (79). The excess CVD risk has been explained by the more adverse cardiovascular risk profile among women with T2D compared with men (78). This may be, at least partly, explained by poorer control of cardiovascular risk factors including poorer glycaemic (80) and blood pressure control (81) among women with diabetes compared with men (82). There is some suggestion that this may be due to women being more likely to be diagnosed with diabetes late (79, 82). Findings regarding gender inequalities in pharmacological management of T2D in the UK are discordant. A cross sectional analysis from the United Kingdom prospective diabetes study reported that women with diabetes were significantly less likely to take aspirin compared with men (83). A recent cohort study found that women had lower rates of initiation and continued statin therapy at 1 year than men, although this difference was no longer present after adjusting for age (84). In contrast, another recent cross-sectional study (85) found no gender differences in prescribing habits for prevention

of CVD, although this study was considering all patients eligible for pharmacological treatments for CVD prevention and not only patients with T2D. Findings from US study support the existence of gender inequalities in diabetes management. A nationwide study (86) evaluating the management of CVD risk factors, found that women were more likely than men to be assigned to a lower risk class despite the similar score obtained by using a 10-year cardiovascular risk algorithm. Socio-economic status might also interact with gender inequalities in clinical outcomes and risk factor control in patients with T2D in a complex way. A systematic review documented that socio-economic inequalities in the incidence of T2D are more pronounced in women than in men (23).

Differences in the risk, trajectories, and management of T2D are also present between ethnic groups (6-8). A recent meta-analysis found that HbA1c level in individuals without T2D is on average 0.26% greater in Black ethnic groups and 0.24% greater in South Asian ethnic groups (6). The increased risk for South Asians might be partially explained by greater insulin resistance than the white population, which is independent of the level and distribution of adiposity. Higher blood glucose levels among South Asian and Black ethic groups is reflected in higher prevalence of T2D in the UK, the US, and worldwide for these minority ethnic groups (87-89) and it is associated with higher complications rates and worse morbidity and mortality (88).

Multi-morbidity, defined as the co-occurrence of two or more long-term conditions in an individual, is common in patients with T2D (90) and, especially in women (91), and might influence the management of T2D. Millett et al (92) found that patients with T2D and additional co-morbidities were more likely to achieve national targets for CVD risk factor control. This could be because patients with T2D and multiple comorbid conditions may

receive greater number of clinical invitations for chronic disease management programmes, but also because patients with multi-morbidity may be more receptive to the intensification of disease management.

1.5 The Increasing Focus on Individuals at High Risk of Developing Type 2 Diabetes

Mean population levels of glycaemia and the prevalence of elevated glycaemia are tracking up with increasingly sedentary lifestyles and obesity levels in many countries (93), resulting in estimated figures projecting a 48% increase in the prevalence of T2D in the next twenty years worldwide (1)(Chapter 1.1). The increasing burden of T2D and its complications pose a serious threat for health systems globally. Therefore, in the past two decades there has been a decisive shift towards prevention of T2D and its complications by targeting individuals at increased risk of T2D for early lifestyle and pharmaceutical management with the purpose of reducing the progression rates to T2D. This has translated into an increasing focus on identifying individuals with blood glucose levels just below the diagnostic cut-point for diabetes i.e. 'non-diabetic hyperglycaemia' or 'intermediate hyperglycaemia' (94-97), also labelled as 'pre-diabetes'. A better understanding of the clinical features of this group of high-risk individuals is important considering that, similarly to the figures reported for T2D in the Chapter 1.1, the prevalence of individuals at high-risk of T2D is also on the rise (98).

Understanding the benefits of the management of this group at high-risk of developing T2D using real-world data is important considering that majority of the available evidence comes from clinical trials and interventional studies, which might have limited applicability to real-world settings. Specifically, despite early enthusiasm for lifestyle interventions, evidence

from clinical trials suggests that they may delay rather than prevent progression to diabetes in individuals at high risk, and have limited impact on longer-term outcomes (99, 100). Similarly, the trial evidence on pharmaceutical interventions involving the use of metformin is conflicting, as it has been reported no effect on reducing CVD and all-cause mortality in individuals at high risk of T2D (101). The use of real-world data to understand the importance of detection and management of individuals at high risk of T2D is also important to assess whether focusing on interventions in high-risk groups may distract attention away from the whole population interventions needed to address the growing societal burden of obesity and diabetes, such as meaningful regulation of the food industry. The next Chapter of this PhD thesis will discuss in detail the available evidence on individuals at high risk of developing T2D and the current gaps in the literature.

1.6 Key Summary for Chapter 1

Diabetes is considered one of the largest global health emergencies due to its rising prevalence, economic burden posed on healthcare systems, and disproportionate impact on health. It has been estimated that 425 million individuals in the world have diabetes, with the figure projected to further increase to 629 million by 2045. In England approximately 3.8 million people live with the condition. T2D accounts for 90% of the cases and its treatment accounts for almost 9% of the annual NHS budget, corresponding to £8.8 million a year.

Diabetes is considered as one of the main risk factors for macrovascular complications, as it confers approximately a two-fold excess risk for coronary heart disease and stroke. Poor glycaemic control causes microvascular damage of the blood vessels that can lead to microvascular complications such as diabetic retinopathy, nephropathy, and neuropathy, often associated with poorer quality of life, increased risk of hospital admission, and

mortality. Socio-demographic differences have been documented in the prevalence, management, and risk of diabetes-related complications.

2 Non-Diabetic Hyperglycaemia: The Implications of Its Management

2.1 Non-Diabetic Hyperglycaemia: Definition and Diagnostic Changes

The Expert Committee on Diagnosis and Classification of Diabetes in 1997 (102) and the World Health Organization (WHO) in 1999 (103) recognised a group of individuals who have elevated glucose levels that do not meet criteria for T2D. After two decades neither a consensus was reached about the terminology to use to define this intermediate status, nor an agreement was achieved about the appropriate diagnostic criteria to adopt for its detection. The next two paragraphs will discuss in detail the debate around the identification and management of Non-Diabetic Hyperglycaemia.

2.1.1 The debate regarding the terminology to adopt

The American Diabetes Association (ADA) in their guideline refers to this high-risk state using the umbrella term 'pre-diabetes' (104, 105). However, this terminology has not been recognised by international bodies such as the International Expert Committee and WHO (106, 107). In the UK the use of the term 'pre-diabetes' has also been discouraged by Diabetes UK in their position statement (108). Scientific bodies have advised against the term 'pre-diabetes' because its use may suggest that progression to T2D is inevitable and may undermine the message that the risk of T2D might be reduced through existing lifestyle interventions (109). Accepted terminologies are 'non-diabetic hyperglycaemia', 'intermediate hyperglycaemia', and 'impaired glucose regulation'(108, 110). In this doctoral thesis the term non-diabetic hyperglycaemia (NDH) will be used to define this high-risk state of progression to T2D.

2.1.2 The debate regarding the diagnostic criteria to adopt

Beyond the issue of agreeing appropriate terminology to use to define this high-risk state much of the debate is focused on appropriate detection thresholds to adopt. Below diagnostic threshold for T2D, measures of glycaemia are continuous with no obvious inflection point for increased vascular or diabetes risk. NDH is an arbitrary category, which was defined to draw a line between normal and abnormal glycaemic levels. There are two linked abnormalities to NDH which can be detected by specific blood glucose tests reflecting different pathways of impaired glucose regulation: i) Impaired Fasting Glucose (IFG), measuring the fasting plasma glucose (FPG), and ii) the Impaired Glucose Tolerance (IGT), using the oral tolerance test (OGTT). According to the WHO definition (110), IFG was defined by a FPG ranging 6.1-6.9 mmol/L (110-125 mg/dL), while IGT was defined by plasma glucose concentration ranging 7.8-11.1 mmol/L (140-200 mg/dL) at the OGTT. In 2003 an American Diabetes Association (ADA) Expert Committee recommended to reduce the threshold for IFG from 6.1 mmol/L to 5.6 mmol/L (100 mg/dL). However, this decision was not endorsed by the WHO, which expressed concerns that considering the proposed diagnostic threshold would almost double the prevalence of individuals with NDH, including those at lower risk of diabetes and cardiovascular disease (110).

After the International Expert Committee recommended in 2009 the use of glycated haemoglobin (HbA1c) as diagnostic test to identify diabetes and NDH (111), this diagnostic test has become more commonly used in primary care settings, considering it is a non-fasting diagnostic test. The Committee identified HbA1c ≥ 6.0% as intervention threshold, defining NDH for HbA1c values ranging 6.0-6.4%. This criterion was also adopted by the WHO in 2011 (112). Successively, ADA reduced the intervention threshold from 6.0 to 5.7% (94). This decision was supported by some international associations like the American

Association of Clinical Endocrinologist (113) but not by the WHO. In 2012 the UK National Institute for NICE published new guidelines for the detection and management of individuals at high risk of T2D which included the HbA1c range endorsed by IEC/WHO (42-47 mmol/l or 6.0-6.4%) for the definition of high-risk individuals but further lowered the ADA range for FPG to 5.5-6.9 mmol/l (Table 1)(27).

Table 1. Diagnostic criteria to define non-diabetic hyperglycaemia

WHO DIAGNOSTIC CRITERIA	
Impaired fasting glucose	6.1-6.9 mmol/L (110-125 mg/dL)
Impaired glucose tolerance	7.8-11.1 mmol/L (140-200 mg/dL) two hours after 75g glucose load
Glycated haemoglobin (HbA1c)	HbA1c ≥ 42 mmol/mol (6.0%) as intervention threshold
ADA DIAGNOSTIC CRITERIA	
Impaired fasting glucose	5.6-6.9 mmol/L (100-125 mg/dL)
Glycated haemoglobin (HbA1c)	HbA1c 39-47 mmol/mol (5.7%-6.4%)
NICE DIAGNOSTIC CRITERIA	
Impaired fasting glucose	5.5-6.9 mmol/L
Glycated haemoglobin (HbA1c)	HbA1c 42-47 mmol/mol (6.0%-6.4%)

Although different international scientific bodies have published criteria that use OGTT, FPG, and HbA1c as diagnostic tests to identify individuals with NDH interchangeably, concerns have been raised because the three tests have different discriminative abilities (i.e. sensitivity and specificity) (114). In a recent meta-analysis Barry and colleagues evaluated

the discriminative abilities of FPG and HbA1c to detect the NDH status in comparison with the OGTT test, calculating their area under the receiver operating characteristics (AUROC) curves. For FPG an AUROC equal to 0.72 was estimated, with a pooled sensitivity equal to 0.25 (95%CI 0.19-0.32) and a specificity equal to 0.94 (95%CI 0.92-0.96). The HbA1c AUROC was lower and estimated to be equal to 0.71, with a pooled sensitivity equal to 0.49 (95%CI 0.40-0.58) and a specificity equal to 0.79 (95%CI 0.73-0.84). Thus, FPG is specific but non sensitive, while HbA1c is neither sensitive nor specific, meaning that with both tests there might be many individuals being falsely reassured due to high number of false negative results, although this proportion might be greater using FPG. Furthermore, due to its low specificity the use of HbA1c, commonly adopted test in primary care as it is a non-fasting test, might be associated with a high number of normoglycaemic individuals incorrectly identified as having NDH.

2.2 The Global Burden of Non-Diabetic Hyperglycaemia

Similarly to T2D the prevalence of NDH is on the rise due to increasingly sedentary lifestyles and obesity levels in many countries (93). The International Diabetes Federation (IDF) estimated the global prevalence of NDH, defined as IGT, to be 7.3% of the adult population in 2017, equivalent to 352.1 million individuals. In accordance with diabetes projections, by 2045 the prevalence was anticipated to further increase to 8.3% of the global adult population, equivalent to an estimated 587 million individuals (1). The IDF model estimated that the North America and Caribbean region had the highest prevalence, equal to 15.4% of the adult population, while the lowest, equal to 3.0% of the adult population, was estimated in the South-Ease Asia region (1). However, IDF estimates only partially overlap with those from other studies. A study from the US reported that the prevalence of NDH among adult

population aged 20-79 years was rapidly rising, from 7.9% in 2008 to 8.3% in 2012. The study reported an annual incidence of NDH in 2012 of 7.1 cases per 1000 individuals (115). A recent meta-analysis estimated that in European countries the prevalence of NDH defined by ADA criteria for IFG was 13.0% (10.7% considering the WHO criteria for IFG)(116). However, the meta-analysis included studies conducted across almost a 30-year time span and did not provide estimates stratified by different time periods, which might have resulted in failure to capture the time trend in glucose trajectories observed by studies conducted in other regions. The lifetime risk of developing NDH is also very high, with a Dutch study reporting that, for normoglycaemic individuals aged 45 years, the lifetime risk of developing NDH is estimated to be around 50%, while three quarters of the individuals with NDH will eventually progress to T2D (117).

The choice of diagnostic methods and criteria for the detection of NDH does have a marked impact on the estimated prevalence of NDH at population level. A cross-sectional analysis of a large representative sample of the adult Chinese population reported that the prevalence of IGT was 8.3% (118). When adopting the ADA criteria for IFG to estimate the prevalence of NDH rose to 27.2% and to 35.4% when the ADA criteria for HbA1c was employed (118). A recent meta-analysis estimated that when using a combined IEC and WHO criteria for the definition of NDH the prevalence of individuals with raised IFG, IGT, and HbA1c levels was 27%. When ADA criteria was used the prevalence doubled to 54% (114). The authors found that using FPG as test is specific but not sensitive, whilst HbA1c is neither specific, nor sensitive (119).

The prevalence of NDH in the UK is high and projected to rise further. The IDF Atlas prevalence model estimated that 6.0% of the UK population had IGT in 2017 (1). Furthermore, data from the Health Survey for England reported that the prevalence of NDH

increased from 12% to 35% between 2003 and 2011 (98). However, compared with the IDF figure, the much higher prevalence in this latter case was mostly explained by the adoption of the expanded ADA criteria for the definition of NDH (97, 114). The prevalence study using data from the Health Survey for England found that there were no sex or social deprivation differences in the estimated prevalence of NDH, while the prevalence was higher in those who were South Asian (39.2%) or Black (35.0%), as compare with those of Mixed/Other ethnic groups (23.0%). Although the prevalence for White (31.9%) was lower than what estimated for South-Asian individuals, estimated confidence intervals overlapped.

2.3 Non-Diabetic Hyperglycaemia and Progression to Type 2 Diabetes

NDH is widely recognised as risk factor for progression to T2D. A longitudinal analysis using data from the Whitehall II study found that for individuals who eventually progressed to T2D an initial linear increase was followed by an abrupt increase in glycaemic levels 3 to 6 years before the clinical diagnosis of T2D (120). A similar design was also adopted in a 10-year follow-up study by Heianza et al on Japanese individuals comparing trajectories of FPG and HbA1c between those who eventually developed T2D and those who did not. The study found that for those who developed T2D FPG levels were significantly higher than controls during the entire follow-up period, but in this cohort the abrupt increase in FPG levels was found in the 1-3 years before progressing to T2D. However, the HbA1c slope significantly differed between those who eventually developed T2D and controls in the year before progression to T2D (121). These studies confirmed previous findings that showed a sudden increase in fasting glucose levels within 1-3 years before a clinical diagnosis of T2D (121-124). Differences in trajectories of IGT and FPG were also reported by additional studies (96,

125), suggesting that these sub-types of NDH reflect different pathways of impaired glucose metabolism and are characterised by different pathophysiological features (126). Whilst the study by Heianza and colleagues found differences in the trajectories of FPG and HbA1c, additional studies suggested similar rates of progression to T2D between those with IFG and elevated HbA1c (127-129). Progression rates to T2D also differ between NDH sub-groups identified by different diagnostic criteria (96). A meta-analysis including findings from 70 prospective observational studies found that highest incidence rate of T2D (47.40 per 1,000 person-year) was found in those with IFG defined by WHO criteria, followed by those with IGT (45.46 per 1,000 person-year), and IFG defined by ADA criteria (35.54 per 1,000 person-year). The meta-analysis also considered the 42-46 mmol/mol (6.0-6.4%) range for increased HbA1c adopted by the WHO and found that this range identified the individuals with the lowest risk of progressing to T2D, although the number of studies included in this sub-analysis was lower than for the others.

2.4 Non-Diabetic Hyperglycaemia and The Risk of Macrovascular Disease and Mortality

NDH has been shown to contribute to the pathogenesis of macrovascular dysfunction that might partly explain the increased risk of CVD morbidity and mortality in NDH and T2D (130-133). A meta-analysis including prospective cohort studies from the general population found that NDH, defined as IFG or IGT, was associated with increased risk of coronary heart disease, stroke, composite CVD events, and all-cause mortality, with these associations remaining consistent when considering both WHO and ADA criteria (131). However, the

findings regarding NDH defined by HbA1c levels were somehow less consistent: raised HbA1c levels defined by both NICE and ADA criteria were found to be associated with increased risk of CHD and composite CVD events, but no association was found for stroke and all-cause mortality (131). A large longitudinal study found that additional assessment of HbA1c values as part of CVD risk assessment provided little incremental benefit for prediction of CVD risk (134). Conversely, a different meta-analysis found a linear association between HbA1c levels and primary cardiovascular events. The effect was still present after adjusting for cardiovascular risk factors. However, no association was found between increased HbA1c levels and all-cause mortality in a recent meta-analysis that categorised HbA1c levels into four groups ranging from 31 to 48 mmol/mol (<31, 31-36, 37-41, 42-48 mmol/mol) (135). In contrast, a previous study found that NDH defined by elevated levels of HbA1c, as compared with IFG, was associated with a higher risk of CVD and death from any-cause (136). Ethnic differences in the risk of CVD associated with NDH have also been documented. A recent study found that NDH is related to both CHD and CVD risk in Europeans but not South Asians, where only the association with stroke was found (52). However, when considering the ADA criteria to define NDH, the association with CVD in European populations was weaker (52). The study considered IFG and IGT conditions for the definition of NDH.

2.5 Non-diabetic Hyperglycaemia and The Risk of Microvascular Disease

Emerging evidence suggests that NDH is also linked to generalised microvascular dysfunction, similar to the vascular damage typical of T2D (130, 132, 137). This implies that the development of T2D-associated microvascular disease may precede the clinical diagnosis of Type 2 diabetes (138). There is evidence linking NDH to early, milder forms of

nephropathy (132, 139-141). A study using representative data from the non-institutionalised US population also estimated that among the NDH population the prevalence of chronic kidney disease (CKD) ranged from 13.1 to 17.1%, depending on the adopted definition for CKD (142, 143). However, the body of evidence supporting this association is inconsistent as other studies reported no statistically significant findings (141, 144). A meta-analysis published in 2016 concluded that NDH is modestly associated with an increase in CKD risk, having estimated a 11% increased risk for those with NDH as compared with the normoglycaemic population (143). It also remains unclear whether the positive association between NDH and risk of nephropathy seen in longitudinal studies is attributable to NDH or partially mediated by the increased incidence of T2D (130). NDH has also been associated with increased risk of peripheral neuropathy, especially autonomic neuropathy, although the relationship with neuropathy remains unclear (130, 145). Finally, NDH has also been associated with increased risk of diabetic retinopathy, although findings are not consistent and vary in relation to the method of detection (130, 132, 139, 146, 147). Findings from the 30-year follow-up study of the Da Qing cluster randomised trial have demonstrated that the long-term risk of retinopathy in individuals with NDH can be reduced with lifestyle interventions (148), however, similarly to the evidence for nephropathy, it has also been questioned whether the risk reduction can at least be partially attributable to the reduced incidence of T2D (130). Microvascular diseases reported in individuals with NDH are usually early stage forms that are generally milder compared with that seen in established T2D (130, 145).

2.6 Lifestyle and Pharmaceutical Interventions

The critical role of lifestyle factors on the causal pathway of T2D has been well established. Observational studies have shown that up to 9 out of 10 of all new T2D cases are attributable to multiple lifestyle factors (149), whilst a recent umbrella review of meta-analyses graded the associations between T2D and the majority of analysed lifestyle risk factors as at least highly suggestive (13).

Furthermore, the potential to prevent or delay T2D in high-risk individuals (e.g. those with NDH) has been established by several clinical trials (93, 150, 151). The majority of these studies used intensive lifestyle interventions in high-risk participants (people with IGT in most studies), and simultaneously promoted increased physical activity, dietary modifications and weight reduction. Two landmark trials, the US Diabetes Prevention Programme (n=3,234) and the Finnish Diabetes Prevention Study (n=522) both found that the risk of T2D was reduced by 58% among people with IGT through a highly structured multicomponent lifestyle intervention, over about a 3-year period (152, 153). Within the multicomponent definition of lifestyle intervention, a key role is played by weight loss as this association has consistently been found in various trials regardless of whether it is achieved through dietary modifications or increased physical activity or the combination of both (154-157). Importantly, lifestyle changes reduced progression to T2D to a greater extent than long-term treatment with drugs such as metformin, and improved cardiovascular risk factors, which were left unaltered by metformin (158). However, majority of the trial evidence comes from clinical trials that were designed to look at the short and medium-term impact of lifestyle intervention. Only few follow-up studies of major trials reported potential long-lasting impacts of lifestyle programmes on diabetes risk and risk factors (100, 154). The China Da Qing Diabetes Prevention Study, but not others, also reported long-term effects on cardiovascular risk and mortality (159).

The evidence regarding the benefits of lifestyle interventions was further strengthened by two recent meta-analyses of clinical trials and interventional studies that estimated a 41% and a 36% reduction in the risk of progression to T2D for those at high-risk participating in lifestyle interventions involving diet and physical activity as compared with those in usual care (114, 157). The meta-analysis by Balk and colleagues also estimated that for those participating in lifestyle interventions the rate of reversion to normoglycaemia was 53% greater, as compared with those in usual care (157). A meta-analysis of clinical trials showed a number-needed-to-treat of 6.4 to prevent or delay one T2D case, through lifestyle interventions lasting from about 2 to 5 years (93). Furthermore, meta-analyses found that lifestyle interventions in individuals at increased risk of T2D are cost effective and safe (160, 161).

The benefit of pharmaceutical interventions remains contested. There is clinical trial evidence to show that metformin can prevent or delay T2D among patients with IGT over about a 3-year period, although to a lesser extent than lifestyle interventions (157, 162). However, studies with longer follow-up suggest that metformin treatment does not prevent T2D in people with NDH, but only delays its onset by around two years. Furthermore, a recent meta-analysis reported no effect on reducing CVD and all-cause mortality in people with NDH (99, 101).

Despite the limited evidence of the efficacy of pharmaceutical treatment in preventing or delaying the progression to T2D for individuals at high-risk, in many countries clinical guidelines have introduced metformin as part of clinical practice to manage individuals at high-risk of T2D. Clinical guidance produced by the ADA considers the treatment with metformin as a possibility for patients with IGT, IFG, or HbA1c between 5.7% and 6.4%, especially for those with BMI > 35 kg/m2, aged 60 years and older, and women with prior

gestational diabetes mellitus. The ADA guidelines have also been adopted by the American Association of Clinical Endocrinologist with a more aggressive pharmacological approach suggested (113). NICE recommends treating patients at increased risk of T2D with metformin when i) blood glucose measures (FPG or HbA1c) show they are still progressing towards T2D, despite their participation in an intensive lifestyle intervention ii) they are unable to participate in lifestyle interventions because of disability or medical reasons (27).

2.7 Screening for Type 2 Diabetes

The increasing prevalence of T2D and its consequences on the population health have led to the introduction of population-based screening programmes for Type 2 diabetes in some countries (114). However, the body of evidence supporting the widespread introduction of such programmes is mixed (114, 163-168). In a recent report the UK National Screening Committee has analysed arguments in favour and against the implementation of a national diabetes screening programme (169). The arguments in favour of the implementation of screening programmes are several. First, the prevalence of diagnosed and undiagnosed diabetes is increasing worldwide, with a proportion of the undiagnosed group who might also develop diabetes-related complications like retinopathy. Second, there has been the diffusion of more convenient, non-fasting blood test like HbA1c and the available risk scores to evaluate the risk of developing T2D have improved in accuracy. Third, the quality of diabetes care has advanced and through the retinal screening test it is also possible to detect early-stage complications. Fourth, diabetes screening might detect individuals with NDH who also have higher cardiovascular risk and those might benefit from tight cardiovascular management. Finally, in 2012 NICE published new guidelines for the

management of individuals at high risk of T2D, which also include guidance on the cut-off levels to adopt to identify those with NDH. However, despite these points supporting screening, due to the inconsistency of the available trial evidence and the poor specificity and sensitivity of HbA1c and FPG test as compared with OGTT, the UK National Screening Committee has advised against the universal diabetes screening for individuals aged forty years and older. However, the Committee concluded that there is a case for selective screening for high-risk individuals as part of overall cardiovascular risk assessment (169). Most of the trial evidence is based on two landmark trials: i) the ADDITION, a cluster-randomised primary care trial that enrolled primary care practices in England, Denmark, and the Netherland and compared intensive care (lifestyle and pharmaceutical intervention) with standard care to manage individuals at high risk and with newly diagnosed T2D (170-172) and ii) a trial of screening for diabetes enrolling individuals from the Ely cohort study (173). The ADDITION trial failed to demonstrate improvements attributable to diabetes screening on long-term health outcomes including microvascular and macrovascular complications and mortality (170, 172, 174). The reduction in cardiovascular risk in favour of the treatment arm was not statistically significant because individuals in the standard arm had similar improvements in cardiovascular risk factor control (e.g. reduction in blood pressure and cholesterol levels), possibly explained by improvement in quality of standard care for individuals at increased risk of T2D (170, 171). In the Ely randomised controlled trials one third of the individuals aged 40 to 65 years were screened three times between 1990 and 2002 using OGTT and compared with the rest of the study population of whom only half was invited for screening for T2D in 2000-02. General practitioners were informed of the screening results but no standard clinical management protocol was established, therefore, they could manage screen-detected patients in a way they considered

appropriate. A study analysed the trial data after a 13-year follow-up and did not find any difference in improvement of cardiovascular profile between the two groups, nor in self-reported outcomes (173). More recently, the U.S. Preventive Services Task Force conducted a systematic review to update their 2008 review on the effectiveness of screening for diabetes in the adult population (163). The systematic review concluded that more evidence was needed given that current trial evidence does not indicate that diabetes screening reduced mortality rates after 10 years of follow-up. On the contrary, a beneficial effect on mortality was found in a lifestyle intervention study after 23 years of follow-up (159). The systematic review also concluded that the treatment of NDH was associated with delayed progression to T2D (163). However, more recent data from trials and prevention programmes has been used to conduct modelling studies which indicated some long-term benefit from screening (175, 176), including major benefits from early detection (166). Additionally, another modelling study suggested that screening for T2D is also cost-effective, especially when using HbA1c to detect individuals at high risk of T2D (177). However, predictions from modelling studies are highly sensitive to the underlying assumptions and these may not reflect real-world conditions (178). Despite the evidence against diabetes screening a community-based diabetes screening programme was developed in India and designed to use both survey-based tools and random glucose tests to identify individuals with NDH and undiagnosed T2D for early clinical management. A study based on microsimulation sought to evaluate the impact of this programme and found that this intervention is anticipated to produce large number of positive results, especially if using survey based screening instruments (179).

2.8 Current Clinical Practice for the Management of Individuals at High Risk of Type 2 Diabetes

Although the UK National Screening Committee has advised against the universal diabetes screening for individuals aged forty years and older, the country has made considerable investments to implement preventive strategies for the detection and early management of individuals at increased risk of T2D, which might have translated into an increase of opportunistic screening for T2D and high-risk states.

The NICE guideline (27) recommends that general practitioners should perform a 2-stage risk assessment for patients considered at increased risk of T2D. Patients who should be encouraged to have a risk assessment are: i) adults aged 40 and older without a diagnosis of diabetes except for pregnant women ii) adults aged 25-39 years of ethnic groups considered at high risk (e.g. South Asian, Chinese, African-Carribean, black African, and other high-risk black and minority ethnic groups) expect pregnant women iii) adults with conditions that increase the risk of T2D (i.e. CVD, hypertension, obesity, etc.). The risk assessment pathway should be as follows:

- Stage one: Use of validated risk assessment tool (i.e. QDiabetes risk calculator (180), Cambridge risk score (181, 182), and the Leicester Risk Assessment score (183)), or validated self-assessment questionnaire (184));
- Stage two: For those with a high risk score a blood test should be offered (FPG or HbA1c) and if the diagnostic criteria (NICE criteria) for NDH are met an intensive lifestyle-change programme should be offered. The programme includes: i) increase physical activity ii) achieve and maintain weight loss iii) increase dietary fibre, reduce fat intake.

However, until the start of the NHS Diabetes Prevention Programme, although lifestyle interventions are a key point in the NICE guidelines to manage patients at increased risk of T2D, general practitioners could not systematically refer those patients for such interventions, with the availability and quality of local weight management programmes being largely non-existent.

Although lifestyle interventions are considered the first approach with patients at increased risk of T2D, pharmaceutical approaches might also be considered in some cases (27). However, prescription of glucose-lowering agents to patients with NDH in the UK is likely to be equally low than what has been found in the USA (185, 186), given that, similarly to ADA, NICE recommends pharmaceutical interventions only for patients considered at high risk to progress towards T2D. For instance, NICE guidelines consider at high risk adults whose blood glucose measures (FPG or HbA1c) show they are still progressing towards T2D, despite their participation in an intensive lifestyle-change programme) (27).

2.9 Risk Assessment Tools to Identify Individuals at Increased Risk of Type 2 Diabetes

As suggested by the NICE risk assessment pathway, risk assessment tools are routinely used in primary care settings to identify individuals at increased risk of developing T2D. Risk assessment tools require routinely collected healthcare data and can be easily used as first-stage for the identification and management of individuals at increased risk of T2D in primary care settings (Chapter 2.8). Using data from trials and cohort studies, several risk assessment tools and risk algorithms to estimate the risk of progression to T2D have been developed (187, 188). In majority of cases these risk assessment tools have different approaches but many are equally valid if appropriately used (187). The most frequently risk

assessment tools used in primary care settings in the UK are those suggested by the NICE guidelines (27). They are the Cambridge score (181, 182), the Leicester risk assessment score, the Leicester practice score (183, 189), and the Qdiabetes (190) (Table 2). Other risk assessment tools used outside of the UK are the FINDRISC, the ARIC (Atherosclerosis Risk in Communities), the San Antonio diabetes prediction model, the Chinese diabetes risk score, the Framingham risk score and the Framingham Offspring Study score, the Dport (Diabetes population at risk tool), and the German diabetes risk score, as well as their modified versions (187). Briefly these are the characteristics of these four commonly used risk assessment tools in the UK:

2.9.1 The Cambridge risk score

The risk score was originally developed to identify individuals with undiagnosed diabetes and for its development it used data from the study population enrolled within two English cohorts: the Ely study and the Wessex study (181). For those without a previous diagnosis of T2D the ascertainment of the diabetes status was conducted using an OGTT test. For the development of the score the study evaluated specificity and sensitivity of the score in differentiating those with previously undiagnosed diabetes from those with either normal glucose levels or NDH. The final equation optimising the test characteristics (e.g. sensitivity, specificity) included the following variables: age, sex, family history of diabetes, BMI, smoking status, prescribed steroids, prescribed antihypertensive medications. Successively, the risk score was also used to evaluate the risk of developing T2D using data from the European Prospective Investigation of Cancer – Norfolk prospective cohort study (182).

2.9.2 The Leicester risk assessment score and the Leicester Practice Risk score

The Leicester risk assessment score and the Leicester Practice Risk score were originally developed to identify individuals at increased risk of IGT or T2D and used data from the ADDITION-Leicester population screening study (183, 189). In both studies the OGTT test was used to ascertain the diabetes status. The two risk scores include a very similar set of variables: age, sex, ethnicity, family history of diabetes, BMI, and prescribed antihypertensive medications are common to both scores, while waist circumference is only included in the Leicester risk assessment score. The main difference between the two scores is that the Leicester risk assessment score is meant to be completed by patients, while the Leicester practice risk score uses routinely collected healthcare information recorded by healthcare personnel working in primary care settings (183, 189).

2.9.3 QDiabetes

Qdiabetes, originally named QDScore, was developed to predict the 10-year risk of developing T2D. For the development of the risk score data from the a retrospective primary care cohort study from the QResearch database was used (180). The diagnosis of T2D was defined by recording of diagnostic Read codes for diabetes (C10). QDiabetes is the risk score that includes the largest number of variables: age, sex, ethnicity, family history of diabetes, BMI, Townsend deprivation score (using 2001 UK census data), smoking status, diagnosis of CVD, treated hypertension, and current treatment with corticosteroids. Subsequently, QDiabetes was externally validated using the CPRD dataset (191). More recently, the algorithm for the risk score has been further implemented (QDiabetes-2018) including additional variables such as atypical antipsychotics, statins, schizophrenia or bipolar affective disorder, learning disability, and gestational diabetes and polycystic ovary

syndrome in women. Furthermore, the risk score has also been derived in a second version which also includes FPG (191).

Table 2. Variables included in four diabetes risk assessment tools commonly used in the UK

Variable	Cambridge risk score	Leicester risk assessment score	Leicester Practice risk score	Qdiabetes
Age	required	required	required	required
Sex	required	required	required	required
Ethnicity	-	required	required	required
Family history of diabetes	required	required	required	required
BMI	required	required	required	required
Waist circumference	-	required	-	-
Townsend deprivation score	-	-	-	required
Smoking status	required	-	-	required
Cardiovascular disease	-	-	-	required
Prescribed steroids	required	-	-	required
High blood pressure or prescribed hypertensive medicine	required	required	required	required

2.9.4 Comparison of the four risk assessment tools

Supported by Public Health England, the National Cardiovascular Intelligence Network recently conducted an analysis to compare sensitivity and specificity of the four risk scores in predicting the risk of NDH (188). To conduct the analysis combined data from five years of the Health Survey for England were used and NDH was defined as an HbA1c value between 42mmol/mol (6.0%) and 47mmo/mol (6.4%). Accuracy was quantified calculating for each

score the area under the curve (AUC), which accounts for both specificity and sensitivity of a given algorithm. All four risk scores had very similar areas under the curve, ranging from 0.76 of the Cambridge risk score to 0.80 of the Leicester Practice Risk score, and with both QDiabetes and the Leicester risk score having an area under the curve equal to 0.78. When comparing the overlap between risk scores in identifying individuals with NDH the Leicester Practice Risk score and QDiabetes had the largest degree of overlap (80.8%). However, all risk scores showed a clear relationship which in most cases displayed some degree of non-linearity (188).

2.10 The Cardiovascular and Diabetes Prevention Programme in England

Over the last decade, considerable investments have been made in England to introduce preventive strategies to reduce the burden of cardiovascular disease and diabetes. National risk assessment and management programmes like the NHS Health Check and the more recently launched NHS Diabetes Prevention Programme have both a strong focus on detection and early management of individuals with NDH, which means that a greater number of individuals with NDH and T2D might have detected, although their management through the programmes might differ from the routine clinical practice.

The NHS Health Check programme, launched in 2009 in England and rolled out nationally, is one of the world's largest cardiovascular risk assessment and management programmes. The programme invites all individuals in England aged 40-74 years who are not registered in a vascular disease register to attend a cardiovascular risk assessment every five years (192). Although its primary focus is cardiovascular risk assessment, the programme also includes a diabetes risk assessment and screening component (Figure 2) (193). The programme best

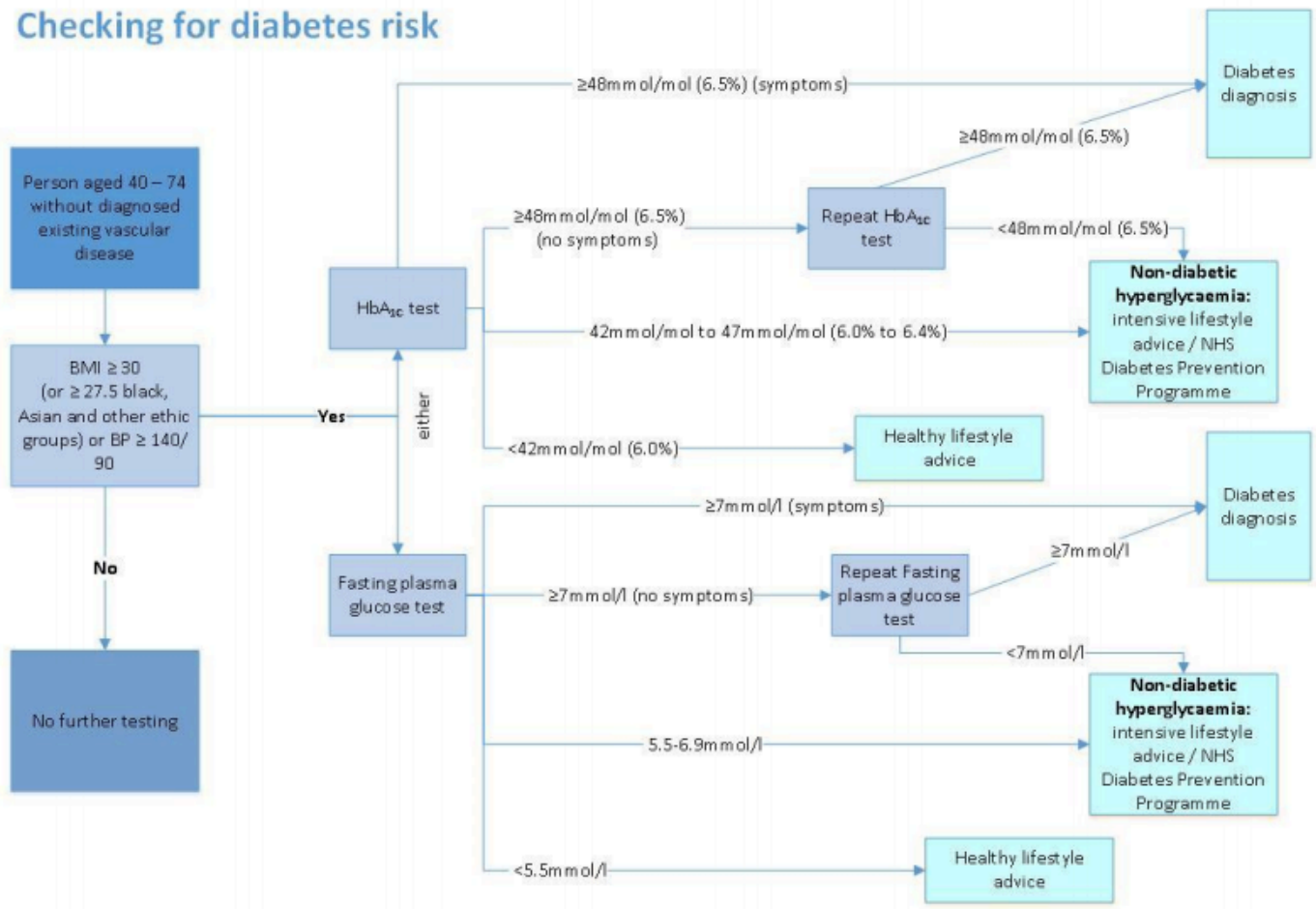
practice guidance has had several updates, which have translated in some changes in how to identify those who might be at high risk of T2D and therefore eligible for a blood glucose test (either HbA1c or FPG) (193). As of 2016, the programme best practice guidance recommends to identify those at increased risk of T2D either using the diabetes filter (BMI: greater than 27.5 kg/m^2 for individuals of Black, Asian, and other non-White ethnic groups and greater than 30 kg/m^2 for individuals of White ethnic groups; blood pressure: systolic blood pressure above 140 mm Hg and/or diastolic blood pressure above 90 mmHg; Figure 2) or one of the diabetes risk assessment tools recommended by the NICE guideline (Cambridge risk score, Leicester risk assessment score, Leicester Practice risk score, and Qdiabetes) (27, 192). Additionally, the programme recognises that other categories might not be picked up by the filter and yet be considered at high risk: individuals with family history of T2D or heart disease, individuals with microvascular disease known to be associated to T2D (e.g. retinopathy, nephropathy, and neuropathy), women with history of gestational diabetes, individuals with conditions known to be associated with T2D (e.g. polycystic ovarian syndrome or severe mental health conditions), and individuals taking medications known to be associated with T2D (e.g. oral corticosteroids). For the patients deemed at high risk of T2D, as part of the NHS Health Check, a FPG or HbA1c test is offered and in case the blood glucose levels are within the NDH range (HbA1c 42mmol/mol to 47 mmol/mol or 6.0% to 6.4%; FPG 5.5 to 6.9 mmol/L) a participation to the NHS Diabetes Prevention Programme can be offered or, alternatively, intensive lifestyle advices (192).

The NHS Diabetes Prevention Programme started its national roll-out in June 2016, with the process expected to be completed in 2019 (188, 194). The programme offers tailored interventions to individuals with NDH, including diet and lifestyle advices, support for weight loss, and physical exercise programmes.

A study aiming to evaluate the Health Check programme found that the programme coverage, at least in the first four years, was relatively low (around 20% on average) (195). The coverage varied widely between English general practices, ranging from 9.4% to 30.7%. However, more recent data show that there have been steady increases in coverage during the last years, which now is more than 40% (196). Additionally, another study found that coverage differs by level of risk, as it was higher among patients considered at higher risk (197). More recently, Chang et al conducted a quasi-experimental difference-in-difference analysis to assess the effect of the programme on cardiovascular disease risk factors, on prescribing of relevant medications, and diagnosis of vascular diseases (198). The study found that the attendance to the programme was associated with a significant but clinically modest improvement in modelled cardiovascular risk and individual cardiovascular risk factors, possibly attributable to a positive underlying trend of improvement also for general practices with low programme coverage. Attendance of the programme was also associated with increase in diagnostic rates of selected vascular diseases, especially T2D and hypertension. However, it is not known to what extent the implementation of the NHS Health Check programme has translated into increased frequency of testing, detection and the quality of the management of people with NDH and newly diagnosed T2D.

As the NHS Diabetes Prevention Programme has been launched after the commencement of this doctoral study, no data is available for the assessment of its impact on the target population.

Figure 2. NHS Health Check diabetes filer for individuals at increased risk of Type 2 diabetes



Notes: source Public Health England (192)

2.11 Key Summary for Chapter 2

Preventive strategies to reduce the burden of diabetes have focused on identifying individuals with blood glucose levels just below the diagnostic cut-point for diabetes i.e. NDH for early management. 7.3% of the global adult population has NDH; in the UK the prevalence is 6.0%. There is no consensus on the terminology and diagnostic criteria for the definition of NDH. NDH is associated with increased risk of and CVD and mortality, with ethnic differences being documented. NDH has also been associated with increased risk of microvascular complications with accumulating evidence, although the burden has not been quantified in real world settings. Lifestyle interventions can reduce the risk of progression to T2D for those with NDH by 36-41%. Evidence on the use of metformin suggests that it can delay progression to T2D in individuals with NDH by around two years.

The UK National Screening Committee has advised against the universal diabetes screening, although recommends a case for selective screening for high-risk individuals as part of overall cardiovascular risk assessment. Little is known about how individuals with NDH are managed in routine primary care settings in the UK. The NHS Health Check programme, includes a diabetes risk assessment and screening component. To date, no previous studies have reported the evaluation of the diabetes screening component of the Health Check programme or the more recently launched NHS Diabetes Prevention Programme.

3 Aim, scope, and justification of this work

3.1 Summary and justification of this work

- In England over 3.0 million people had diagnosed diabetes in 2017 and 940,000 adults had undiagnosed diabetes. T2D accounts for 90% of the cases and its treatment accounts for almost 9% of the annual NHS budget, corresponding to £8.8 million a year.
- Diabetes is one of the strongest risk factors for CVD, as it confers approximately a two-fold excess risk for coronary heart disease and stroke.
- Poor glycaemic control causes microvascular damage of the blood vessels that can lead to microvascular complications such as diabetic retinopathy, nephropathy, and neuropathy, often associated with poorer quality of life, increased risk of hospital admission, and mortality.
- As part of preventive strategies to reduce the burden of diabetes there has been an increasing focus on identifying individuals with blood glucose levels just below the diagnostic cut-point for diabetes i.e. NDH for early management.
- There is no consensus on the diagnostic criteria to adopt for the definition of NDH. Different diagnostic criteria identify different groups of individuals who differ in progression rates to Type 2 diabetes and risk of associated morbidity raising the question of whether those who might benefit the most from tight clinical management are effectively identified as high-risk by each criterion.
- The International Diabetes Federation estimated the global prevalence of NDH, defined as IGT, to be 7.3% of the adult population in 2017, equivalent to 352.1 million individuals. The prevalence in the UK was estimated to be 6.0%.

- NDH is a major risk factor for progression to T2D. NDH is also associated with increased risk of CHD, stroke, composite CVD events, and all-cause mortality, with ethnic differences being documented regarding these associations.
- NDH status has also been associated with increased risk of microvascular complications. Specifically, it is linked to early, milder forms of nephropathy and also modestly associated with increased risk of CKD. Findings on the association between NDH and diabetic retinopathy are not entirely consistent.
- There is no evidence on whether the prevalence of vascular complications at time of diagnosis of T2D varies by prior NDH status. Additionally, the association between NDH and microvascular disease differs by ethnic groups.
- Despite good trial evidence on the benefit of lifestyle interventions for those at increased risk of T2D, the UK National Screening Committee has advised against the universal diabetes screening for individuals aged forty years and older, although it concluded that there is a case for selective screening for high-risk individuals as part of overall cardiovascular risk assessment.
- Little is known about how individuals with NDH and with newly diagnosed T2D are managed in routine primary care settings in the UK.
- The NHS Health Check programme, launched in 2009 in England and rolled out nationally, is one of the world's largest cardiovascular risk assessment and management programmes. Although its primary focus is cardiovascular risk assessment, the programme also includes a diabetes risk assessment and screening component. To date, no previous studies have reported the evaluation of the diabetes screening component of the Health Check programme.

3.2 Aim

The aim of this PhD is to examine whether glycaemic testing, detection, and management of NDH before diagnosis of T2D is associated with the risk of vascular disease and all-cause mortality following the diagnosis of T2D. A secondary aim of this PhD is to assess whether the NHS Health Check programme increased the detection of T2D and NDH, and improved control of blood glucose and cardiovascular risk factors among newly diagnosed cases.

3.3 Objectives

1) To assess whether glycaemic testing and detection of NDH before the diagnosis of T2D is associated with occurrence of microvascular and macrovascular disease at the time of T2D diagnosis; and whether associations vary between ethnic groups
2) To assess whether glycaemic testing and detection of NDH before the diagnosis of T2D is associated with the risk of incident microvascular and macrovascular disease following the diagnosis of T2D
3) To assess whether glycaemic testing and detection of NDH before the diagnosis of T2D is associated with the risk of mortality following the diagnosis of T2D
4) To assess whether the coverage of the NHS Health Check programme is associated with increased detection of NDH and T2D
5) To assess whether the coverage of the NHS Health Check programme is associated with improved control of blood glucose and cardiovascular risk factors among newly diagnosed NDH and T2D cases

3.4 Research hypotheses

My research includes both hypothesis generating and hypothesis testing components. Firstly, emerging evidence suggests that NDH is associated with increased risk of vascular disease, which might be explained by the prolonged elevated glycaemic levels. For the majority of those who progress to T2D glycaemic levels increase 3 to 6 years before the diagnosis of T2D. However, a proportion of those progressing to T2D might rapidly progress from the normoglycaemic status to T2D, with different clinical features and risk of complications as compared with those with prior T2D (Chapter 3.3-3.4). Therefore, statistical models were constructed to test the hypothesis that the prevalence of vascular disease at the time of diagnosis of T2D differs in those who progress to T2D transitioning through the NDH status, as compared with those who rapidly progress to T2D from a prior normoglycaemic status. Secondly, while ethnic differences in the association between NDH and macrovascular disease have been documented, no study has explored whether the association between NDH and microvascular disease differs by ethnic groups. Therefore, statistical models were constructed to test the hypothesis that the prevalence of vascular disease at time of T2D diagnosis differs by groups defined by the interaction between ethnicity and prior glycaemic status. Thirdly, for those who progress to T2D it remains unclear whether glycaemic testing, NDH testing, and early interventions before T2D development can affect long-term risk of vascular disease and CVD mortality. Therefore, statistical models were constructed to test the hypothesis that the risk of incident vascular disease and all-cause and CVD mortality following the diagnosis of T2D differs by glycaemic testing and NDH detection before the diagnosis of T2D. Finally, in light of the presence of a diabetes screening component within the programme, I hypothesised that the NHS Health Check programme increased the detection of T2D and NDH and improved control of blood glucose and cardiovascular risk

factors among newly diagnosed cases and tested this hypothesis constructing a statistical model associating programme coverage with selected outcomes.

4 Methods – Data Source and Study Population

4.1 The Clinical Practice Research Datalink

The Clinical Practice Research Datalink (CPRD) is one of the largest databases of electronic medical records in the world (199). CPRD routinely collects longitudinal and anonymized primary care data from participating general practices in the United Kingdom (UK) (199). The CPRD database that collects data from primary care practices using the Vision® software system is called CPRD Gold. It covers approximately 7% of the UK population and it is representative in terms of age, sex, and ethnicity (199, 200). Distribution of risk factors like BMI is also comparable to data from the Health Survey for England (201). CPRD provides linkage to hospital episode statistics (HES) and Office for National Statistics (ONS) mortality data (199). Currently, 75% of CPRD practices in England registered with CPRD Gold have consented to linkage (202). Data are subject to regular quality checks and are widely used for research studies (199, 203). Considering the unique characteristics of CPRD, this database has been widely used in the evaluation of national strategies implemented in a primary care and other settings in England and the UK like the NHS Health Check programme (198) and the Quality and Outcomes Framework (204-206).

In 2018 CPRD launched CPRD Aurum, which includes data from primary care practices using the EMIS® software system (199).As CPRD Aurum was made available only towards the end of my PhD I have only used CPRD Gold for my analyses.

4.2 The health data in CPRD and its use in research

CPRD routinely collects primary care data, which includes data on diagnoses, symptoms, referrals, prescriptions, and tests (202, 207). For the majority of English practices registered with CPRD

linked data is also available, which includes ONS mortality and HES data. CPRD uses Read codes version 2 and 3 for the recording of clinical diagnoses, symptoms, and patient's management (199, 201, 207). Read codes are a coded thesaurus of clinical terms, which have been used in the NHS since 1985 (208). This coded thesaurus can be considered as a standard vocabulary that can be used by healthcare personnel to record patients findings and procedures (208).

To identify conditions or procedures for research purposes algorithms that consider a combination of all available information in CPRD are often designed and validated. Therefore, many algorithms developed for CPRD include comprehensive lists of diagnostic and management Read codes. For instance, in my PhD to identify individuals with a diagnosis of T2D I used an established method published by Gray et al that consider both diagnostic (C10) and management (66A) Read codes for the identification of T2D cases (209). Additionally, to assess coverage of the NHS Health Check programme, I used a validated algorithm by Chang et al (195), which consider the measurement and recording of four risk factors (as for NHS Health Check Best Practice Guidance) within a six-month window during the intervention period.

4.3 Study population

The research questions in my PhD consider different stages of the potential progression from high risk status to T2D. My first three objectives focus on individuals who eventually progressed to T2D to assess whether selected outcomes differ according to prior NDH status, while objectives 4-5 focus on eligible population for the NHS Health Check programme. Therefore, I specified different study populations from CPRD to address these objectives. Specifically, I extracted data from two different study populations from CPRD, as specified below.

4.3.1 Study population for the objectives 1-3

I defined a cohort of individuals who were newly diagnosed with Type 2 diabetes between 1 January 2004 and 30 September 2017. Participants included in the cohort were registered with one of the 75% of CPRD practices with linked hospital admission and mortality data. Participants also had to have been continuously registered with a practice for at least one year before the diagnosis of Type 2 diabetes and with availability of historical data in clinical records. Diagnoses of Type 2 diabetes were identified using both diagnostic (C10) and management (66A) Read codes for Type 2 diabetes based on an established method (209). Individuals who were diagnosed with Type 2 diabetes under the age of 35 years who were prescribed insulin within three months of diagnosis and who were not prescribed oral hypoglycaemic agents for longer than three months were excluded, because these individuals were likely to have Type 1 diabetes (210). As this part of the PhD focuses on detection of NDH before Type 2 diabetes diagnosis, individuals who had glycaemic values within the diabetes range recorded more than three months before the date of the first diagnosis of Type 2 diabetes were excluded from this study, as in this case testing might not be attributable to the diagnostic process but to mis-classification.

4.3.2 Study population for objectives 4-5

To evaluate the diabetes screening component of the NHS Health Check Programme I used CPRD data to obtain a large representative sample of the English population eligible for the programme. Specifically, I obtained data for a computer-selected random sample of 387,460 individuals aged 40-74 years who were continuously registered with 455 CPRD general practices in England between 1 January 2009 and 31 December 2014. As the random sample was meant to be eligible for the NHS Health Check programme, I further excluded individuals with a diagnosis of CVD and T2D before 1 January 2009, which reduced the sample to 348,987 individuals. To allow a longer

follow-up of our study population, I also obtained an update of CPRD data that capture study outcomes up to 31 May 2016.

4.4 Index of multiple deprivation

In CPRD a linkage to different measures of deprivation can be obtained using the general practice postcode. Currently, CPRD provides linkage to the following deprivation measures (199):

- 2015 English Index of Multiple Deprivation (composite and individual domains)
- 2016 Scottish Index of Multiple Deprivation (composite and individual domains)
- 2017 Northern Ireland Index of Multiple Deprivation (composite and individual domains)
- 2014 Welsh Index of Multiple Deprivation (composite and individual domains)
- Carstairs Index: England, Wales and Scotland calculated using 2011 census data

As CPRD only permits one deprivation measure per data extraction which is linked at practice level, I therefore requested data linkage to the general practice IMD for the data I used in this doctoral thesis. The English Indices of Deprivation 2015 are based on 37 separate indicators, organised across seven distinct domains of deprivation, which are combined, using appropriate weights, to calculate the IMD 2015 (211). The seven district domains are:

- Income Deprivation
- Employment Deprivation
- Education, Skills and Training Deprivation
- Health Deprivation and Disability
- Crime
- Barriers to Housing and Services
- Living Environment Deprivation

Considering the IMD is a continuous measure, CPRD provides either quintiles or deciles of this measure. Previous versions of the Index of Multiple Deprivation (IMD) can also be obtained. However, I requested the 2015 English IMD because I would have encountered missing data issues requesting previous versions, considering that linkage might have been created for CPRD practices no longer registered with CPRD and, similarly, the measure would have not been available for practices that recently joined CPRD.

4.5 Ethical approval

CPRD has been granted Multiple Research Ethics Committee approval (05/MRE04/87) to undertake purely observational studies with external data linkages, including hospital admission and mortality data. The present studies are based on anonymised and unidentifiable CPRD data. Ethical approvals for the study protocols were granted by the Independent Scientific Advisory Committee of the CPRD (protocol number: 15_250R; 18_208R). All the study methods were performed in accordance with the relevant guidelines and regulations and in accordance with best scientific practice.

5 Association Between Non-diabetic Hyperglycaemia and Microvascular and Macrovascular Disease in Newly Diagnosed Type 2 Diabetes

5.1 Abstract

5.1.1 Background

The association between detection of NDH before the diagnosis of T2D and prevalence of vascular disease following diagnosis of T2D in real-world settings is unknown.

5.1.2 Aim

I examined the presence of microvascular and macrovascular disease in newly diagnosed T2D individuals by glycaemic status within 3 years before diagnosis. I also examined whether this association varies by different ethnic groups.

5.1.3 Methods

I identified 159,736 individuals with newly diagnosed T2D from the CPRD database in England between 2004 and 2017. I used logistic regression models to compare presence of microvascular (retinopathy and nephropathy) and macrovascular (coronary heart disease, cerebrovascular and peripheral arterial disease) disease at the time of T2D diagnosis by prior glycaemic status. A secondary analysis included an interaction term between prior NDH status and ethnic groups.

5.1.4 Results

Half of the study population (49.9%) had at least one vascular disease, over one-third (37.4%) had microvascular disease, and almost a quarter (23.5%) had a diagnosed macrovascular disease at the time of T2D diagnosis. Compared with individuals with glycaemic values within the normal range, those detected with NDH before the diagnosis had 76% and 14% increased odds of retinopathy and nephropathy (retinopathy: AOR 1.76, 95%CI 1.69-1.85; nephropathy: AOR 1.14, 95%CI 1.10-1.19), and 7% higher odds of the diagnosis of coronary heart disease (OR 1.07, 95%CI 1.03-1.12) in fully adjusted models at time of diabetes diagnosis. Among those detected with NDH those of White ethnic groups had 45% increased odds (OR 1.45, 95% CI 1.40-1.51), those of South Asian ethnic groups 64% increased odds (OR 1.64, 95% CI 1.48-1.82), and those of other ethnic groups

92% increased odds (OR 1.92, 95% CI 1.75-2.09) of having at least one microvascular complication at time of T2D diagnosis, as compared with individuals of White ethnic groups with glycaemic values within the normal range.

5.1.5 Conclusions

Microvascular and macrovascular diseases are detected in 37-24% of people with newly diagnosed T2D. NDH before diagnosis of T2D is associated with increased odds of microvascular disease and coronary heart disease. Within the NDH group odds of microvascular disease are greater for those of non-White ethnic groups. Detection of NDH might represent an opportunity for reducing the burden of microvascular and macrovascular disease through heightened attention to screening for vascular complications.

5.2 Introduction

The clinical benefits of identifying individuals with NDH for early management to prevent progression to T2D has been intensively debated (114, 212-214). Clinical trials demonstrating that lifestyle modification and drug-based interventions could prevent or delay progression to T2D provide some robust evidence (114, 157). However, critics argue that only a subset of individuals with NDH will develop T2D, and the population benefits of intervening are outweighed by the potential negative effects due to over-testing, unnecessary medicalisation, and uncertainties in benefits of prevention strategies outside the research environment, amongst other factors (114, 130, 134, 212). Additionally, no agreement has been reached on diagnostic tests and glycaemic thresholds for the detection of NDH (27, 107, 112, 215). Various diagnostic criteria have been adopted by different organisations that have been repeatedly revised over time (212). Different diagnostic criteria identify different groups of individuals who differ in progression rates to T2D and risk of associated morbidity (96, 131, 216, 217), raising the question of whether those who might benefit the most from tight clinical management are effectively identified as high-risk by each criterion (114).

NDH has been shown to contribute to the pathogenesis of macrovascular dysfunction that might partly explain the increased risk of CVD morbidity and mortality in NDH and T2D (130-133). Ethnic differences in this relationship have also been documented. Although evidence suggests that South Asians have greater prevalence of T2D and are at increased risk of CVD as compared with white population (218, 219), a recent study found that NDH is related to both CHD and CVD risk in Europeans but not South Asians, where only an association with stroke was found (52).

NDH is also linked to generalised microvascular dysfunction similar to the vascular damage typical to T2D (130, 132, 137, 220). This suggests that the development of T2D-associated microvascular disease may precede the clinical diagnosis of T2D (138). Early stages of retinopathy, neuropathy, nephropathy, that are generally milder forms compared with that seen in established T2D, have been reported in people with NDH (130, 145, 220), and prevention studies have demonstrated that their risk can be reduced with lifestyle interventions (148). However, little is known about whether the associated risk of microvascular disease in individuals with NDH differs by ethnic groups.

The emerging body of evidence on the association between NDH and vascular disease may have important implications for preventive strategies, and it is important to understand whether glycaemic testing and detection of NDH in real world settings affect the development of microvascular and macrovascular disease among individuals who subsequently develop T2D.

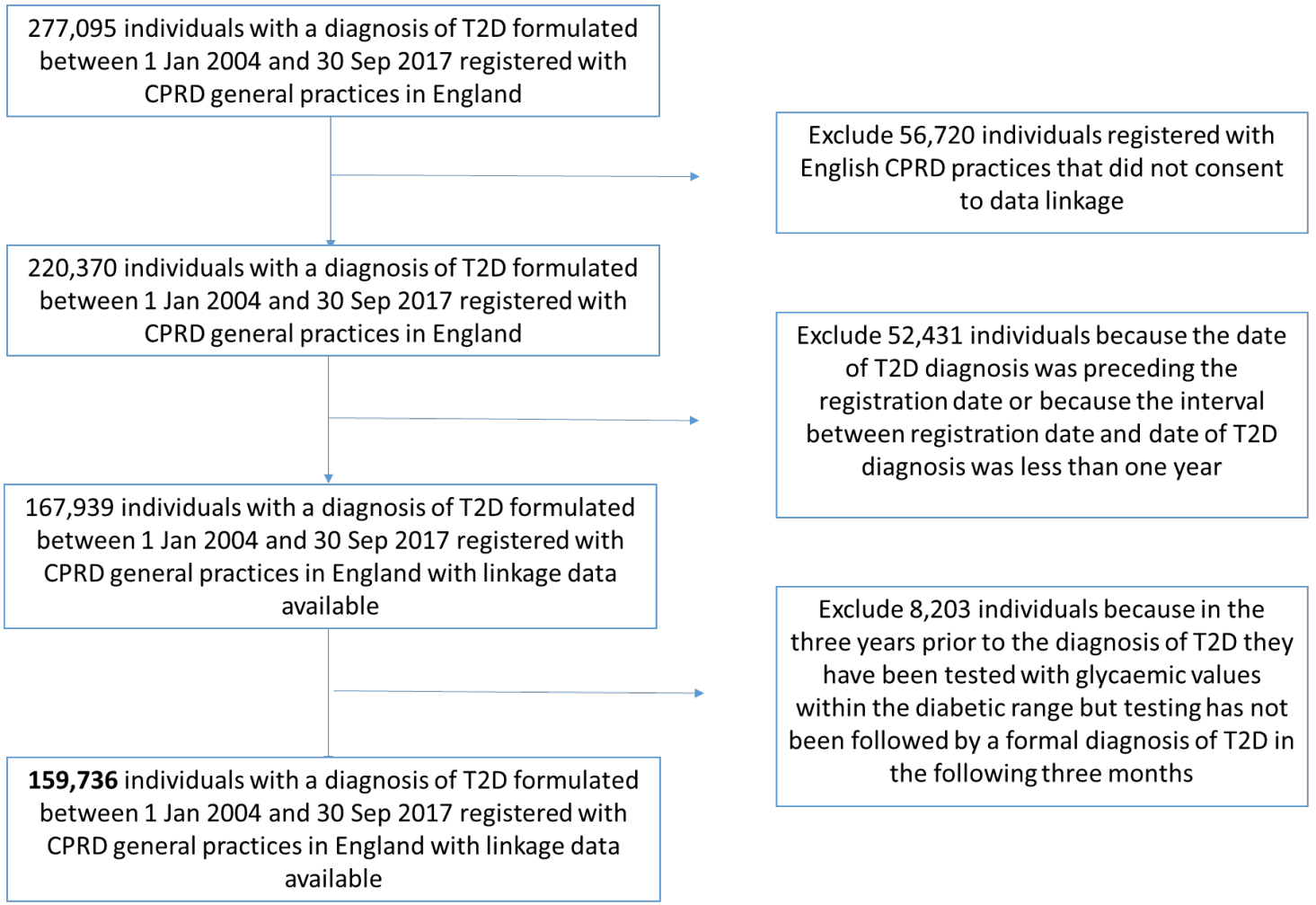
The main study aims were to examine whether the occurrence of vascular disease differs in individuals newly diagnosed with T2D with prior NDH compared with those with normal glycaemic levels in real world settings. A secondary aim of this study was to explore whether this association differs by ethnic groups. I assessed this using different diagnostic criteria currently applied to NDH.

5.3 Methods

5.3.1 Study population

I used data from the UK CPRD, one of the largest databases of electronic medical records globally (199). Characteristics of the study population have been described in detail in the Chapters 4.1 and 4.3.1. Briefly, I defined a cohort of individuals who were newly diagnosed with T2D between 1 January 2004 and 30 September 2017 and registered with CPRD practices in England that consented to data linkage. As this study focuses on detection of NDH before T2D diagnosis, individuals who had glycaemic values within the diabetes range recorded more than three months before the date of the first diagnosis of T2D were excluded from this study, as in this case testing might not be attributable to the diagnostic process but to mis-classification. A study diagram summarising inclusion and exclusion criteria is shown in Figure 3.

Figure 3. Study diagram



Abbreviations: T2D: Type 2 diabetes.

5.3.2 Detection of NDH in primary care settings

For the detection of NDH, I adopted diagnostic criteria published by the World Health Organization (WHO) and International Expert Committee (IEC): 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%)(106, 112). To identify glycaemic values within the NDH range, I used all available clinical data within three years before the date of T2D diagnosis considering that among the majority of individuals progressing to T2D, a marked increase in glycaemic levels is observed within two to three years before the diagnosis of T2D (121, 130). Individuals with multiple glycaemic recordings were classified as having NDH if at least one measurement met the detection criteria for NDH. Diagnostic codes in primary care records for Impaired Fasting Glucose (IFG), Impaired Glucose Tolerance (IGT) or other (e.g. "pre-diabetes" or "Intermediate Hyperglycaemia") were also used to identify NDH cases. In case of multiple records over time, the date of the earliest available NDH detection was used. Individuals were classified as: i) glycaemic values within the normal range before T2D diagnosis; ii) NDH detected before T2D diagnosis; or iii) no glycaemic measures recorded within three years before T2D diagnosis.

5.3.3 Ethnicity recording in CPRD

A recent study found that the ethnicity breakdown of the individuals registered with CPRD general practices is comparable to the UK censuses and quality of ethnicity recording in CPRD greatly improved from 2006 (221). To improve completeness of ethnicity information I extrapolated data from both CPRD and linked HES data. In cases of missing information, the individual's ethnic group was classified as 'Unknown'. Therefore, in line with previous research assessing the consistency and representativeness of routinely collected ethnicity data in both primary and secondary care settings (221), in the main analysis ethnicity groups were classified as White, South Asian, Black, Others, and Unknown. However, due to sample size constraints, in the secondary analysis, aiming to explore the association between NDH status and vascular outcomes at time of diagnosis of T2D

by different ethnic groups, ethnicity was re-classified as White/Unknown, South-Asians, and Others (221-223).

5.3.4 Study outcomes

Study outcomes included the diagnosis of microvascular (retinopathy and nephropathy) and macrovascular diseases (cerebrovascular disease, coronary heart disease, and peripheral arterial disease) at the time of diagnosis of T2D. Diagnoses were defined based on the combination of laboratory tests, diagnostic codes in primary care records, and ICD-10 codes on hospital admissions (see Supplementary Table S1). Microvascular disease at the time of the diagnosis was defined by the recording of a microvascular disease within 5 years before or 15 months after the diagnosis of T2D (224). The 15-month period was defined based on the time periods of specific process of care indicators of the Quality and Outcomes Framework (QOF) for diabetic retinopathy screening and urine microalbumin testing (12 months and 15 months, respectively) (10). Macrovascular disease at time of diagnosis was defined by the recording of a macrovascular disease any time before or within 1 year of the diagnosis of T2D.

5.3.5 Study covariates

Study covariates included age, sex, ethnicity, smoking status, blood pressure (systolic and diastolic), body mass index (BMI), total cholesterol, number of diagnosed co-morbid conditions (list (225)), prescription of anti-hypertensive (Angiotensin-converting-enzyme inhibitor (ACEi) or Angiotensin receptor blocker (ARB); others), anti-platelet, lipid-lowering, and anti-diabetic medications (biguanides, sulphonylureas, insulin, others) and number of primary care visits during the year before the diagnosis of T2D and quintile of the index of multiple deprivation (IMD) at practice level (226). Information on covariates was collected in the year following the diagnosis of T2D. In case of multiple measurements for the same individual, the mean value was calculated for continuous variables and the latest data recorded within the year was used for binary variables. To reduce missing data for study covariates in the year following the diagnosis of T2D, I used the

latest clinical recording for individuals with missing values within 5 years before the start of the study period (198). Individuals with missing data on smoking were classified as non-smokers if there was no indication in the past of the patient being a smoker (198).

5.3.6 Secondary analyses

I undertook three secondary analyses. The first secondary analysis compared results obtained adopting diagnostic criteria for the detection of NDH published by the WHO/IEC with those obtained using those published by the American Diabetes Association (ADA; 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%) and the UK National Institute for Health and Care Excellence(27) (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%) (Appendix Table 1). An additional secondary analysis was undertaken to explore whether among individuals with NDH clinical outcomes differed according to whether diagnostic coding for NDH in electronic health records was assigned following the detection of NDH. Assigning a diagnostic code for NDH might be associated with a more intensive clinical management of cardiovascular risk factors among individuals who were classified as having NDH. Analysis was undertaken using various diagnostic criteria (WHO/IEC, ADA and NICE) for NDH. Finally, an additional analysis was undertaken to explore whether the association between prior NDH status and vascular disease at time of T2D diagnosis differed by ethnic groups.

5.3.7 Statistical analysis

Missing data was present for blood pressure (0.5%), BMI (2.8%), total cholesterol (7.0%), and HbA1c (24.1%). I conducted a missing pattern analysis employing logistic regression analyses and using graphical tools and I concluded that missing data were at random (data not shown) (227). Therefore, I used multiple imputation by chained equations (10 copies) to estimate missing data for these variables. I included the following variables in the imputation model as likely to be associated with recording of risk factors: age, sex, ethnicity, smoking status, number of diagnosed co-morbid conditions, number of primary care consultations in the year before the diagnosis of

T2D, general practice IMD, presence of coronary heart disease, cerebrovascular and peripheral arterial disease, and prescription of ACEi or ARB, lipid-lowering, and anti-diabetic medications.

I compared population characteristics according to glycaemic status before the diagnosis of T2D (NDH, normal glycaemic status and not recorded) using Chi-square test and ANOVA, as appropriate. Multivariable logistic regression models were employed to assess the odds of having microvascular and macrovascular disease at the time of T2D diagnosis in individuals with NDH and those without glycaemic measures recorded compared with individuals with normal glycaemic values before the diagnosis of T2D. To explore whether the association between NDH status in the three years before the diagnosis of T2D and vascular outcomes at time of diagnosis of T2D varied by ethnic groups an interaction term between prior NDH status and ethnicity was fitted. The ethnicity variable was further grouped in White/Unknown, South Asians, Other ethnic groups. HbA1c was not included as covariate in the statistical models because the NDH definition is based on glycaemic values. To assess what variables to include in the multivariable models other study variables were tested for multicollinearity calculating the variance-inflation factor and correlation coefficients. Thus, BMI and the use of medications were also excluded due to collinearity with NDH and other risk factors. Therefore, statistical models were adjusted for age, sex, ethnicity, smoking status, mean systolic and diastolic blood pressure, total cholesterol, and number of diagnosed co-morbid conditions, number of primary care visits in the year before the diagnosis of T2D, general practice IMD. Statistical models were further adjusted for the year of diagnosis of T2D during the study period (2004-2017). National guidance in England published in 2012 set out a proactive approach to T2D prevention through identification and improved clinical management of NDH (27). Therefore, I also assessed whether the inclusion of a dummy variable defining whether diagnosis of T2D occurred before or after 2012 would improve my model. I compared the goodness of fit of the two models considering multiple parameters, as previously suggested (228,

229). The pool of parameters included the Akaike's information criterion (AIC), the Bayesian information criterion (BIC), and the AUROC curve.(229). My model selection was not based on AUROC solely because large odds ratios (OR) from single covariates in the multivariable logistic regression model may have little impact on the AUROC (228). When comparing the two models the AUROC curve values did not differ, while the combination of BIC and AIC favoured the most parsimonious model including only the year of diagnosis of Type 2 diabetes as additional covariate. Therefore, this latter model was preferred (data not shown). OR and 95% confidence intervals (95% CI) were estimated and results were considered significant if $p<0.05$. Statistical analyses were conducted using Stata SE 15.1.

5.4 Results

In the three years before the diagnosis of T2D, 65,787 individuals (41.2% of the study population) had at least one glycaemic measure recorded and of these 43,885 individuals (66.7%) reached detection thresholds for NDH (Table 3). 74.4% of individuals detected with NDH had recorded at least one FPG measurement, 58.2% at least one HbA1c measurement, and 22.6% at least one OGTT measurement, while 53% had recorded a combination of these glycaemic measures. During the three-year period before the diagnosis of T2D, the time interval from first glycaemic measurement recorded to T2D diagnosis was 33.0 months for individuals who reached detection thresholds for NDH and 33.1 months for those with normoglycaemia. As compared with individuals with normoglycaemia, Individuals who reached detection threshold for NDH before diagnosis of T2D had also higher HbA1c values at time of T2D diagnosis (normoglycaemia: 47.0 (19.1) mmol/mol; NDH: 50.4 (18.9) mmol/mol). Individuals with NDH were older and more likely to be males and smokers compared with individuals with prior normoglycaemia and those without for glycaemic measurement before the diagnosis of T2D (Table 3). They also had higher BMI and systolic blood pressure levels in the year following T2D diagnosis compared with the other two

groups. The number of individuals with NDH identified by the WHO/IEC criteria was lower than that for NICE and ADA diagnostic cut-points (27.4%, 32.2% and 32.2%, respectively) with small differences in patient characteristics between groups (Appendix Table 2-4).

Table 3. Characteristics of the study population in the year following the diagnosis of T2D stratified by whether individuals were tested and reached detection thresholds for NDH before the diagnosis of T2D.

Notes: Results are presented using World Health Organization/International Expert Committee criteria for the definition of Non-diabetic Hyperglycaemia.Clinical data within three years before the diagnosis of T2D were used to define the detection of NDH. P-values from Chi-square, ANOVA, and Kruskal-Wallis tests, as appropriate, are reported for comparison between the three groups defined by testing and detection of NDH. Abbreviations: T2D: T2D, FPG: fasting plasma glucose, OGTT: glucose tolerance test (2-hour after 75 g glucose load), BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, ACEi: Angiotensin-converting-enzyme inhibitor, ARBs: Antiotensin II receptor blockers.

WHO/ International Expert Committee criteria to define NDH: 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%

¥ Chi-square test was performed to assess the unadjusted difference between groups

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

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

*If an individual was prescribed multiple medications from different anti-diabetic classes, each class was considered (e.g. for an individual who was prescribed biguanides and sulphonylureas in the year following the diagnosis of T2D, data were recorded as follows: anti-diabetic YES; biguanides YES; sulphonylureas YES; insulin NO; other anti-diabetic NO).

	Total	No glycaemic measures recorded before the diagnosis of T2D	Glycaemic values within the normal range before the diagnosis of T2D	NDH detected before the diagnosis of T2D	p-values
N	159,736	93,949	21,902	43,885	
%		58.8	13.7	27.4	
Type of glycaemic measures recorded before diagnosis of T2D (%)					
FPG			82.1	74.4	
HbA1C			38.4	58.2	
OGTT			4.5	22.6	
Multiple tests			23.7	53.0	
Time from testing to diagnosis of T2D, months; mean (SD)	33.0 (6.1)		33.1 (6.0)	33.0 (6.2)	
Female (%)	49.2	48.8	55.6	46.7	<0.001¥
Age, years (SD)	61.5 (14.4)	60.2 (14.8)	61.3 (14.8)	64.3 (12.6)	<0.001§
Ethnicity (%)					
White	83	82.7	84.5	82.9	<0.001¥
South Asian	3.6	3.1	4.3	4.3	
Black	2.4	2.2	3.1	2.7	
Other	3.1	2.9	3.4	3.3	<0.001¥
Unknown	7.9	9.2	4.7	6.9	
Smoking status (%)					
Non-smoker	35.4	36.8	35.8	32.3	
Ex-smoker	51.6	43.4	46.3	51.6	<0.001¥
Current smoker	16.1	19.8	17.9	16.1	

(continued)

	Total	No glycaemic measures recorded before the diagnosis of T2D	Glycaemic values within the normal range before the diagnosis of T2D	NDH detected before the diagnosis of T2D	p-values
HbA1c at diagnosis, mmol/mol; mean (SD)	55.2 (20.7)	59.4 (20.8)	47.0 (19.1)	50.4 (18.9)	<0.001§
BMI, kg/m2; mean (SD)	30.30 (6.7)	30.0 (6.7)	29.7 (7.0)	31.3 (6.5)	<0.001§
SBP, mm Hg; mean (SD)	136.4 (15.9)	136.4 (16.6)	134.0 (15.7)	137.4 (14.3)	<0.001§
DBP, mm Hg; mean (SD)	79.7 (9.4)	80.1 (9.6)	78.7 (9.3)	79.5 (8.8)	<0.001§
Total cholesterol, mmol/L; mean (SD)	5.1 (1.1)	5.2 (1.1)	5.0 (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§
Medications (%)					
Anti-hypertensive	53.8	47.5	53.2	67.6	<0.001¥
ACEi/ARBs	39	34.1	37.9	50.2	<0.001¥
Anti-lipid medications	49.6	44.2	45.1	63.3	<0.001¥
Anti-diabetic*	38.4	44.7	19.5	34.3	<0.001¥
Biguanides	34.6	39.8	17	32.3	<0.001¥
Sulphonylureas	8.5	11.4	3.8	4.5	<0.001¥
Insulin	2.7	3.5	2.1	1.2	<0.001¥
Other	0.1	0.1	0.1	0.2	0.015¥
Anti-platelet	27.0	24.2	26.3	33.1	<0.001¥
Number of primary care visits in the year before T2D diagnosis; mean (SD)	12.9 (11.7)	11.1 (10.9)	16.8 (13.5)	14.7 (11.6)	<0.001Ω
Index of Multiple Deprivation quintiles (%)					
1 Q - least deprived	14.1	14.6	12.6	13.7	<0.001¥
2 Q	19.1	19.5	19.1	18.2	
3 Q	19	19.1	17.9	19.4	<0.001¥
4 Q	22.3	21.1	23.7	24.2	
5 Q - most deprived	25.6	25.8	26.7	24.5	

5.4.1 Microvascular disease

Half of the study population (49.9%) had at least one microvascular or macrovascular disease at the time of T2D diagnosis. Over one-third, (37.4%) had microvascular disease. Based on the WHO/IEC criteria, 30.7% of those with prior normal glycaemic values, 42.4% of those with prior NDH, and 36.7% of those without glycaemic measures recorded had either retinopathy or nephropathy. At the time of T2D diagnosis, 13.9% of individuals with prior normal glycaemic values, 25.2% of individuals with prior NDH, and 22.9% of individuals without glycaemic measures recorded had retinopathy (Figure 4). When adjusting for confounders, those with NDH had 76% increased odds of having retinopathy at diagnosis (OR 1.76, 95%CI 1.69-1.85), while those without glycaemic measures recorded had 50% increased odds (OR 1.50, 95%CI 1.44-1.57), compared with those with normal glycaemic values.

The prevalence of diagnosed nephropathy present at time of diagnosis of T2D was similar between those with normal glycaemic values and those without glycaemic values recorded (20.7% and 19.0%, respectively), while the prevalence was higher (23.8%) for those with NDH. After adjusting for confounders, those with NDH had 14% increased odds of having nephropathy at diagnosis (OR 1.14, 95%CI 1.10-1.19), compared with those with prior normal glycaemic values.

The prevalence of both microvascular diseases being present at time of diagnosis was 3.9%, 6.4%, and 5.2% in patients with prior normal glycaemic values and NDH, and those without glycaemic measures recorded, respectively. Individuals who reached detection thresholds for NDH had 53% increased odds of having both diseases at time of diagnosis (OR 1.53, 95%CI 1.41-1.65), while those without glycaemic measures recorded had 35% increased odds (OR 1.35, 95% CI 1.25-1.47), as compared with those with normal glycaemic values (Figure 5).

Figure 4. Prevalence of microvascular (retinopathy and nephropathy) and macrovascular (coronary heart disease, cerebrovascular, and peripheral arterial disease) diseases present at time of the diagnosis of T2D according to glycaemic status in the three years before the diagnosis of T2D.

Notes: A microvascular disease was considered being present at time of T2D diagnosis if the condition was diagnosed between five years before and fifteen months after the diagnosis of T2D. A macrovascular disease was considered being present at time of T2D diagnosis if the condition was diagnosed any time before the diagnosis and during the year following the diagnosis of T2D. For the detection of NDH the World Health Organization/International Expert Committee diagnostic criteria were adopted (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%).

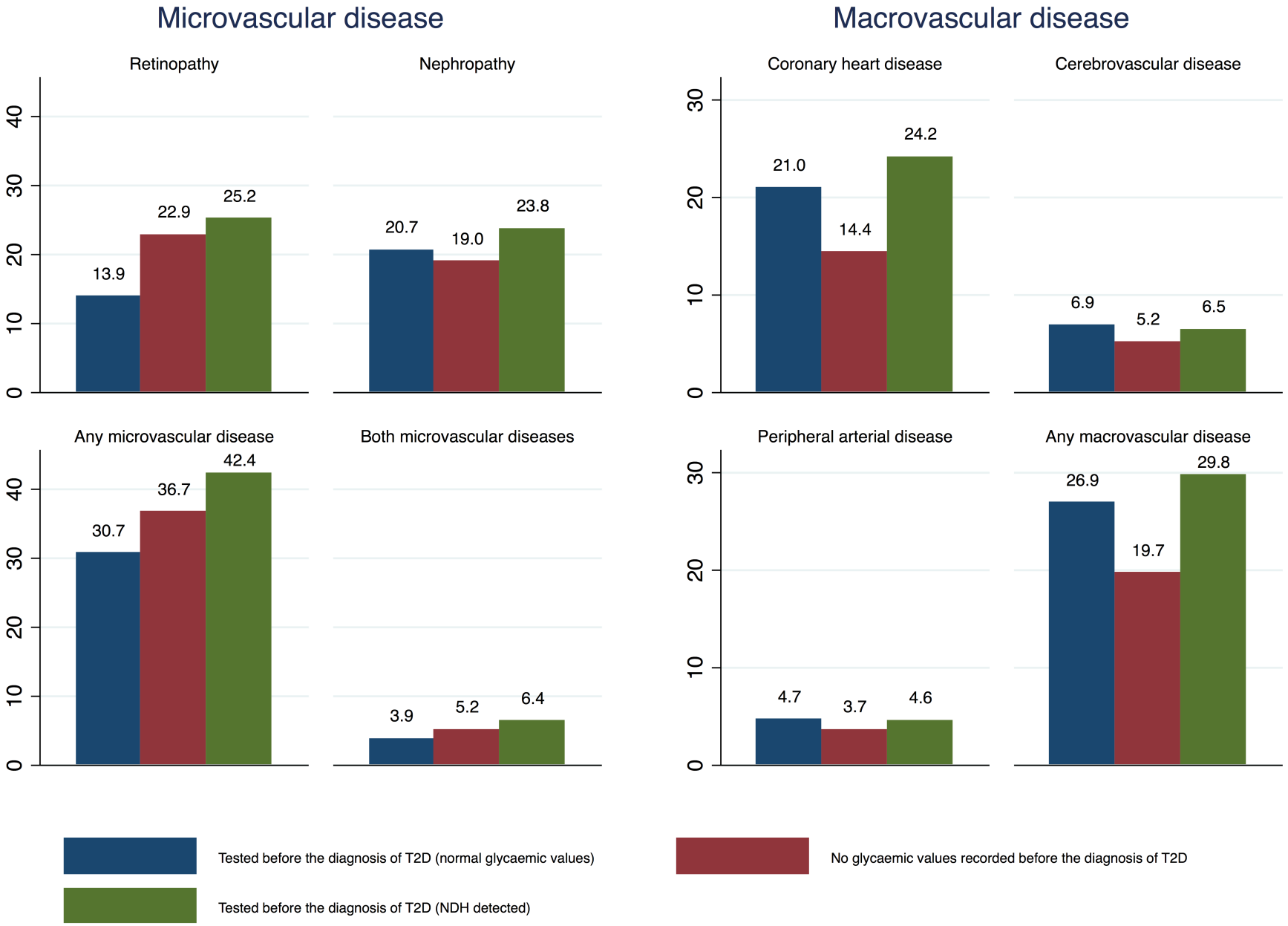
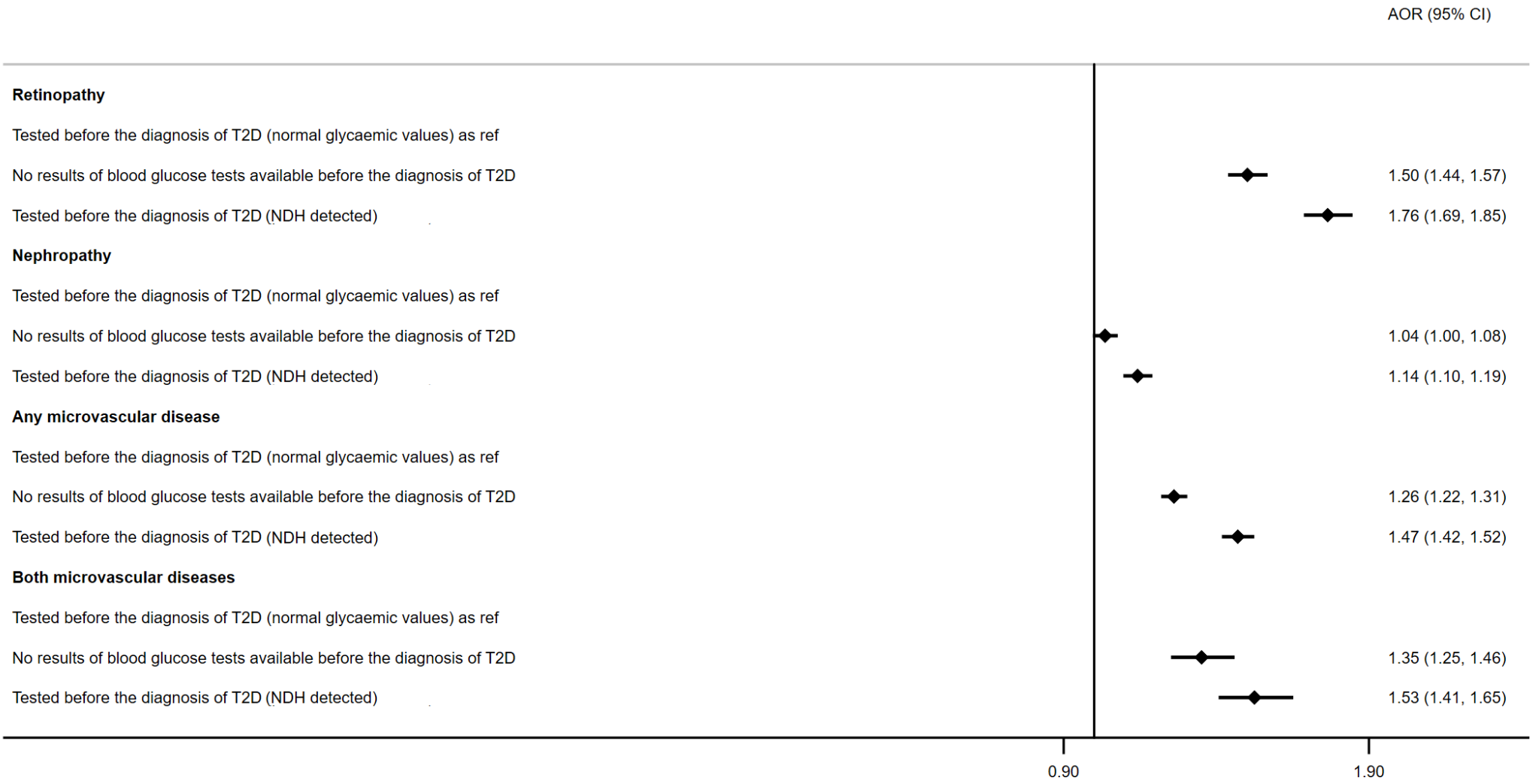

Microvascular disease
Retinopathy
Nephropathy
Any microvascular disease
Both microvascular diseases
Macrovascular disease
Coronary heart disease
Cerebrovascular disease
Peripheral arterial disease
Any macrovascular disease
0
10
20
30
40
13.9
22.9
25.2
20.7
19.0
23.8
30.7
36.7
42.4
3.9
5.2
6.4
21.0
14.4
24.2
6.9
5.2
6.5
4.7
3.7
4.6
26.9
19.7
29.8
Tested before the diagnosis of T2D (normal glycaemic values)
No glycaemic values recorded before the diagnosis of T2D
Tested before the diagnosis of T2D (NDH detected)

Figure 5. Association between glycaemic testing and detection of Non-diabetic Hyperglycaemia 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 T2D. Abbreviations: T2D: Type 2 Diabetes; NDH: Non-diabetic Hyperglycaemia.

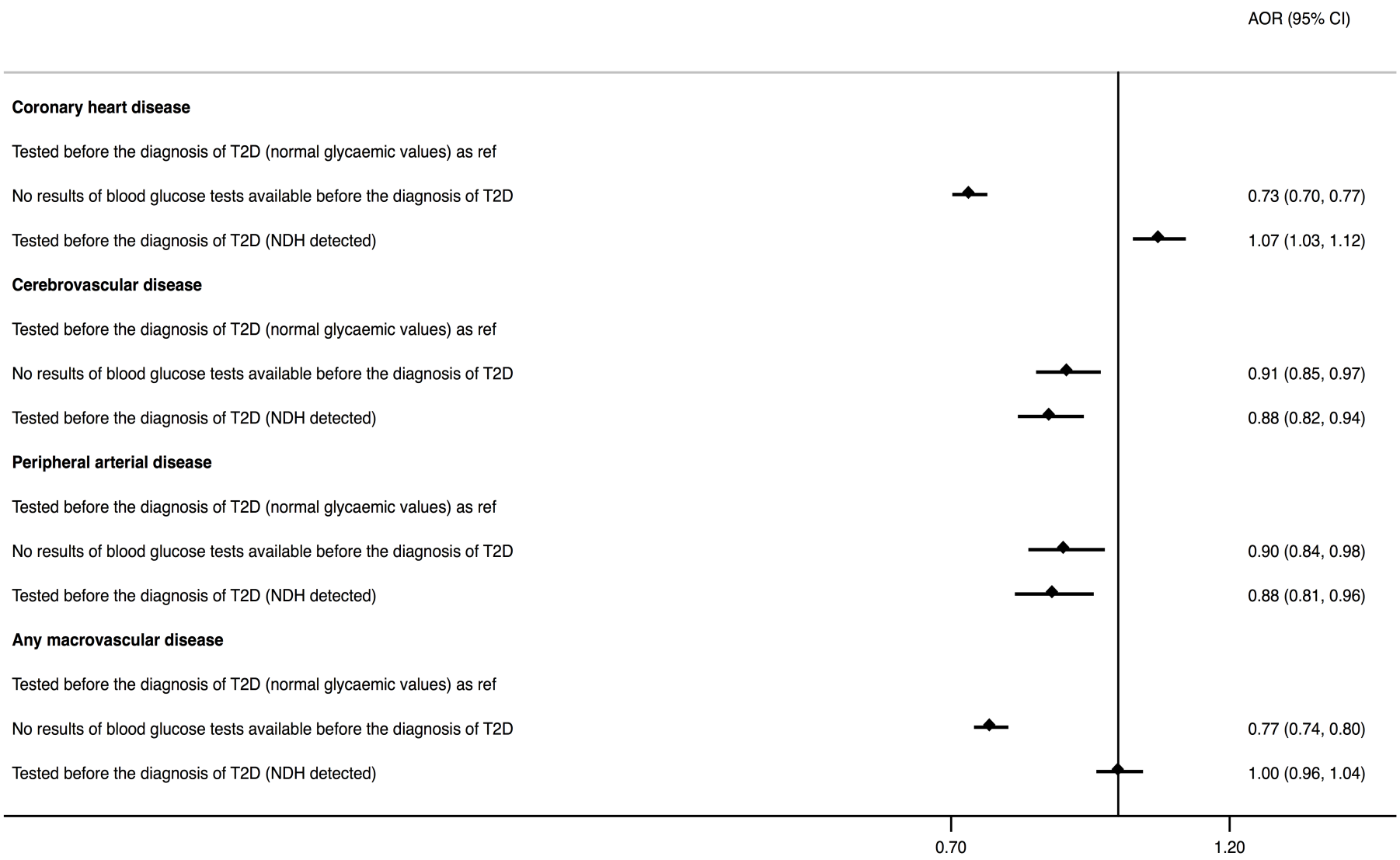

AOR (95% CI)
Retinopathy
Tested before the diagnosis of T2D (normal glycaemic values) as ref
No results of blood glucose tests available before the diagnosis of T2D
1.50 (1.44, 1.57)
Tested before the diagnosis of T2D (NDH detected)
1.76 (1.69, 1.85)
Nephropathy
Tested before the diagnosis of T2D (normal glycaemic values) as ref
No results of blood glucose tests available before the diagnosis of T2D
1.04 (1.00, 1.08)
Tested before the diagnosis of T2D (NDH detected)
1.14 (1.10, 1.19)
Any microvascular disease
Tested before the diagnosis of T2D (normal glycaemic values) as ref
No results of blood glucose tests available before the diagnosis of T2D
1.26 (1.22, 1.31)
Tested before the diagnosis of T2D (NDH detected)
1.47 (1.42, 1.52)
Both microvascular diseases
Tested before the diagnosis of T2D (normal glycaemic values) as ref
No results of blood glucose tests available before the diagnosis of T2D
1.35 (1.25, 1.46)
Tested before the diagnosis of T2D (NDH detected)
1.53 (1.41, 1.65)
0.90
1.90

5.4.2 Macrovascular disease

At time of T2D diagnosis, 23.5% of the study population had at least one diagnosed macrovascular disease. Using the WHO/IEC criteria, 26.9% of patients with normal glycaemic values, 29.8% of those with prior NDH, and 19.7% of those without glycaemic measures recorded had a macrovascular disease. Individuals with glycaemic measures within the normal range had the highest unadjusted prevalence of cerebrovascular disease (6.9%), while those who reached detection thresholds for NDH had the highest prevalence of coronary heart disease at time of diagnosis of T2D (24.2%) (Figure 6). When adjusting for confounders, individuals with prior NDH had 7% higher odds of previous diagnosis of coronary heart disease (OR 1.07, 95%CI 1.03-1.12), 12% lower odds of diagnosis of cerebrovascular events (OR 0.88, 95%CI 0.82-0.94), and peripheral arterial disease (OR 0.88, 95%CI 0.81-0.96), as compared with those with normal glycaemic values recorded before the diagnosis of T2D. Those without glycaemic measures recorded had 27% lower odds of diagnosis of coronary heart disease (OR 0.73, 95%CI 0.70-0.77), 9% lower odds of diagnosis of cerebrovascular disease (OR 0.91, 95%CI 0.85-0.97), 10% lower odds of diagnosis of peripheral arterial disease (OR 0.90, 95%CI 0.84-0.98), and 23% lower odds of diagnosis of any macrovascular disease (OR 0.77, 95%CI 0.74-0.80).

Figure 6. Association between glycaemic testing and detection of Non-diabetic Hyperglycaemia 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 T2D. Abbreviations: NDH: non-diabetic hyperglycaemia, T2D: T2D.


AOR (95% CI)
Coronary heart disease
Tested before the diagnosis of T2D (normal glycaemic values) as ref
No results of blood glucose tests available before the diagnosis of T2D
0.73 (0.70, 0.77)
Tested before the diagnosis of T2D (NDH detected)
1.07 (1.03, 1.12)
Cerebrovascular disease
Tested before the diagnosis of T2D (normal glycaemic values) as ref
No results of blood glucose tests available before the diagnosis of T2D
0.91 (0.85, 0.97)
Tested before the diagnosis of T2D (NDH detected)
0.88 (0.82, 0.94)
Peripheral arterial disease
Tested before the diagnosis of T2D (normal glycaemic values) as ref
No results of blood glucose tests available before the diagnosis of T2D
0.90 (0.84, 0.98)
Tested before the diagnosis of T2D (NDH detected)
0.88 (0.81, 0.96)
Any macrovascular disease
Tested before the diagnosis of T2D (normal glycaemic values) as ref
No results of blood glucose tests available before the diagnosis of T2D
0.77 (0.74, 0.80)
Tested before the diagnosis of T2D (NDH detected)
1.00 (0.96, 1.04)
0.70
1.20

5.4.3 Secondary analyses

Results obtained using NICE and ADA criteria for the detection of NDH were broadly similar to the findings for the WHO/IEC criteria (Appendix Figure 1-4). However, when using the NICE and ADA criteria, individuals without glycaemic measures recorded had 12% and 9% increased odds of nephropathy present at time of the diagnosis of T2D, respectively, as compared with those with prior normal glycaemic values (Appendix Figure 3). Furthermore, patients who reached the detection thresholds for NDH had 8% increased odds of having any macrovascular disease at diagnosis, as compared with those with normal glycaemic values (Appendix Figure 4).

When further classifying patients with prior NDH into two groups based on having or not having a diagnostic code recorded for NDH, the odds ratios for having vascular diseases were lower among individuals with a NDH diagnostic code assigned for most study outcomes. For instance, compared with individuals with normal glycaemic values recorded, individuals with a diagnostic code for NDH had 43% higher odds of any microvascular disease at the time of T2D diagnosis, while those without diagnostic codes had 51% increased odds (diagnostic assigned: OR 1.43, 95%CI 1.37-1.49; without diagnostic code: OR 1.51, 95%CI 1.45-1.57). Full results are shown in Appendix Figure 5 and 6.

Overall, among individuals who were tested and detected with NDH in the three years before the diagnosis of T2D, non-White ethnic groups had greater odds of having microvascular disease already present at time of T2D as compared with White individuals. As compared with individuals from White ethnic groups with normoglycaemia before the diagnosis of T2D, those from White ethnic groups with prior NDH had 73% increased odds of having retinopathy at time of diagnosis of T2D (OR: 1.73, 95% CI 1.64-1.81), while those from South Asian ethnic groups and of other ethnic groups with prior NDH had 2.1 and 2.7-fold increased odds of having retinopathy at time of diagnosis of T2D, respectively (South Asian: OR 2.12, 95% CI 1.88-2.39; Other ethnic groups: 2.68,

95% CI 2.43-2.96). Similarly, as compared with individuals from White ethnic groups who had normal glycaemic values recorded in the three years before the diagnosis of T2D, those who were tested with NDH had increased odds of having any microvascular disease at time of diagnosis of T2D. Specifically, those from White ethnic groups had 45% increased odds (OR 1.45, 95% CI 1.10-1.20), those from South Asian ethnic groups 64% increased odds (OR 1.64, 95% CI 1.48-1.82), and those from other ethnic groups 92% increased odds (OR 1.92, 95% CI 1.75-2.09). Differences in the odds of having nephropathy at time of T2D diagnosis across groups of different NDH status and ethnicity were instead less pronounced (Appendix Table 5, Figure 7). Among non-White populations who were detected with NDH before the diagnosis of T2D odds of having microvascular disease at time of diagnosis were generally greater for those who also had a diagnostic Read code assigned for NDH (Appendix Figure 7).

In contrast with findings regarding microvascular disease, those for macrovascular disease were not completely consistent for non-White ethnic groups. As compared with individuals from White ethnic groups with normoglycaemia before the diagnosis of T2D, those detected with NDH before the diagnosis of T2D from South Asian ethnic groups were more likely to have coronary heart disease (OR 1.22, 95% CI 1.06-1.40), less likely to have cerebrovascular disease (OR 0.72, 95% CI 0.56-0.94), and less likely to have peripheral arterial disease (OR 0.65, 95% CI 0.46-0.93) at time of diagnosis of T2D. Those detected with NDH before the diagnosis of T2D of other ethnic groups were less likely to have coronary heart disease (OR 0.73, 0.64-0.84), peripheral arterial disease (OR 0.46, 95% CI 0.33-0.64), and any macrovascular disease (OR 0.69, 95% CI 0.61-0.78) (Figure 8). Generally, those with prior NDH from the non-White population were less likely at time of diagnosis of T2D to have macrovascular disease (Appendix Figure 8).

Figure 7. Association between glycaemic testing and detection of Non-diabetic Hyperglycaemia, ethnicity, 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. An interaction term between NDH status before the diagnosis of Type 2 diabetes and ethnicity (White, South Asian, others) was fitted. Models were also adjusted for age, sex, 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: NDH: non-diabetic hyperglycaemia.

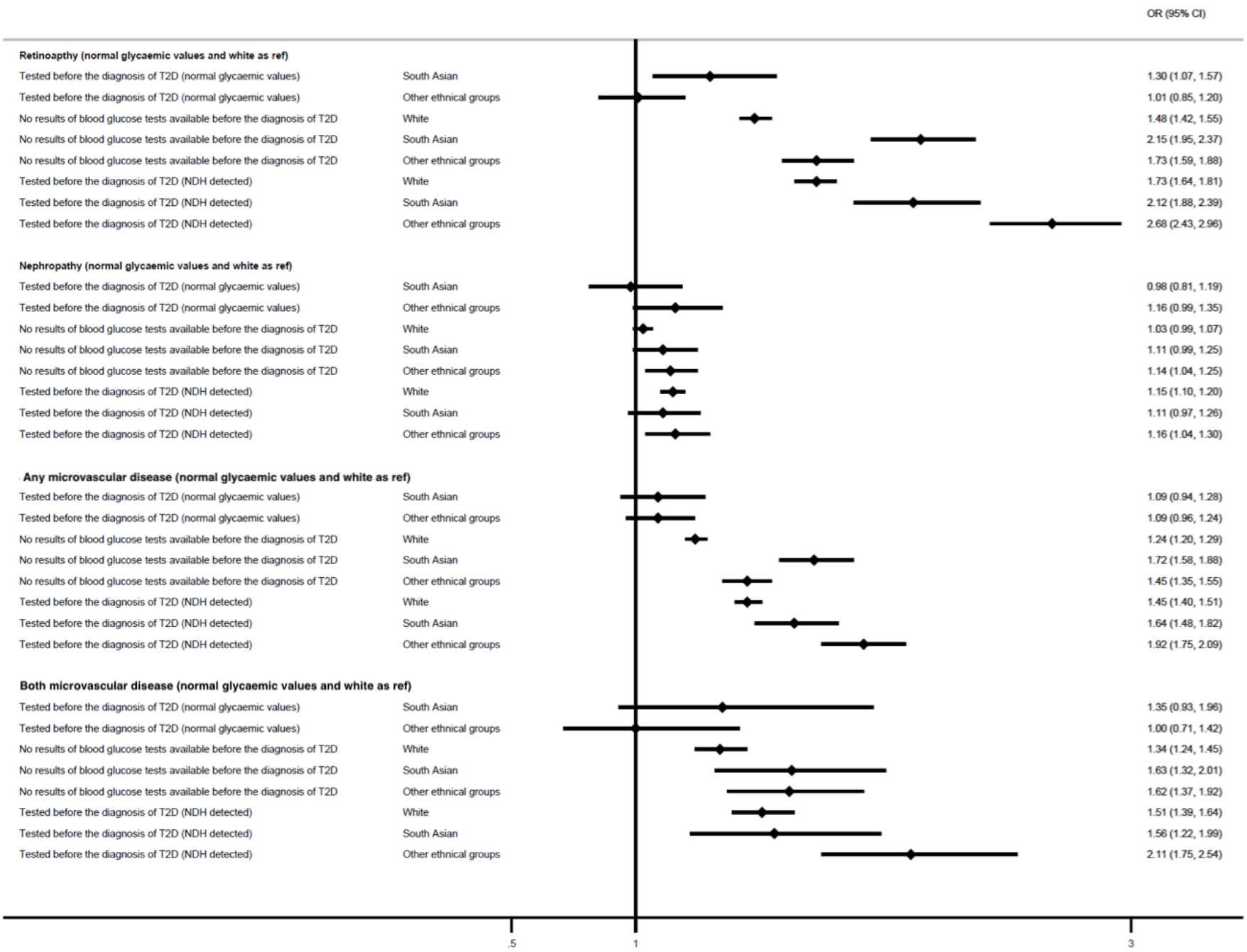
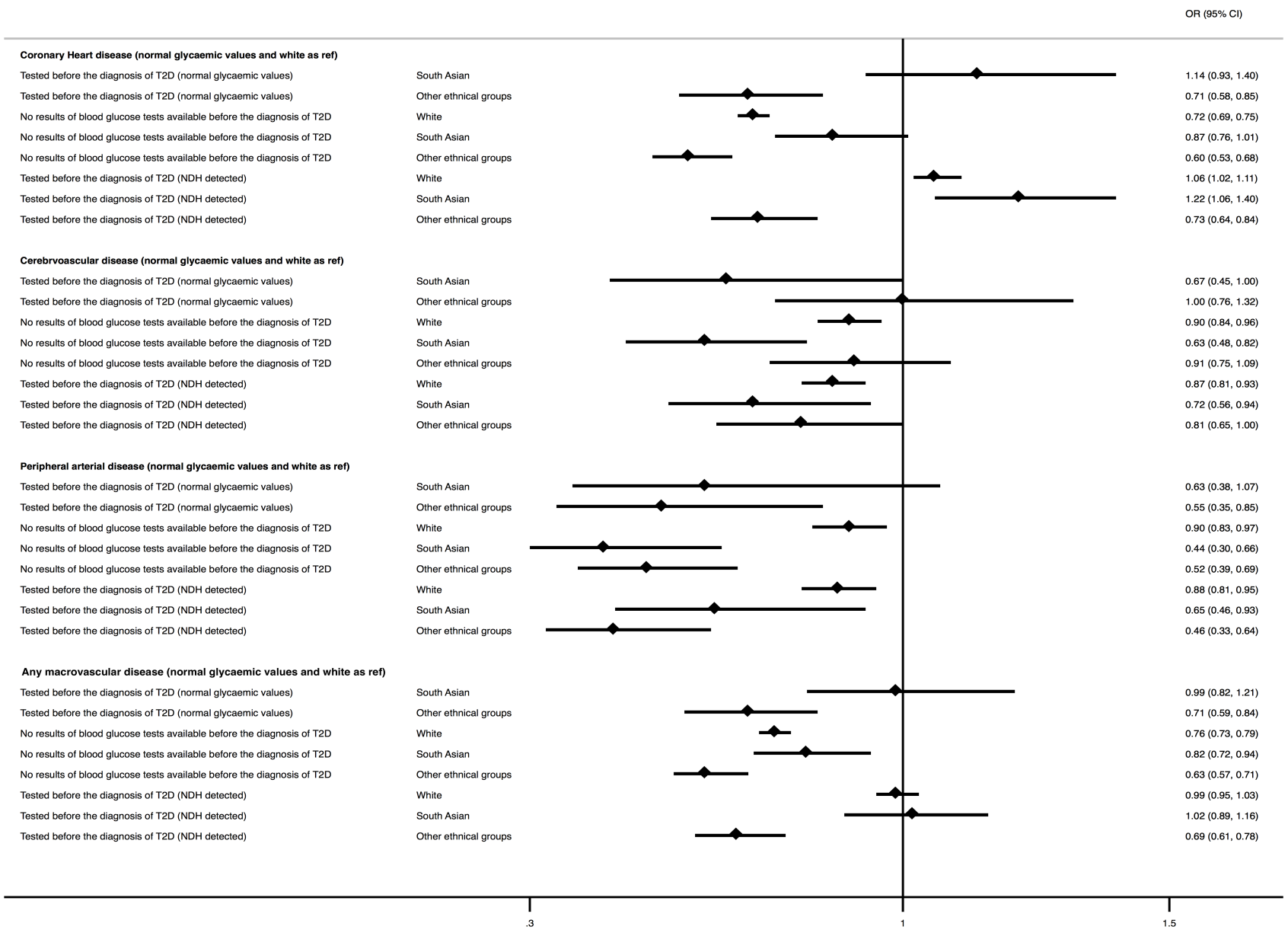

OR (95% CI)
Retinoapthy (normal glycaemic values and white as ref)
Tested before the diagnosis of T2D (normal glycaemic values) South Asian 1.30 (1.07, 1.57)
Tested before the diagnosis of T2D (normal glycaemic values) Other ethnical groups 1.01 (0.85, 1.20)
No results of blood glucose tests available before the diagnosis of T2D White 1.48 (1.42, 1.55)
No results of blood glucose tests available before the diagnosis of T2D South Asian 2.15 (1.95, 2.37)
No results of blood glucose tests available before the diagnosis of T2D Other ethnical groups 1.73 (1.59, 1.88)
Tested before the diagnosis of T2D (NDH detected) White 1.73 (1.64, 1.81)
Tested before the diagnosis of T2D (NDH detected) South Asian 2.12 (1.88, 2.39)
Tested before the diagnosis of T2D (NDH detected) Other ethnical groups 2.68 (2.43, 2.96)
Nephropathy (normal glycaemic values and white as ref)
Tested before the diagnosis of T2D (normal glycaemic values) South Asian 0.98 (0.81, 1.19)
Tested before the diagnosis of T2D (normal glycaemic values) Other ethnical groups 1.16 (0.99, 1.35)
No results of blood glucose tests available before the diagnosis of T2D White 1.03 (0.99, 1.07)
No results of blood glucose tests available before the diagnosis of T2D South Asian 1.11 (0.99, 1.25)
No results of blood glucose tests available before the diagnosis of T2D Other ethnical groups 1.14 (1.04, 1.25)
Tested before the diagnosis of T2D (NDH detected) White 1.15 (1.10, 1.20)
Tested before the diagnosis of T2D (NDH detected) South Asian 1.11 (0.97, 1.26)
Tested before the diagnosis of T2D (NDH detected) Other ethnical groups 1.16 (1.04, 1.30)
Any microvascular disease (normal glycaemic values and white as ref)
Tested before the diagnosis of T2D (normal glycaemic values) South Asian 1.09 (0.94, 1.28)
Tested before the diagnosis of T2D (normal glycaemic values) Other ethnical groups 1.09 (0.96, 1.24)
No results of blood glucose tests available before the diagnosis of T2D White 1.24 (1.20, 1.29)
No results of blood glucose tests available before the diagnosis of T2D South Asian 1.72 (1.58, 1.88)
No results of blood glucose tests available before the diagnosis of T2D Other ethnical groups 1.45 (1.35, 1.55)
Tested before the diagnosis of T2D (NDH detected) White 1.45 (1.40, 1.51)
Tested before the diagnosis of T2D (NDH detected) South Asian 1.64 (1.48, 1.82)
Tested before the diagnosis of T2D (NDH detected) Other ethnical groups 1.92 (1.75, 2.09)
Both microvascular disease (normal glycaemic values and white as ref)
Tested before the diagnosis of T2D (normal glycaemic values) South Asian 1.35 (0.93, 1.96)
Tested before the diagnosis of T2D (normal glycaemic values) Other ethnical groups 1.00 (0.71, 1.42)
No results of blood glucose tests available before the diagnosis of T2D White 1.34 (1.24, 1.45)
No results of blood glucose tests available before the diagnosis of T2D South Asian 1.63 (1.32, 2.01)
No results of blood glucose tests available before the diagnosis of T2D Other ethnical groups 1.62 (1.37, 1.92)
Tested before the diagnosis of T2D (NDH detected) White 1.51 (1.39, 1.64)
Tested before the diagnosis of T2D (NDH detected) South Asian 1.56 (1.22, 1.99)
Tested before the diagnosis of T2D (NDH detected) Other ethnical groups 2.11 (1.75, 2.54)
.5
1
3

Figure 8. Association between glycaemic testing and detection of Non-diabetic Hyperglycaemia, ethnicity, 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. An interaction term between NDH status before the diagnosis of Type 2 diabetes and ethnicity (White, South Asian, others) was fitted. Models were also adjusted for age, sex, 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: NDH: non-diabetic hyperglycaemia.


OR (95% CI)
Coronary Heart disease (normal glycaemic values and white as ref)
Tested before the diagnosis of T2D (normal glycaemic values) South Asian 1.14 (0.93, 1.40)
Tested before the diagnosis of T2D (normal glycaemic values) Other ethnical groups 0.71 (0.58, 0.85)
No results of blood glucose tests available before the diagnosis of T2D White 0.72 (0.69, 0.75)
No results of blood glucose tests available before the diagnosis of T2D South Asian 0.87 (0.76, 1.01)
No results of blood glucose tests available before the diagnosis of T2D Other ethnical groups 0.60 (0.53, 0.68)
Tested before the diagnosis of T2D (NDH detected) White 1.06 (1.02, 1.11)
Tested before the diagnosis of T2D (NDH detected) South Asian 1.22 (1.06, 1.40)
Tested before the diagnosis of T2D (NDH detected) Other ethnical groups 0.73 (0.64, 0.84)
Cerebrvoascular disease (normal glycaemic values and white as ref)
Tested before the diagnosis of T2D (normal glycaemic values) South Asian 0.67 (0.45, 1.00)
Tested before the diagnosis of T2D (normal glycaemic values) Other ethnical groups 1.00 (0.76, 1.32)
No results of blood glucose tests available before the diagnosis of T2D White 0.90 (0.84, 0.96)
No results of blood glucose tests available before the diagnosis of T2D South Asian 0.63 (0.48, 0.82)
No results of blood glucose tests available before the diagnosis of T2D Other ethnical groups 0.91 (0.75, 1.09)
Tested before the diagnosis of T2D (NDH detected) White 0.87 (0.81, 0.93)
Tested before the diagnosis of T2D (NDH detected) South Asian 0.72 (0.56, 0.94)
Tested before the diagnosis of T2D (NDH detected) Other ethnical groups 0.81 (0.65, 1.00)
Peripheral arterial disease (normal glycaemic values and white as ref)
Tested before the diagnosis of T2D (normal glycaemic values) South Asian 0.63 (0.38, 1.07)
Tested before the diagnosis of T2D (normal glycaemic values) Other ethnical groups 0.55 (0.35, 0.85)
No results of blood glucose tests available before the diagnosis of T2D White 0.90 (0.83, 0.97)
No results of blood glucose tests available before the diagnosis of T2D South Asian 0.44 (0.30, 0.66)
No results of blood glucose tests available before the diagnosis of T2D Other ethnical groups 0.52 (0.39, 0.69)
Tested before the diagnosis of T2D (NDH detected) White 0.88 (0.81, 0.95)
Tested before the diagnosis of T2D (NDH detected) South Asian 0.65 (0.46, 0.93)
Tested before the diagnosis of T2D (NDH detected) Other ethnical groups 0.46 (0.33, 0.64)
Any macrovascular disease (normal glycaemic values and white as ref)
Tested before the diagnosis of T2D (normal glycaemic values) South Asian 0.99 (0.82, 1.21)
Tested before the diagnosis of T2D (normal glycaemic values) Other ethnical groups 0.71 (0.59, 0.84)
No results of blood glucose tests available before the diagnosis of T2D White 0.76 (0.73, 0.79)
No results of blood glucose tests available before the diagnosis of T2D South Asian 0.82 (0.72, 0.94)
No results of blood glucose tests available before the diagnosis of T2D Other ethnical groups 0.63 (0.57, 0.71)
Tested before the diagnosis of T2D (NDH detected) White 0.99 (0.95, 1.03)
Tested before the diagnosis of T2D (NDH detected) South Asian 1.02 (0.89, 1.16)
Tested before the diagnosis of T2D (NDH detected) Other ethnical groups 0.69 (0.61, 0.78)
.3
1
1.5

5.5 Discussion

In this large retrospective study of a cohort of individuals newly diagnosed with T2D in England, it was found that the presence of microvascular and macrovascular disease varied substantially by glycaemic status before diagnosis. Compared with individuals with glycaemic levels within the normal range within three years before T2D diagnosis, individuals with prior NDH and those without glycaemic testing were significantly more likely to have microvascular disease at the time of T2D diagnosis. Individuals with prior NDH were also more likely to have a previous diagnosis of coronary heart disease at the time of diagnosis. Conversely, patients with prior NDH were less likely to have cerebrovascular and peripheral arterial disease compared with those who had glycaemic values within the normal range before T2D diagnosis. There were only small variations in these findings across various NDH diagnostic criteria employed by WHO/IEC, ADA and NICE. Individuals who had a diagnostic label for NDH in their health records had lower odds of microvascular and macrovascular diseases compared with those with NDH without a diagnostic code. Individuals with prior NDH of non-White ethnic groups were also more likely to have microvascular disease at time of diagnosis of T2D as compared with their White counterparts.

This study specifically focused on individuals who eventually progressed to T2D to examine how prior glycaemic testing and status is linked to vascular disease in a population which would benefit the most from preventative interventions. Over one-third of individuals in this study were diagnosed with either retinopathy or nephropathy at the time of T2D diagnosis, one-fifth had at least one macrovascular disease, and half of them had at least one microvascular or macrovascular disease. These findings correspond with previous studies reporting a high burden of vascular disease among newly diagnosed individuals with T2D (230-232). NDH is

associated with an excess risk for the development of both macrovascular and microvascular diseases with a continuum of risk across the glycaemic range of NDH (130, 132, 233). In the majority of people who progress to T2D, an abrupt increase in glycaemic measures has been described within two to three years before diagnosis (121, 130). In our study, the higher burden of retinopathy among individuals with NDH compared with individuals with normoglycemia might be explained by prolonged exposure to mild hyperglycaemia.

Accordingly, individuals with glycaemic values within the normal range might include a subgroup of individuals with a more rapid progression to T2D or could represent people with a similar glycaemic trajectory leading to diabetes but with a diagnosis earlier in the natural history of the disease (see the lower HbA1c value at diagnosis in this group) or most likely a combination of these mechanisms (120, 130). It is also important to note that while more than 80% of this group had recorded measures of FPG in the three years before the diagnosis of T2D, only less than a quarter (23.7%) had recorded measures of more than one type of glycaemic test, which might suggest that this group was less frequently and accurately tested. Considering the predominant use of FPG, which has lower sensitivity than HbA1c, the very low proportion of this group (lower than 5%) being also tested with OGTT, and the intermittent nature of glycaemic values during the NDH status (120, 234), a proportion of those identified with normoglycaemia might have been incorrectly identified with glycaemic values within the normal range.

Importantly, 59% of individuals did not have a recorded glycaemic measurement in the three years before T2D diagnosis. Individuals without glycaemic measurements had a notably higher mean HbA1c following T2D diagnosis compared with those with glycaemic testing (with or without NDH), potentially indicating late diagnosis of T2D and leading to delayed treatment.

The clinical characteristics of these people are compatible with at least two explanations: First, these people may be less health conscious and have a worse adherence with preventive procedures reflected by their higher prevalence of smoking and a lower number of primary care visits. Second, they may be tested less frequently as they have a lower number of chronic diseases, leading to lower number of primary care visits with subsequent less opportunities for screening tests. In addition, they may also have worse adherence to recommended lifestyle changes for people with NDH, potentially explaining the excess burden of retinopathy in this group.

The differences for nephropathy were less pronounced between the glycaemic groups compared with that for retinopathy. These findings suggest that the association between pre-existing NDH and nephropathy might not be as strong as that for retinopathy. This is in line with the findings of a recent meta-analysis that concluded that the association between NDH and nephropathy was significant but modest, and this might be partially explained by underlying confounding or common causes contributing to both hyperglycaemia and kidney disease (130, 143). A small proportion of individuals (5.4% considering the whole sample) had both retinopathy and nephropathy in this study, potentially indicating prolonged exposure to chronic hyperglycaemia or non-diabetic glomerular disease in some individuals that, at least partly, may explain the different patterns of renal involvement (235, 236).

Only small variations in findings were found across NDH sub-groups defined by the WHO/IEC, NICE, and ADA, suggesting that when focusing on the proportion of the NDH population who eventually progresses to T2D, differences are less pronounced then what has been found in

studies focusing on the whole NDH population, including those who will never progress to T2D (96).

Individuals with NDH detected before the diagnosis of T2D were more likely to have a previous diagnosis of coronary heart disease but were less likely to have cerebrovascular and peripheral arterial disease at time of T2D diagnosis. These findings correspond with previous studies showing that chronic hyperglycaemia contributes to the pathogenesis of macrovascular dysfunction (130-133). While hyperglycaemia has been shown to be strongly associated with an increased risk of coronary heart disease (130, 237), the association with cerebrovascular disease is less clear (238). These findings are also compatible with a potential surveillance bias: people with any cardiovascular disease are more likely to be screened for diabetes and intermediate hyperglycaemia compared with the general population and thus have a higher chance of earlier diagnosis of diabetes.

Individuals with prior NDH from non-White ethnic groups were more likely to have microvascular disease at time of diagnosis of T2D than their White counterparts. Odds were relatively greater for individuals from ethnic minorities other than South Asians. Whilst no study has previously evaluated this specific association, these findings are in line with previous studies suggesting that the risk of microvascular disease is higher for South Asians and other ethnic minorities (63, 88). Interestingly, odds of macrovascular disease at time of T2D diagnosis were lower for non-White ethnic groups with prior NDH. This is in line with a recent study that found that CVD risk is greater for White ethnic groups then South Asians (52).

5.5.1 Strengths and limitations

To my knowledge, this is the first large population-based study to examine associations between glycaemic status before T2D diagnosis and the presence of microvascular and macrovascular disease in individuals newly diagnosed with T2D. I used routinely collected primary and secondary care data representative of the English population to better understand these associations in real world settings. While the implementation of a national retinopathy screening programme in the UK and increased surveillance due to the QOF has ensured good quality data for the diagnosis of retinopathy and nephropathy, I did not include diabetic neuropathy in the analyses because the diagnosis and coding of this condition appears sub-optimal in primary care settings in England (239). Additional study limitations include the presence of missing data for clinical variables such as blood pressure, BMI, total cholesterol, and HbA1c. However, I overcame the latter issue by using multiple imputation by chained equations. It was not possible to assess differences in adherence to lifestyle interventions, as I did not have data on diet and physical activity. Finally, when using routinely collected data, concerns have been raised about miscoding, misclassification and misdiagnosis. However, CPRD is subject to regular quality checks and is widely used for health research (199).

5.5.2 Implications for clinical practice

Microvascular and macrovascular diseases were present in 37-24% of people with newly diagnosed T2D, with over half not having any glycaemic measurement within three years before their diagnosis. While there are many unanswered questions regarding its detection, NDH has significant clinical implications for microvascular and macrovascular diseases and T2D outcomes, and similarly to T2D the likehihood might be greater for individuals of ethnic minorities. A major consideration is whether targeted preventive strategies that identify

patients with NDH for interventions would provide opportunities for vascular risk reduction (220, 233), considering that major benefits are likely to occur from early diagnosis and treatment (166). While discussions on the pathophysiological differences between NDH subtypes continue, there have been calls to move away from a glucocentric definition towards a multifactorial detection strategy for NDH that reflects the presence of other risk factors for T2D as well as early manifestation of vascular disease (130, 240).

5.6 Conclusion

This large observational study using real world data has shown that both microvascular and macrovascular diseases were frequently detected at the time of T2D diagnosis. Microvascular disease was more frequent among individuals with newly diagnosed T2D who were previously detected with NDH. The prevalence was greater among those from non-White ethnic groups. The identification of NDH and specific clustering of NDH with other risk factors for T2D might prompt earlier assessment for risk factors and tailored cardiovascular risk reduction strategies during the NDH phase to reduce the burden of vascular disease but further research is needed to confirm this.

6 The Association between detection of non-diabetic hyperglycaemia and incident microvascular and macrovascular disease and mortality following the diagnosis of Type 2 Diabetes: a population-based retrospective cohort study

6.1 Abstract

6.1.1 Background

Little is known about whether the associated risk of vascular disease for individuals with NDH persists in the long-term following the diagnosis of T2D.

6.1.2 Aim

I assessed whether glycaemic testing and detection of NDH before the diagnosis of T2D is associated with the hazard of incident microvascular and macrovascular disease and all-cause mortality following the diagnosis of T2D.

6.1.3 Methods

I identified 159,736 individuals with newly diagnosed T2D from the CPRD database in England between 2004 and 2017. The outcome of interest was the time to incident retinopathy, nephropathy, composite macrovascular disease (including coronary heart disease, cerebrovascular disease, and peripheral arterial disease), and all-cause mortality.

I employed time-partitioned Cox regression models partitioning the 10-year follow-up period into four equal time segments (each of 2.5 years) to model differences in rates of study outcomes between groups with different glycaemic testing and detection in the three years before diagnosis of T2D.

6.1.4 Results

As compared with individuals with glycaemic values within the normal range, following the diagnosis of T2D those with NDH detected had 86% increased rates of retinopathy in the first thirty months, 58% increased rates in the period 31-60 months, and 42% increased rates in the period 61-90 months (0-30 months: HR 1.86, 95%CI 1.69-2.04; 31-60 months: HR 1.58, 95%CI 1.37-1.84; 61-90 months: HR 1.42, 95%CI 1.10-1.83). They also had 16% and 25% increased rates of nephropathy in the period 0-30 months and 31-60 months, respectively (0-30 months: HR 1.16, 95%CI 1.07-1.26; 31-60 months: HR 1.25, 95%CI 1.09-1.42). Multivariate analysis estimated that individuals with prior NDH had 19% reduced rate of macrovascular disease in the first thirty months of the study period (HR 0.81, 95%CI 0.71-0.93), as compared with individuals with glycaemic values within the normal range.

6.1.5 Conclusions

Individuals detected with NDH had increased hazard of microvascular disease up to 7.5 years following the diagnosis of T2D as compared with individuals with glycaemic values within the normal range before the diagnosis of T2D. Estimated differences were greater for retinopathy then nephropathy, although in both cases they progressively attenuated over the study period. Timely testing and identification of NDH and specific clustering of NDH with other risk factors for T2D might prompt earlier assessment for risk factors and tailored cardiovascular risk reduction strategies during the NDH phase to reduce the burden of vascular disease following the diagnosis of T2D.

6.2 Introduction

As previously discussed in Chapter 2.4, current evidence shows that NDH contributes to the pathogenesis of macrovascular dysfunction that might partly explain the increased risk of CVD morbidity and mortality in NDH and T2D (130-133). Individuals with NDH are at increased risk of CHD, stroke, composite CVD events, and all-cause mortality (131). These associations remained consistent using both WHO and ADA criteria for the detection of NDH (131), although the association between NDH defined by HbA1c levels and risk of macrovascular disease and all-cause mortality appear to be less consistent (131, 134-136).

The association between NDH and microvascular disease is still debated (130, 132, 137). The development of T2D-associated microvascular disease may precede the clinical diagnosis of Type 2 diabetes (138), considering that NDH has been associated with early, milder forms of nephropathy (132, 139-141). Some studies have also found that higher prevalence of CKD in individuals with NDH (142, 143), although the body of evidence supporting this association is not consistent (141, 143, 144). NDH has also been associated with increased risk of diabetic retinopathy, although findings are not entirely consistent and vary in relation to the method of detection (130, 132, 139, 146, 147). However, It remains unclear whether the positive association between NDH and risk of microvascular disease seen in longitudinal studies is attributable to NDH itself or partially mediated by the increased incidence of T2D (130, 132).

In the previous research chapter of this doctoral thesis I aimed to examine whether the occurrence of vascular disease differs in individuals newly diagnosed with T2D with prior NDH compared with those with normal glycaemic levels in real world settings. From the analysis of the data I found that microvascular and macrovascular diseases are detected in 37% and 24%, respectively, of individuals with newly diagnosed T2D. Individuals detected with NDH before

the diagnosis of T2D had increased odds of microvascular disease and coronary heart disease already present at time of T2D diagnosis, supporting previous findings linking NDH to microvascular and macrovascular dysfunction. However, little is known about whether the associated risk of vascular disease for individuals with NDH persists in the long-term following the diagnosis of T2D (130, 132). Therefore, the aim of this research study is to assess whether glycaemic testing and detection of NDH before the diagnosis of T2D is associated with the hazard of incident microvascular and macrovascular disease and all-cause mortality following the diagnosis of T2D.

6.3 Methods

6.3.1 Study population

The study population was drawn from the UK CPRD database. Inclusion and exclusion criteria have been described in detail in the Chapters 4.1, 4.3.1, and 5.3.1. Briefly, I defined a cohort of individuals who were newly diagnosed with T2D between 1 January 2004 and 30 September 2017 and registered with CPRD practices in England that consented to data linkage. Two additional sub-populations were drawn according to the presence of vascular complications at time of diagnosis of T2D. Specifically, a study population comprising individuals without microvascular disease at time of T2D diagnosis was used when assessing differences in incident retinopathy and nephropathy, whilst a study population comprising individuals without macrovascular disease at time of T2D diagnosis was used when assessing differences in incident macrovascular disease at time of T2D diagnosis. A study diagram summarising inclusion and exclusion criteria is shown in Figure 1.

6.3.2 Detection of NDH in primary care settings

In line with the previous research described in this thesis (Chapter 5), for the detection of NDH, I adopted diagnostic criteria published by the WHO and IEC: 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%)(106, 112). To identify glycaemic values within the NDH range, I used all available clinical data within three years before the date of T2D diagnosis. Individuals with multiple glycaemic recordings were classified as having NDH if at least one measurement met the detection criteria for NDH. Diagnostic codes in primary care records for IFG, IGT or other (e.g. “pre-diabetes” or “Intermediate Hyperglycaemia”) were also used to identify NDH cases. Individuals were classified as: i) glycaemic values within the normal range before T2D diagnosis; ii) NDH detected before T2D diagnosis; or iii) no glycaemic measures recorded within three years before T2D diagnosis.

6.3.3 Study outcomes

Study outcomes included incident retinopathy, nephropathy, macrovascular diseases (composite outcome including cerebrovascular disease, coronary heart disease, and peripheral arterial disease), and all-cause mortality following the diagnosis of T2D. Diagnoses of vascular events were defined based on the combination of laboratory tests, diagnostic codes in primary care records, and ICD-10 codes on hospital admissions (Appendix Table 1). Retinopathy and nephropathy diagnosed within 15 months following the diagnosis of T2D were considered as microvascular disease present at time of T2D diagnosis considering the time periods of specific process of care indicators of the QOF framework for diabetic retinopathy screening and urine microalbumin testing (12 months and 15 months, respectively) (10). Thus, incident retinopathy and nephropathy were defined by the recording of a microvascular disease 15 months after the diagnosis of T2D (224). Macrovascular disease recorded within 1 year of the diagnosis of T2D were considered as present at time of diagnosis of T2D. Therefore, all macrovascular disease diagnosed 1 year following the diagnosis of T2D were considered as incident diagnoses.

6.3.4 Study covariates

Study covariates included age, sex, ethnicity, smoking status, blood pressure (systolic and diastolic), body mass index (BMI), total cholesterol, number of diagnosed co-morbid conditions (list (225)), prescription of anti-hypertensive (Angiotensin-converting-enzyme inhibitor (ACEi) or Angiotensin receptor blockers (ARB); others), anti-platelet, lipid-lowering, and anti-diabetic medications (biguanides, sulphonylureas, insulin, others) and number of primary care visits during the year before the diagnosis of T2D and quintile of the IMD at practice level (226). Information on covariates was collected in the year following the diagnosis of T2D. A description on how each variable was defined can be found in Chapter 5.3.5.

6.3.5 Secondary analyses

In line with the previous research described in Chapter 5, I undertook two secondary analyses. The first secondary analysis compared results obtained adopting diagnostic criteria for the detection of NDH published by the WHO/IEC with those obtained using those published by the American Diabetes Association (ADA; 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%) and the UK National Institute for Health and Care Excellence(27) (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%) (Appendix Table 1). An additional secondary analysis was undertaken to explore whether among individuals with NDH clinical outcomes differed according to whether diagnostic coding for NDH in electronic health records was assigned following the detection of NDH.

6.3.6 Statistical analysis

The outcome of interest was the time to incident retinopathy, nephropathy, composite macrovascular disease (including coronary heart disease, cerebrovascular disease, and peripheral arterial disease), and all-cause mortality. Individuals who survived or, for other analyses, did not receive a diagnosis of interest were censored at transfer out date or last collection date for the practice, whichever came first.

At baseline missing data was present for blood pressure (0.5%), BMI (2.8%), total cholesterol (7.0%), and HbA1c (24.1%). Therefore, I used multiple imputation by chained equations (10 copies) to estimate missing data for these variables as described in Chapter 5.3.7.

For the three study populations I compared individuals' characteristics according to glycaemic status before the diagnosis of T2D (NDH, normal glycaemic status and not recorded) using Chi-square test, Kruskal-Wallis test, and ANOVA, as appropriate.

I assessed crude survival with the Kaplan-Meier estimator, stratified for the glycaemic status in the three years before the diagnosis of T2D. I employed the Cox proportional regression model to estimate the adjusted hazard of occurrence of selected study outcomes according to glycaemic status before the diagnosis of T2D when controlling for covariates. Although competing events might be identified for the selected study outcomes, I employed the Cox proportional hazard regression models rather than the Fine and Gray competing risk regression model as I was mostly interested in directly quantifying the hazard ratios among those individuals who are actually at risk of developing the event of interest, as previously suggested (241, 242). I tested the Cox proportional hazard assumption using plots of log(−log survival time) against log survival time and Schoenfeld residuals against survival time. In addition, I used linear regression of Schoenfeld residuals on time to test for independence between residuals and time. The interaction between prior NDH status and time was statistically significant when considering the entire study period, which means that the proportional hazards assumption was violated. However, the proportionality held when considering only the first three years of the follow-up period. Therefore, I employed time-partitioned Cox regression models partitioning the 10-year follow-up period into four equal time segments (each of 2.5 years)(243-246). Proportionality of hazards within each time segment was tested using the above described approach. Statistical models were adjusted for age, sex, ethnicity (White, South-Asian, Black, Other, and Unknown), smoking status (smoker, ex-smoker, non-smoker), body mass index, systolic and diastolic blood pressure, total cholesterol, baseline HbA1c, number of co-morbidites, medications (ACEi/ARB, other anti-hypertensive, lipid-lowering, biguanides, sulphonylureas, other anti-diabetic medications), number of primary care visits in the year prior the T2D diagnosis, Index of Multiple Deprivation quintiles, and year of diagnosis of Type 2

diabetes. Adjusted Hazard Ratios (HR) and 95% CI were estimated and results were considered significant if $p<0.05$. Statistical analyses were conducted using Stata SE 15.1.

6.4 Results

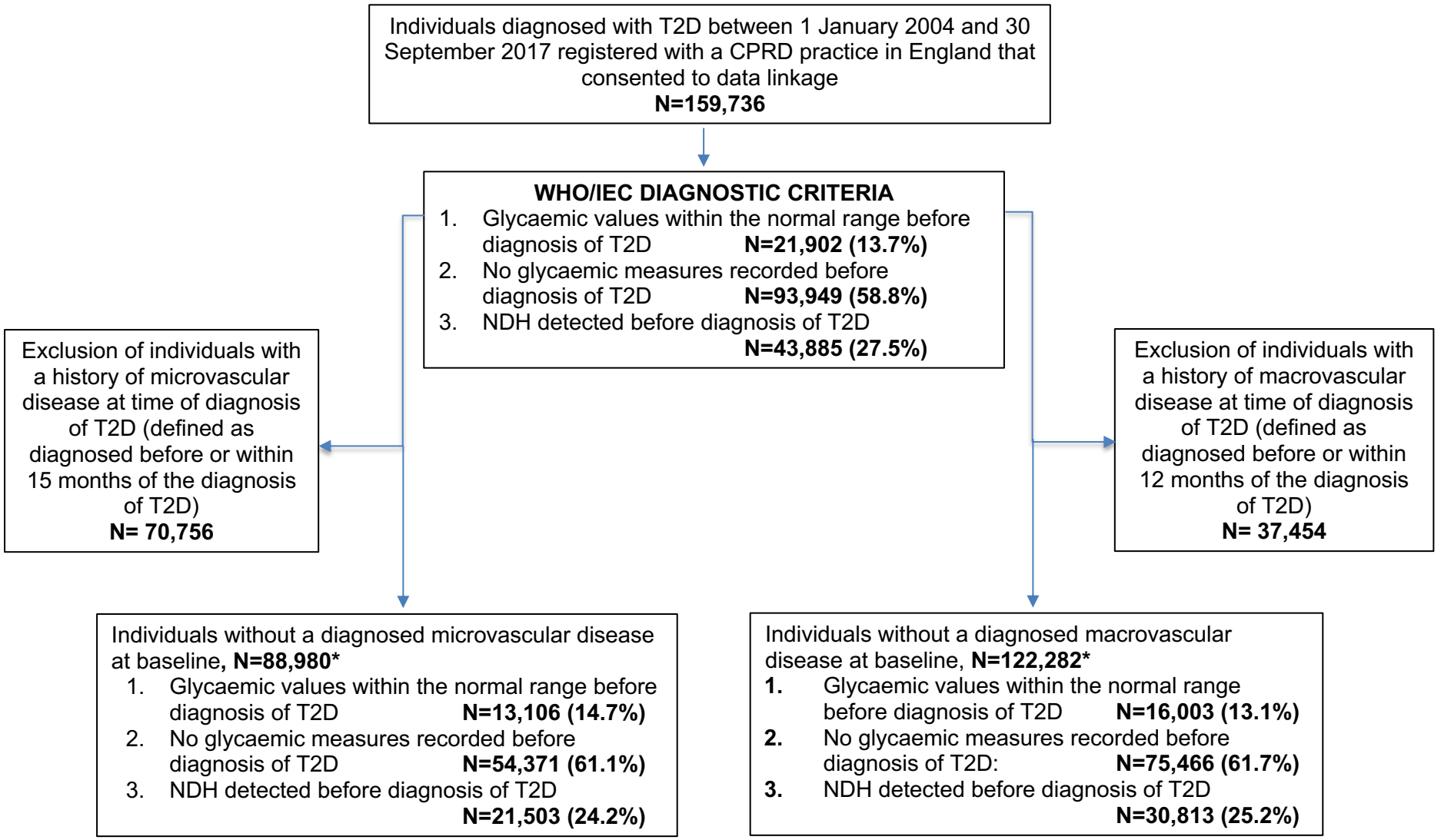
A sample of 159,736 individuals with a diagnosis of T2D formulated between 1 January 2004 and 30 September 2017. Characteristics of the study population have been described in detail in Chapter 5. 88,980 individuals (55.7% of the sample) did not have a diagnosis of microvascular disease, while 122,282 individuals (76.6% of the sample) did not have a diagnosis of macrovascular disease at the time of T2D diagnosis. A flowchart for individuals' inclusion and exclusion criteria is summarised in Figure 9.

Considering the population without a diagnosis of microvascular disease, 61.1% of them did not have glycaemic measures recorded, 14.7% had glycaemic values within the normal range, and 24.2% had NDH detected in the three years before the diagnosis of T2D. Those with NDH detected were on average more than four years older, more likely to be male, and ex-smokers. They also had higher BMI and blood pressure and were more likely treated with anti-hypertensive anti-lipid medications (Table 4). Individuals with glycaemic values within the normal range had on average a greater number of primary care visits in the year before the diagnosis and were more likely to be registered with a general practice in the most deprived quintile (Table 4). At the time of diagnosis of T2D individuals without glycaemic measures recorded in the three years before had on average higher values of HbA1c and a smaller number of chronic conditions (2.2, 2.8 for those with NDH detected, and 2.9 for those with glycaemic values within the normal range) at time of diagnosis.

The proportion of individuals without macrovascular disease at time of diagnosis of T2D who were tested for NDH in the three years before was similar to those without microvascular

disease at time of diagnosis. Those with NDH detected, representing the 25.2% of the sample, were older, more likely to be ex-smoker, obese, and more likely to take anti-hypertensive, anti-lipid, and anti-diabetic medications. Individuals with glycaemic values within the normal range before the diagnosis of T2D comprised the 13.1 of the sample. They had also greater number of primary care visits in the year before the diagnosis of T2D and were more likely to be registered with general practices in the most deprived quintile. Individuals without glycaemic measures recorded in the three years before the diagnosis of T2D had higher values of HbA1c and total cholesterol at time of diagnosis. They also had lower number of chronic conditions (Table 4).

Figure 9. Flowchart for individual inclusion and exclusion criteria in the Type 2 diabetes cohort



Note: *The two groups of patients without a diagnosed microvascular and without a diagnosed macrovascular complication at baseline are not mutually exclusive and individuals are included in either or both groups.

Table 4. Baseline characteristics of patients with T2D diagnosed between 1 January 2004 and 30 September 2017 in the CPRD database without a microvascular complication and without a macrovascular complication at time of T2D diagnosis

	No microvascular disease at the time of T2D diagnosis					No macrovascular disease at the time of T2D diagnosis				
	No glycaemic measures recorded before T2D diagnosis[#]	Glycaemic values within normal range before T2D diagnosis[#]	NDH detected before T2D diagnosis[#]	p-value	Total	No glycaemic measures recorded before T2D diagnosis*	Glycaemic values within normal range before T2D diagnosis*	NDH detected before T2D diagnosis*	p-value	Total
N (%)	54,371 (61.1)	13,106 (14.7)	21,503 (24.2)		88,980 (100)	75,466 (61.7)	16,003 (13.1)	30,813 (25.2)		122,282
Female (%)	48.2	55.6	43.7[¥]	<0.001[¥]	48.2	58.6	60.2	50.4[¥]	<0.001[¥]	51.8
Age, yrs, mean (SD)	56.2 (13.8)	56.3 (13.4)	60.6 (11.8)[§]	<0.001[§]	57.3 (13.4)	57.8 (14.3)	57.8 (14.3)	61.8 (12.5)[§]	<0.001[§]	58.8 (14.0)
Ethnicity (%)										
White	80.7	82.3	80.2		80.8	80.3	81.5	79.1		80.1
South Asian	3.2	4.9	5.0		3.9	3.4	4.9	5.0		4.0
Black	2.3	3.3	2.7	<0.001[¥]	2.5	2.5	3.8	3.3	<0.001[¥]	2.8
Other	3.3	3.9	3.7		3.5	3.2	3.9	3.9		3.5
Unknown	10.5	5.6	8.5		9.3	10.7	5.9	8.8		9.6
Smoking status (%)										
Non-smoker	38.3	37.5	33.4		37.0	39.4	39.6	36.4	<0.001[¥]	38.7
Ex-smoker	39.7	42.4	48.4	<0.001[¥]	42.2	40.6	42.3	47.5		42.6
Current smoker	22.0	20.1	18.1		20.8	19.9	18.1	16.0		18.7

HbA1c, mmol/mol, mean (SD)	60.0 (24.2)	46.0 (20.2)	51.0 (16.5)	<0.001§	55	61 (24.1)	46 (20.6)	51 (16.8)	<0.001§	56 (23.3)
Body mass index, kg/m2, mean (SD)	29.9 (6.9)	29.8 (7.1)	31.7 (6.7)	<0.001§	30.3 (6.9)	30.2 (6.9)	30.0 (7.2)	31.7 (6.7)	<0.001§	30.5 (6.9)
Systolic blood pressure, mm Hg, mean (SD)	135.0 (16.8)	132.8 (15.8)	137.0 (14.4)	<0.001§	135.1 (16.1)	136.3 (16.6)	133.8 (15.7)	137.9 (14.2)	<0.001§	136.4 (16.0)
Diastolic blood pressure, mm Hg, mean (SD)	80.4 (9.7)	79.3 (9.3)	80.4 (8.7)	<0.001§	80.3 (9.4)	80.8 (9.5)	79.6 (9.2)	80.6 (8.6)	<0.001§	80.6 (9.3)
Total cholesterol, mmol/L, mean (SD)	5.2 (1.1)	5.1 (1.1)	5.0 (1.1)	<0.001§	5.2 (1.1)	5.3 (1.1)	5.2 (1.1)	5.1 (1.1)	<0.001§	5.2 (1.1)
Number of chronic diseases, mean (SD)	2.2 (1.8)	2.9 (2.0)	2.8 (1.9)	<0.001Ψ	2.4 (1.9)	2.3 (1.9)	3.0 (2.1)	2.9 (1.9)	<0.001Ψ	2.5 (1.9)
Medications (%)										
Anti-hypertensive	37.4	41.4	59.9		43.4	40.3	43.3	59.7		45.6
ACEi/ARBs	26.4	28.6	43.9		31.0	28.9	30.1	43.9		32.8
Anti-lipid	36.6	36.7	58.0		41.8	37.0	33.0	54.1		40.8
Anti-diabetic*	35.9	29.8	15.3	<0.001¥	31.4	40.8	17.8	30.9	<0.001¥	35.3
Insulin	31.8	13.4	28.2		28.2	36.4	15.6	29.2		31.8
Biguanides	7.3	2.2	2.8		5.5	8.7	2.7	3.1		6.5
Sulphonylureas	2.9	1.9	1.0		2.3	2.9	2.0	1.1		2.3
Other	0.1	0.1	0.1		0.1	0.1	0.1	0.1		0.1
Number of primary care visits in the year before T2D diagnosis, mean (SD)	10.1 (10.1)	15.1 (12.3)	13.4 (10.7)	<0.001Ψ	11.7 (10.8)	10.1 (10.0)	15.2 (12.3)	13.1 (10.3)	<0.001Ψ	11.5 (10.6)

Index of Multiple Deprivation quintiles (%)										
Quintile 1: least deprived	15.5	12.3	13.7		14.6	14.9	12.9	14.0		14.4
2	19.5	19.0	17.8		19.0	19.8	19.5	18.6		19.4
3	19.5	18.2	19.7	<0.001¥	19.4	19.3	18.1	19.7	<0.001¥	19.2
4	20.7	23.5	24.9		22.1	20.9	22.9	23.4		21.8
Quintile 5: most deprived	24.8	27.0	23.9		24.9	25.2	26.6	24.3		25.1

***Notes**:* Abbreviations: T2D: Type 2 Diabetes; NDH: non-diabetic hyperglycaemia; ACEi: Angiotensin-converting-enzyme inhibitor; ARBs: Angiotensin II receptor blockers.

* Individuals were defined as having a microvascular disease at baseline who were diagnosed with retinopathy or nephropathy within five years before and fifteen months after the diagnosis of T2D, and were excluded from the cohort.

** Individuals were defined as having a macrovascular disease at baseline with a history of macrovascular disease or diagnosis within one year after the diagnosis of T2D, and were excluded from the cohort.

Glycaemic status was defined based on diagnostic codes and clinical data within three years before the diagnosis of Type 2 diabetes using the WHO/International Expert Committee criteria as follows: 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%.

¥ Chi-square test, § ANOVA test, Ψ Kruskal Wallis test. P≤0.001 for all.

6.4.1 Microvascular disease

Over the 10-year study period, since the diagnosis of T2D 12,446 new diagnoses of retinopathy were recorded with an estimated incidence of 427.0 (419.5-434.5) cases per 10,000 person-years. Estimated incidence was 466.7 (451.3-482.5), 454.5 (444.7-464.5), and 226.0 (211.5-241.4) cases per 10,000 person-years for individuals with NDH detected, without glycaemic measures recorded, and with glycaemic values within the normal range, respectively, in the three years before the diagnosis of T2D (Figure 10). Differences in hazards of incident retinopathy progressively reduced over the study period. As compared with individuals with glycaemic values within the normal range, following the diagnosis of T2D those with NDH detected had 86% increased hazard in the first thirty months, 58% increased hazard in the period 31-60 months, and 42% increased hazard in the period 61-90 months (0-30 months: HR 1.86, 95%CI 1.69-2.04; 31-60 months: HR 1.58, 95%CI 1.37-1.84; 61-90 months: HR 1.42, 95%CI 1.10-1.83). Similarly, hazard ratios for individuals without glycaemic measures recorded before the diagnosis of T2D were 74% higher in the period 0-30 months, 45% higher in the period 31-60 months, and 49% higher in the period 61-90 months (0-30 months: HR 1.74, 95%CI 1.60-1.91; 31-60 months: HR 1.45, 95%CI 1.26-1.67; 61-90 months: HR 1.49, 95%CI 1.18-1.89) following the diagnosis of T2D. No differences in hazard ratios of incident retinopathy were observed between the three groups for the last thirty months of the 10-year study period.

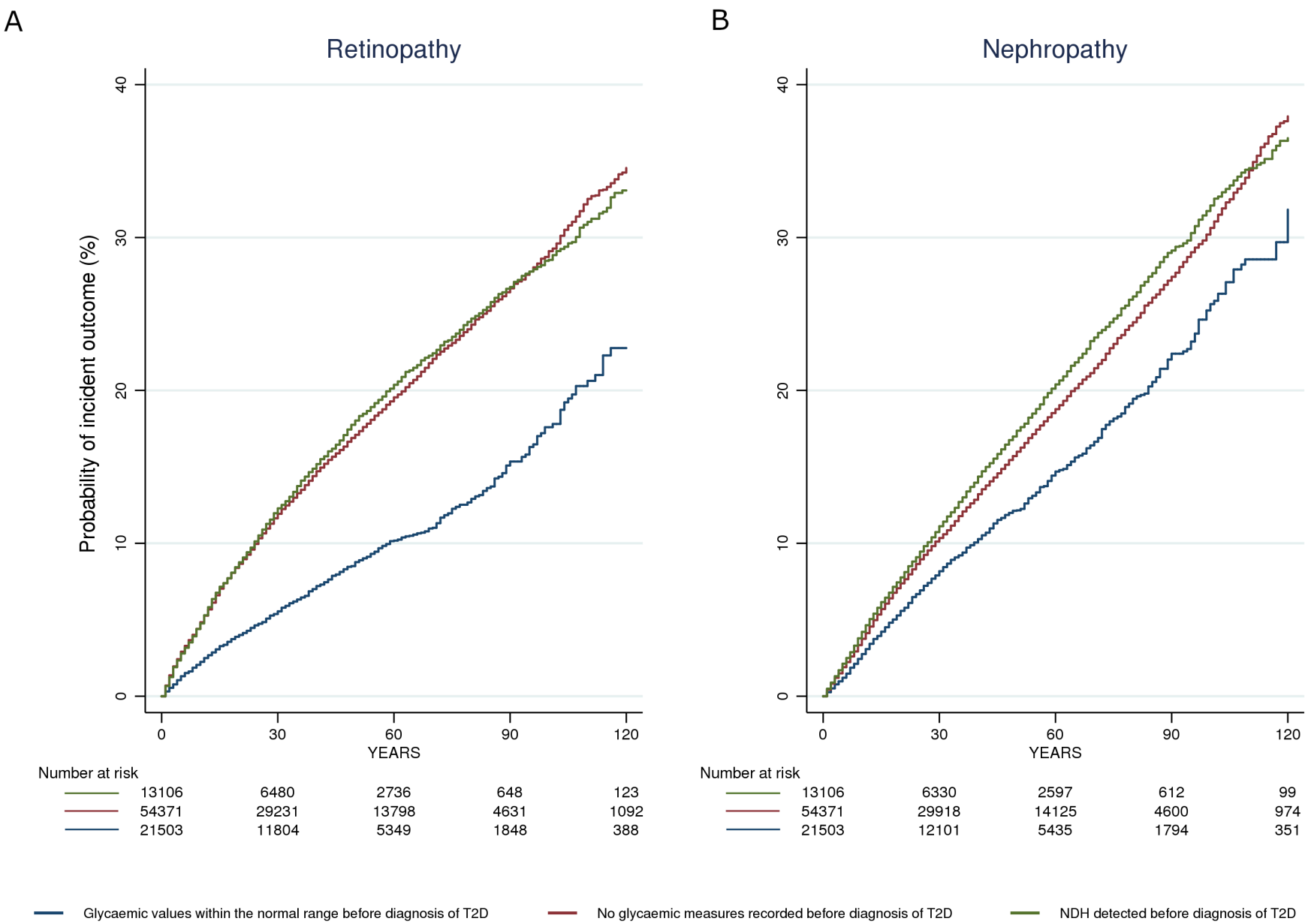
In the ten years following the diagnosis of T2D, 12,562 new cases of nephropathy were diagnosed with and estimated incidence rate equal to 427.0 (419.6-434.5) cases per 10,000 person-years. Incidence was higher and equal to 463.6 (448.4-479.4) cases per 10,000 person-years for individuals with glycaemic values meeting diagnostic criteria for NDH. For those without glycaemic values recorded before the diagnosis of T2D the estimated incidence rate was 432.6 (423.1-442.2) cases per 10,000 person-years, whilst for those with glycaemic values within the normal range the estimated

incidence was 328.9 (311.2-347.6) cases per 10,000 person-years. As compared with individuals with glycaemic values within the normal range in the three years before the diagnosis of T2D, those with glycaemic values meeting diagnostic criteria for NDH before the T2D diagnosis had 16% and 25% increased hazard of incident nephropathy in the period 0-30 months and 31-60 months, respectively (0-30 months: HR 1.16, 95%CI 1.07-1.26; 31-60 months: HR 1.25, 95%CI 1.09-1.42), while those without glycaemic values recorded before the T2D diagnosis had 18% and 24% increased hazard of nephropathy in the period 0-30 and 31-60 months, respectively (0-30 months: HR 1.18, 95%CI 1.09-1.27; 31-60 months: HR 1.24, 95%CI 1.10-1.40). No differences were observed in the period 61-120 months in the hazard ratios of incident nephropathy between the three groups.

Figure 10. Kaplan Meier curves for microvascular disease following the diagnosis of T2D by glycaemic status before the diagnosis of T2D. A. Retinopathy; B. Nephropathy. Log rank test to compare the difference between groups for both outcomes <0.001.

***Notes**:* Abbreviations: T2D = Type 2 diabetes, NDH = non-diabetic hyperglycaemia, FPG = fasting plasma glucose, OGTT = oral glucose tolerance test, HbA1c = glycated haemoglobin.

Glycaemic status was defined based on diagnostic codes and clinical data within three years before the diagnosis of Type 2 diabetes using the WHO/International Expert Committee criteria as follows: 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%.


A
Retinopathy
Probability of incident outcome (%)
0
10
20
30
40
0
30
60
90
120
YEARS
Number at risk
13106 6480 2736 648 123
54371 29231 13798 4631 1092
21503 11804 5349 1848 388
B
Nephropathy
0
10
20
30
40
0
30
60
90
120
YEARS
Number at risk
13106 6330 2597 612 99
54371 29918 14125 4600 974
21503 12101 5435 1794 351
Glycaemic values within the normal range before diagnosis of T2D
No glycaemic measures recorded before diagnosis of T2D
NDH detected before diagnosis of T2D

6.4.2 Macrovascular disease

Over the 10-year study period, 11,394 new cases of macrovascular disease were diagnosed, corresponding to 17.8 (17.5-19.7) estimated cases per 10,000 person-years. Specifically, it was estimated that for individuals with NDH detected in the three years before the diagnosis of T2D incident rate of macrovascular disease was 19.0 (18.3-19.7) cases per 10,000 person-years, while it was 17.5 (17.1-18.0) cases for individuals without glycaemic measures recorded and 16.7 (15.7-17.6) cases for individuals with glycaemic measures within the normal range in the three years before the diagnosis of T2D (Figure 12). Multivariate analysis estimated that individuals with NDH in the three years before the diagnosis of T2D had 19% reduced hazard of macrovascular disease in the first thirty months of the study period (HR 0.81, 95%CI 0.71-0.93), as compared with individuals with glycaemic values within the normal range. No other differences were observed between groups during the study period.

6.4.3 Mortality

Over the 10-year study period, 26,983 deaths were registered, with an estimated mortality rate of 31.3 (31.0-31.7) cases per 10,000 person-years. Estimated incidence was 29.2 (28.5-29.9), 31.6 (31.2-32.1), and 34.7 (33.6-35.9) cases per 10,000 person-years for individuals with NDH detected, without glycaemic measures recorded, and with glycaemic values within the normal range, respectively, in the three years before the diagnosis of T2D (Figure 13). Individuals with NDH detected had 30% and 18% reduced hazard of mortality in the periods 0-30 and 31-60 months (0-30 months: HR 0.70, 95%CI 0.65-0.74; 31-60 months: HR 0.82, 95%CI 0.76-0.88) following the diagnosis of T2D, as compared with individuals with glycaemic values within the normal range before the T2D diagnosis (Figure 14).

Figure 11. Kaplan Meier curves for composite macrovascular disease following the diagnosis of T2D by glycaemic status before the diagnosis of T2D. Log rank test to compare the difference between groups <0.001.

Notes: Abbreviations: T2D = Type 2 diabetes, NDH = non-diabetic hyperglycaemia, FPG = fasting plasma glucose, OGTT = oral glucose tolerance test, HbA1c = glycated haemoglobin.

Glycaemic status was defined based on diagnostic codes and clinical data within three years before the diagnosis of Type 2 diabetes using the WHO/International Expert Committee criteria as follows: 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%.

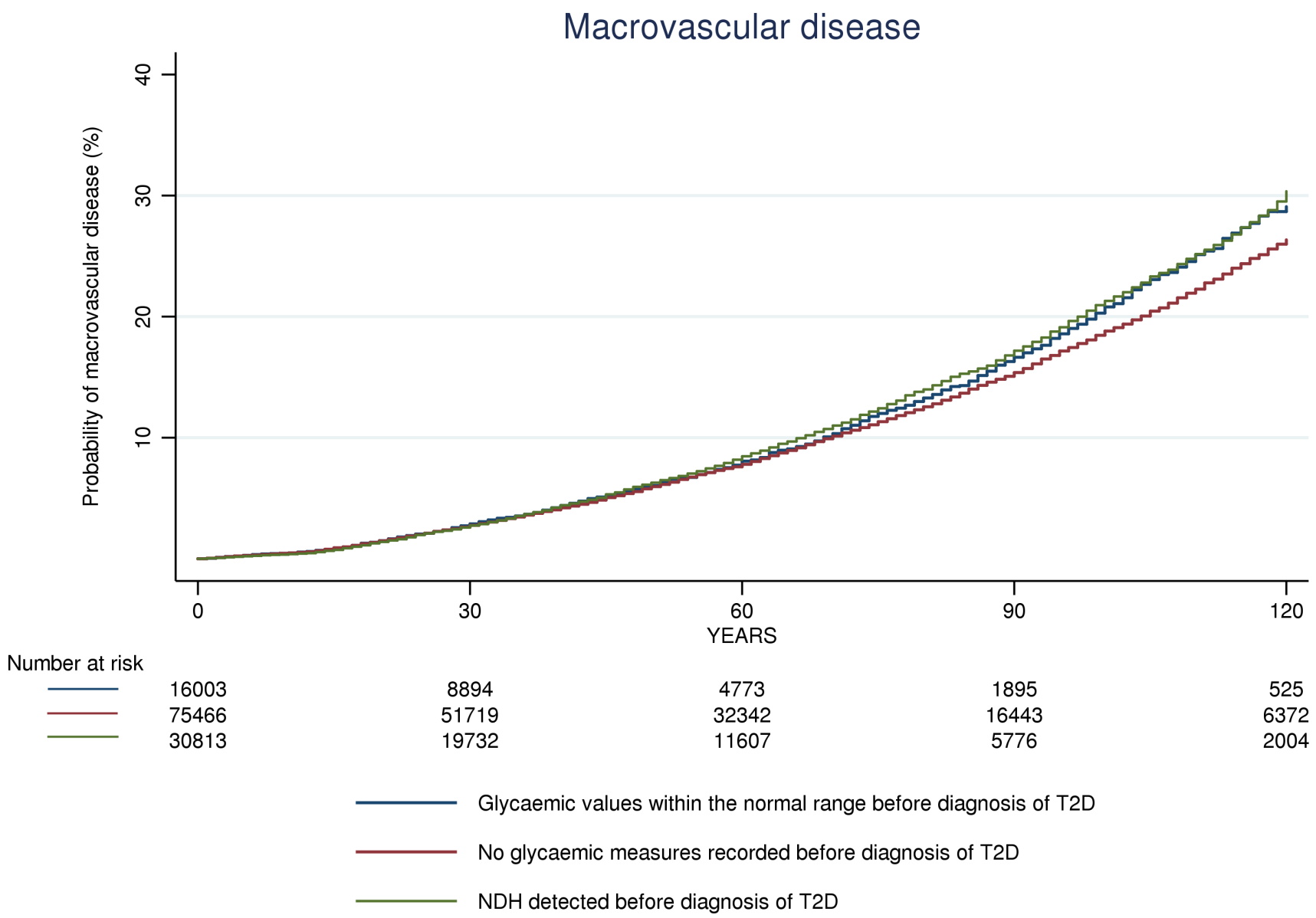

Macrovascular disease
Probability of macrovascular disease (%)
10
20
30
40
0
30
60
90
120
YEARS
Number at risk
16003 8894 4773 1895 525
75466 51719 32342 16443 6372
30813 19732 11607 5776 2004
Glycaemic values within the normal range before diagnosis of T2D
No glycaemic measures recorded before diagnosis of T2D
NDH detected before diagnosis of T2D

Figure 12. Kaplan Meier estimation of survival curves among patients newly diagnosed with Type 2 diabetes according to glycaemic status before the diagnosis of T2D. Log rank test to compare the difference between groups <0.001.

***Notes*:** Abbreviations: T2D = Type 2 diabetes, NDH = non-diabetic hyperglycaemia, FPG = fasting plasma glucose, OGTT = oral glucose tolerance test, HbA1c = glycated haemoglobin.

Glycaemic status was defined based on diagnostic codes and clinical data within three years before the diagnosis of Type 2 diabetes using the WHO/International Expert Committee criteria as follows: 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%.

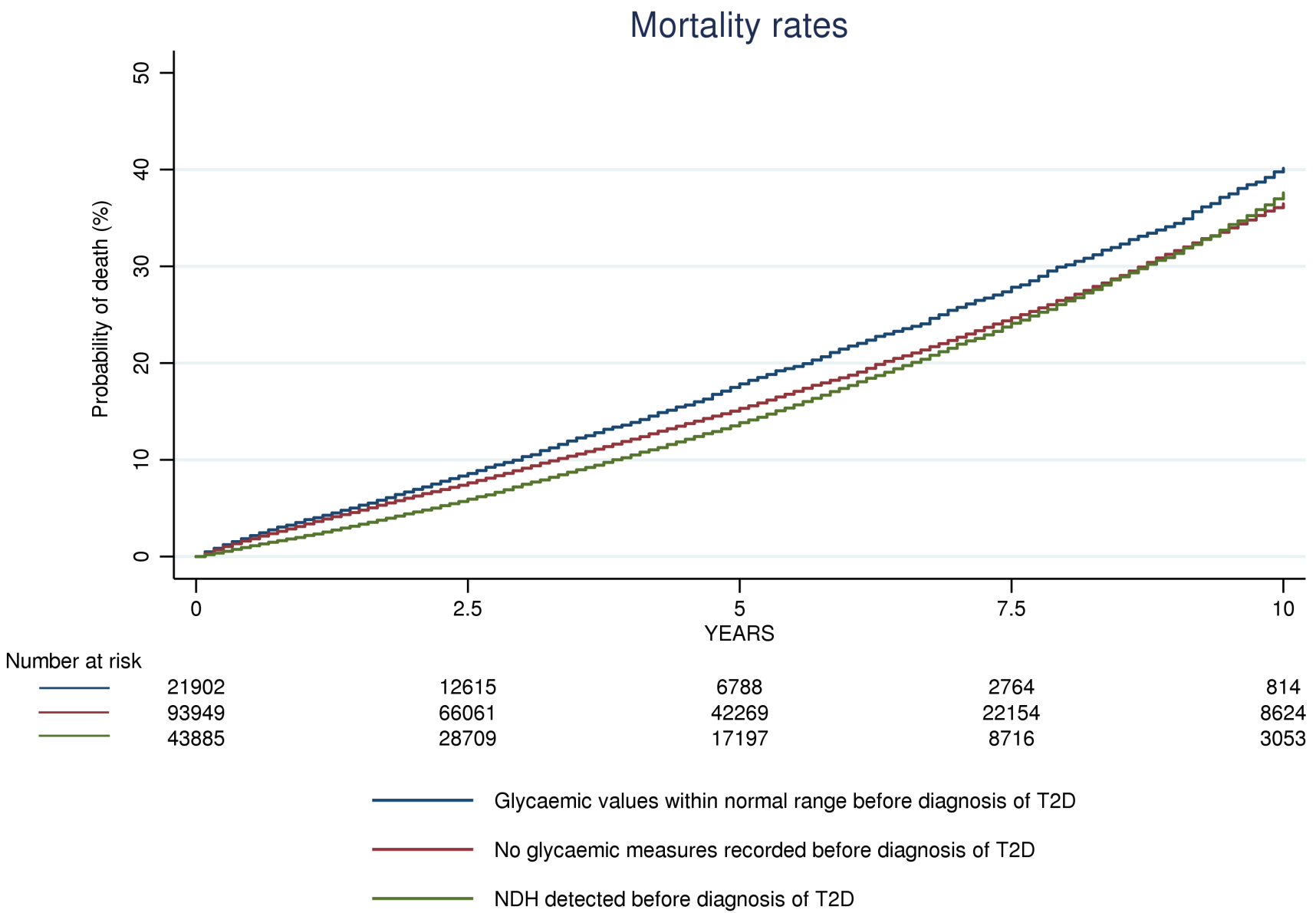

Mortality rates
Probability of death (%)
0
10
20
30
40
50
0
2.5
5
7.5
10
YEARS
Number at risk
21902 12615 6788 2764 814
93949 66061 42269 22154 8624
43885 28709 17197 8716 3053
Glycaemic values within normal range before diagnosis of T2D
No glycaemic measures recorded before diagnosis of T2D
NDH detected before diagnosis of T2D

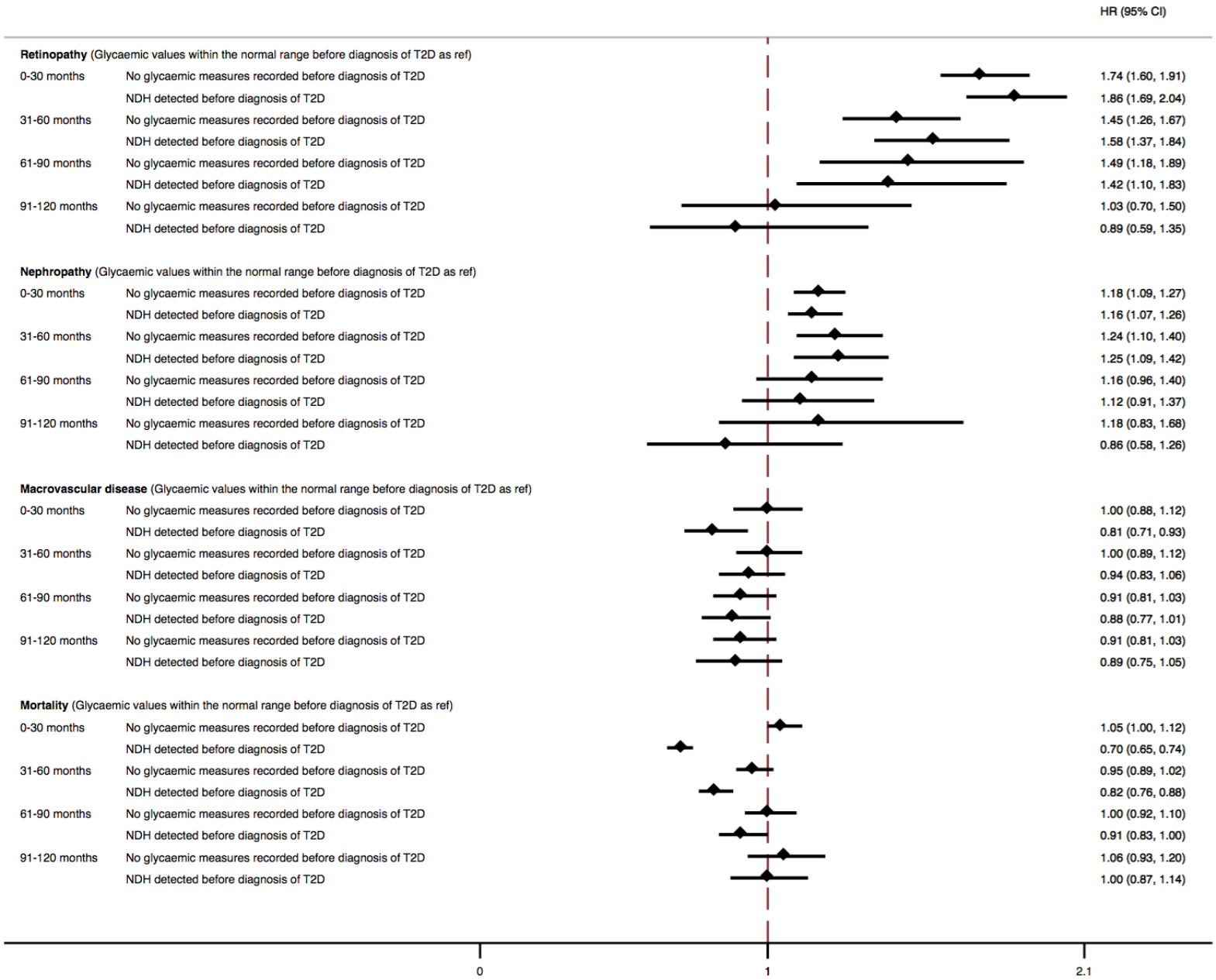
Figure 13. Association between detection of NDH before the diagnosis of T2D and incident vascular diseases and mortality following the diagnosis of T2D

***Notes*:** Abbreviations: T2D = Type 2 diabetes, NDH = non-diabetic hyperglycaemia, FPG = fasting plasma glucose, OGTT = glucose tolerance test, HbA1c = glycated haemoglobin.

Glycaemic status was defined based on diagnostic codes and clinical data within three years before the diagnosis of Type 2 diabetes using the WHO/International Expert Committee criteria as follows: 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%.

Hazard ratios are obtained from time-partitioned Cox regression models partitioning the 10-year follow-up period into four equal time segments.

Models were adjusted for age, sex, ethnicity (White, South-Asian, Black, Other, and Unknown), smoking status (smoker, ex-smoker, non-smoker), body mass index, systolic and diastolic blood pressure, total cholesterol, baseline HbA1c, number of co-morbidites, medications (ACEi/ARB, other anti-hypertensive, lipid-lowering, biguanides, sulphonylureas, other anti-diabetic medications), number of primary care visits in the year prior the T2D diagnosis, Index of Multiple Deprivation quintiles, and year of diagnosis of Type 2 diabetes.


HR (95% CI)
Retinopathy (Glycaemic values within the normal range before diagnosis of T2D as ref)
0-30 months
No glycaemic measures recorded before diagnosis of T2D
1.74 (1.60, 1.91)
NDH detected before diagnosis of T2D
1.86 (1.69, 2.04)
31-60 months
No glycaemic measures recorded before diagnosis of T2D
1.45 (1.26, 1.67)
NDH detected before diagnosis of T2D
1.58 (1.37, 1.84)
61-90 months
No glycaemic measures recorded before diagnosis of T2D
1.49 (1.18, 1.89)
NDH detected before diagnosis of T2D
1.42 (1.10, 1.83)
91-120 months
No glycaemic measures recorded before diagnosis of T2D
1.03 (0.70, 1.50)
NDH detected before diagnosis of T2D
0.89 (0.59, 1.35)
Nephropathy (Glycaemic values within the normal range before diagnosis of T2D as ref)
0-30 months
No glycaemic measures recorded before diagnosis of T2D
1.18 (1.09, 1.27)
NDH detected before diagnosis of T2D
1.16 (1.07, 1.26)
31-60 months
No glycaemic measures recorded before diagnosis of T2D
1.24 (1.10, 1.40)
NDH detected before diagnosis of T2D
1.25 (1.09, 1.42)
61-90 months
No glycaemic measures recorded before diagnosis of T2D
1.16 (0.96, 1.40)
NDH detected before diagnosis of T2D
1.12 (0.91, 1.37)
91-120 months
No glycaemic measures recorded before diagnosis of T2D
1.18 (0.83, 1.68)
NDH detected before diagnosis of T2D
0.86 (0.58, 1.26)
Macrovascular disease (Glycaemic values within the normal range before diagnosis of T2D as ref)
0-30 months
No glycaemic measures recorded before diagnosis of T2D
1.00 (0.88, 1.12)
NDH detected before diagnosis of T2D
0.81 (0.71, 0.93)
31-60 months
No glycaemic measures recorded before diagnosis of T2D
1.00 (0.89, 1.12)
NDH detected before diagnosis of T2D
0.94 (0.83, 1.06)
61-90 months
No glycaemic measures recorded before diagnosis of T2D
0.91 (0.81, 1.03)
NDH detected before diagnosis of T2D
0.88 (0.77, 1.01)
91-120 months
No glycaemic measures recorded before diagnosis of T2D
0.91 (0.81, 1.03)
NDH detected before diagnosis of T2D
0.89 (0.75, 1.05)
Mortality (Glycaemic values within the normal range before diagnosis of T2D as ref)
0-30 months
No glycaemic measures recorded before diagnosis of T2D
1.05 (1.00, 1.12)
NDH detected before diagnosis of T2D
0.70 (0.65, 0.74)
31-60 months
No glycaemic measures recorded before diagnosis of T2D
0.95 (0.89, 1.02)
NDH detected before diagnosis of T2D
0.82 (0.76, 0.88)
61-90 months
No glycaemic measures recorded before diagnosis of T2D
1.00 (0.92, 1.10)
NDH detected before diagnosis of T2D
0.91 (0.83, 1.00)
91-120 months
No glycaemic measures recorded before diagnosis of T2D
1.06 (0.93, 1.20)
NDH detected before diagnosis of T2D
1.00 (0.87, 1.14)
0
1
2.1

6.4.4 Secondary analysis

6.4.4.1 Comparison between different diagnostic criteria for the detection of NDH

Results obtained using NICE and ADA criteria for the detection of NDH were broadly similar to results obtained using WHO/IEC criteria, although in some cases differences in hazards of the study outcomes persisted for a longer study period adopting NICE-ADA criteria (Appendix Table 6-9). For instance, differences in hazard ratios of incident retinopathy between groups were found for the study periods 0-30, 31-60, and 61-90 months regardless of the adopted diagnostic criterion for the detection of NDH. However, for those without glycaemic measures recorded in the three years before the diagnosis of T2D hazard of incident retinopathy was 94% greater (HR 1.94, 95%CI 1.37-2.73) then for those with glycaemic values within the normal range also in the study period 91-120 months when applying the NICE criteria. Similarly, differences in hazard ratios of incident nephropathy persisted for a longer period from the diagnosis of T2D when adopting both NICE and ADA criteria. Specifically, as compared with individuals with glycaemic measures within the normal range in the three years before the diagnosis of T2D, hazards of incident nephropathy were 31% and 28% greater using the NICE and ADA criteria, respectively, in individuals without glycaemic measures recorded in the period 61-90 months following the diagnosis of T2D (NICE: HR 1.31, 95%CI 1.02-1,70; ADA: HR 1.28, 95%CI 1.00-1.62). Interestingly, following the diagnosis of T2D differences in the hazard ratios of incident macrovascular disease observed in the study period 0-30 months between those with prior NDH detected and normoglycaemic values were perfectly comparable when using the WHO/IEC and ADA criteria for the detection of NDH, while when adopting the NICE criteria differences were only observed in the study period 61-90 months. Specifically, as compared with individuals with glycaemic values within the normal range in the three years before the diagnosis of T2D, those with NDH detected and those without glycaemic measures recorded before

the diagnosis of T2D had, respectively, 17% and 15% lower hazard of incident macrovascular disease in the study period 61-90 months (NDH: HR 0.83, 95%CI 0.71-0.97; no glycaemic measures recorded: HR 0.85, 95%CI 0.73-1.00) when adopting the NICE criteria. Findings regarding differences in mortality following the diagnosis of T2D were overall quite similar when comparing different diagnostic criteria.

6.4.4.2 Assignment of a diagnostic code for NDH

No clear differences were observed in the hazard ratios of incident vascular disease following the diagnosis of T2D in individuals with prior NDH status with and without an assigned diagnostic code for NDH (Appendix Table 6-8). On the contrary, those with a diagnostic code assigned for NDH had lower hazard of mortality in the first five years following the diagnosis of T2D (Appendix Table 9). As compared with individuals with glycaemic values within the normal range in the three years before the diagnosis of T2D, those with NDH detected without a diagnostic code assigned had 25% and 11% decreased hazard of mortality in the study period 0-30 and 31-60 months, respectively (0-30 months: HR 0.75, 95%CI 0.70-0.81; 31-60 months: HR 0.89, 95%CI 0.82-0.97), while those with NDH detected with a diagnostic code assigned had 37% and 26% decreased hazard of mortality in the study period 0-30 and 31-60 months, respectively (0-30 months: HR 0.63, 95%CI 0.58-0.69; 31-60 months: HR 0.74, 95%CI 0.67-0.81).

6.5 Discussion

In this population-based retrospective cohort study including individuals newly diagnosed with T2D between 1 January 2004 and 30 September 2017 and registered with CPRD practices in England, I found that differences in hazard ratios of incident microvascular disease according to glycaemic

status in the three years before the diagnosis of T2D persisted up to 7.5 years following the diagnosis of T2D. As compared with individuals with glycaemic status within the normal range in the three years before the diagnosis of T2D, those detected with prior NDH had increased hazard of incident retinopathy in the first 7.5 years following the diagnosis of T2D, while increased hazard of incident nephropathy was observed within the first 5 years. Estimated differences were wider for retinopathy than nephropathy, although in both cases they progressively attenuated over the study period. In the 10 years following the diagnosis of T2D no differences were observed in incident rates of macrovascular disease according to glycaemic status before the diagnosis of T2D, with the only exception for those detected with prior NDH who had lower rates in the first 2.5 years following the diagnosis of T2D then those with prior normoglycaemic status. Individuals detected with NDH in the three years before the diagnosis of T2D has also lower mortality rates than those with prior normoglycaemic status in the 5 years following the diagnosis of T2D. Similarly to what found for microvascular disease, differences progressively attenuated over the study period.

This study specifically focused on how the risk of incident vascular disease and mortality following the diagnosis of T2D differed in individuals with T2D according to glycaemic testing and status before the T2D diagnosis. Findings from this study are important to better assess the long-term risk of vascular disease and mortality associated with prolonged exposure to hyperglycaemia and, therefore, improve characterisation of the population which would benefit the most from preventative interventions. In line with findings from the previous research chapter, prior NDH status was associated with increased risk of microvascular disease, with differences persisting up to 7.5 years from the diagnosis of T2D. In the majority of people who progress to T2D, an abrupt increase in glycaemic measures has been described within two to three years before diagnosis (121, 130). In my study, the higher burden of retinopathy among individuals with NDH compared with

individuals with normoglycemia might be explained by prolonged exposure to mild hyperglycaemia. Interestingly, differences observed for nephropathy between groups with different testing and glycaemic status before the diagnosis of T2D were less pronounced then for retinopathy. These findings suggest that the association between pre-existing NDH and incident nephropathy might not be as strong as that for retinopathy, which is in line with previous findings (130, 143).

In line with findings from the previous research chapter, individuals with glycaemic values within the normal range had the lowest crude rates and adjusted hazard ratios of incident microvascular disease. As this subgroup of individuals might be characterised by a more rapid progression to T2D or could represent people with a similar glycaemic trajectory leading to diabetes but with a diagnosis earlier in the natural history of the disease (see the lower HbA1c value at diagnosis in this group), or most likely a combination of these mechanisms, these findings might be explained by the shorter exposure to the negative effects associated with hyperglycaemia. These findings are also compatible with a potential surveillance bias: people with any cardiovascular disease are more likely to be screened for diabetes and intermediate hyperglycaemia compared with the general population and thus have a higher chance of earlier diagnosis of diabetes. However, individuals with glycaemic values within the normal range also had higher hazard of incident macrovascular and mortality then the NDH group in the 2.5-5 years following the diagnosis of T2D. Whilst the highest mortality might be, at least partially, considered as additional feature of this fast-progressing group, another possible explanation is that this group might have been tested and diagnosed with T2D earlier than the NDH group due to other co-existing chronic conditions (in fact, they had larger number of co-existing chronic conditions and primary care visits in the year before the diagnosis of T2D).

Importantly, 59% of individuals did not have a recorded glycaemic measurement in the three years before T2D diagnosis. This proportion was 61-62% when considering populations at baseline without microvascular or macrovascular disease. Individuals without glycaemic measurements had a notably higher mean HbA1c following T2D diagnosis compared with those with glycaemic testing (with or without NDH), potentially indicating late diagnosis of T2D and leading to delayed treatment. While this is reflected by higher hazard of incident microvascular disease, I did not find differences in hazard ratios of incident macrovascular disease and mortality as compared with those with glycaemic values within the normal range before the diagnosis of T2D. A possible explanation for these findings is that this group might have been tested less frequently because of the lower cardiovascular risk, partially reflected by the lower number of co-existing chronic conditions and proportion taking anti-hypertensive medications at time of T2D diagnosis.

Only small variations in findings were found across NDH sub-groups defined by the different diagnostic criteria. Results for retinopathy, which is the outcome more strongly associated with prior glycaemic status before the diagnosis of T2D, were almost perfectly overlapping when comparing findings by different diagnostic criteria, while the small differences were mostly seen for the other outcomes, which have shown to be more weakly associated with prior glycaemic status. This might be partially explained considering that different diagnostic test and thresholds identify different groups of individuals who differ in progression rates to Type 2 diabetes and risk of associated morbidity (96, 131, 216, 217).

6.5.1 Strengths and limitations

To my knowledge, this is the first large population-based study to examine associations between glycaemic status before T2D diagnosis and the risk of incident microvascular and macrovascular disease following the diagnosis of T2D. I used routinely collected primary and secondary care data representative of the English population to better understand these associations in real world settings. Additional study limitations include the presence of missing data for clinical variables such as blood pressure, BMI, total cholesterol, and HbA1c. However, I overcame the latter issue by using multiple imputation by chained equations. It was not possible to assess differences in adherence to lifestyle interventions, as I did not have data on diet and physical activity. Differences in the risk of incident vascular outcomes and mortality have often been assessed using survival analysis methods that account for competing interests (i.e. Fine and Gray competing risk regression models) (241, 242). However, as previously discussed, I have employed Cox proportional hazard regression models to assess differences in the hazard of event occurrence across groups to directly quantify the hazard ratios among those individuals who are actually at risk of developing the condition. However, this method might lead to overestimation of the hazard when competing interests are present, because subjects with a competing (and thus censored) event are treated as if they could experience the event of interest in the future (241, 242). Finally, when using routinely collected data, concerns have been raised about miscoding, misclassification and misdiagnosis. However, CPRD is subject to regular quality checks and is widely used for health research (199).

6.5.2 Implications for clinical practice

Individuals with NDH detected in the three years before the diagnosis of T2D had greater risk of retinopathy and nephropathy but also reduced risk of macrovascular disease and all-cause mortality following the diagnosis of T2D then individuals with prior normoglycaemic status. Differences in

incident microvascular diseases were greater than those found for macrovascular disease and mortality. The group of individuals with glycaemic values within the normal range in the three years before the diagnosis of T2D might include 'fast-progressors', characterised by specific clinical features such as more rapid T2D progression and increased mortality risk. However, this group might also include individuals incorrectly identified as normoglycaemic or tested for glycaemia due to the presence of other medical conditions. Appropriate risk assessment and glycaemic testing has, therefore, significant clinical implications for T2D-related outcomes, considering the long-term risk of microvascular disease associated with prolonged exposure to hyperglycaemia. A major consideration is whether targeted preventive strategies that identify individuals at increased risk of T2D for interventions would provide opportunities for vascular risk reduction (220, 233), considering that major benefits are likely to occur from early diagnosis and treatment (166). A multifactorial detection strategy for NDH would improve identification and management of other risk factors for T2D as well as prevent manifestation of vascular disease (130, 240).

6.6 Conclusion

In this population-based retrospective cohort study including individuals newly diagnosed with T2D between 1 January 2004 and 30 September 2017 those detected with NDH had increased hazard of incident microvascular disease up to 7.5 years following the diagnosis of T2D as compared with individuals with glycaemic values within the normal range before the diagnosis of T2D. Estimated differences were greater for retinopathy then nephropathy, although in both cases they progressively attenuated over the study period. Timely testing and identification of NDH and specific clustering of NDH with other risk factors for T2D might prompt earlier assessment for risk

factors and tailored cardiovascular risk reduction strategies during the NDH phase to reduce the burden of vascular disease following the diagnosis of T2D.

7 Evaluation of the Diabetes Screening Component the NHS Health Check programme: a Retrospective Cohort Study

7.1 Abstract

7.1.1 Introduction

T2D is increasing but the effectiveness of large-scale diabetes screening programmes is debated. I assessed the associations between coverage of a national cardiovascular and diabetes risk assessment programme in England (NHS Health Check) and detection and management of incident cases of NDH and T2D.

7.1.2 Methods

Retrospective analysis employing propensity score covariate adjustment method of prospectively collected data of 348,987 individuals aged 40-74 years and registered with 455 general practices in England (January 2009-May 2016) participating in the CPRD. I examined differences in diagnosis of NDH and T2D, and changes in blood glucose levels and cardiovascular risk score between individuals registered with general practices with different levels (tertiles) of programme coverage.

7.1.3 Results

Over the study period 7,126 cases of NDH and 12,171 cases of T2D were detected. Compared with low coverage practices, incidence rate of detection in medium and high coverage practices were 15% and 19% higher for NDH and 10% and 9% higher for T2D, respectively. Individuals with NDH in high coverage practices had 0.2 mmol/L lower mean fasting plasma glucose and 0.9% lower cardiovascular risk score at follow-up.

7.1.4 Conclusions

General practices actively participating in the programme had higher detection of NDH and T2D and improved management of blood glucose and cardiovascular risk factors.

7.2 Introduction

Globally the prevalence of diabetes is on the rise, with projections suggesting that the number of adults with the condition will increase from 425 million to 642 million between 2016 and 2040 (1, 3). Worldwide it is estimated that 175 million people have undiagnosed diabetes (247) and 230 million people have NDH (1, 248) (94, 96). The scale of this problem has led to the introduction of population-based screening programmes for diabetes in some countries (114). However, as discussed in Chapter 2, the evidence supporting the widespread introduction of such programmes is mixed (114, 163-168). Randomised clinical trials have not demonstrated improvements attributable to diabetes screening on long-term health outcomes including microvascular and macrovascular diabetes and mortality (170, 174, 249). While modelling studies indicate some long-term benefit from screening (175, 176), predictions are highly sensitive to the underlying assumptions and these may not reflect real-world conditions (178). This lack of evidence has led many government and professional organisations, including the UK's National Screening Committee, to advise against systematic population-based screening (169, 170).

In England in 2009 the NHS Health Check programme was launched and rolled out nationally. The NHS Health Check programme is one of the world's largest cardiovascular risk assessment and management programmes. Although its primary focus is cardiovascular risk assessment, the programme also includes a diabetes risk assessment and screening component (Figure 2, Chapter 2) (250). A strong political commitment to the programme within the context of a health system with universal coverage, and with well-developed primary care and high penetration of electronic health records, presents an important opportunity to determine whether population-based screening for diabetes produces health

benefit in real world settings. To date, no previous studies have reported the evaluation of the diabetes screening component of the Health Check programme.

This retrospective cohort study aims to determine whether the NHS Health Check programme increased the detection of T2D and NDH, and improved control of blood glucose and cardiovascular risk factors among newly diagnosed cases. Coverage of the NHS Health Check programme within general practice (defined for each general practice as the number of programme attendees divided by the total number of individuals registered with the practice who are eligible to attend the programme) was considered as exposure. I consider this approach superior to directly comparing outcomes between Health Checks attendees and non-attendees for several reasons. Firstly, the programme is largely delivered through general practices but there have been substantial variations in implementation (0-73% programme coverage in 2013) (195, 197), due to administration of the programme at a local level, differences in the characteristics of practice populations (195) and ongoing controversy about its effectiveness. Secondly, programme coverage is a proxy of general practices' behaviour towards prevention. General practices' active engagement in the NHS Health Check programme may be associated with increased opportunistic screening outside of the programme that would not be captured by comparing attendees and non-attendees. This is supported by the finding of a national evaluation of the NHS Health Check that showed a strong underlying trend of improvements in the testing and management of CVD risk factors among those who did not attend the programme (251). Thirdly, similar analytical approaches are often used in policy evaluations as well as clinical trials (i.e. intention-to-screen analysis) to quantify benefits among people targeted by the intervention irrespective of their actual participation, providing an estimate of the effectiveness of the intervention (252).

7.3 METHODS

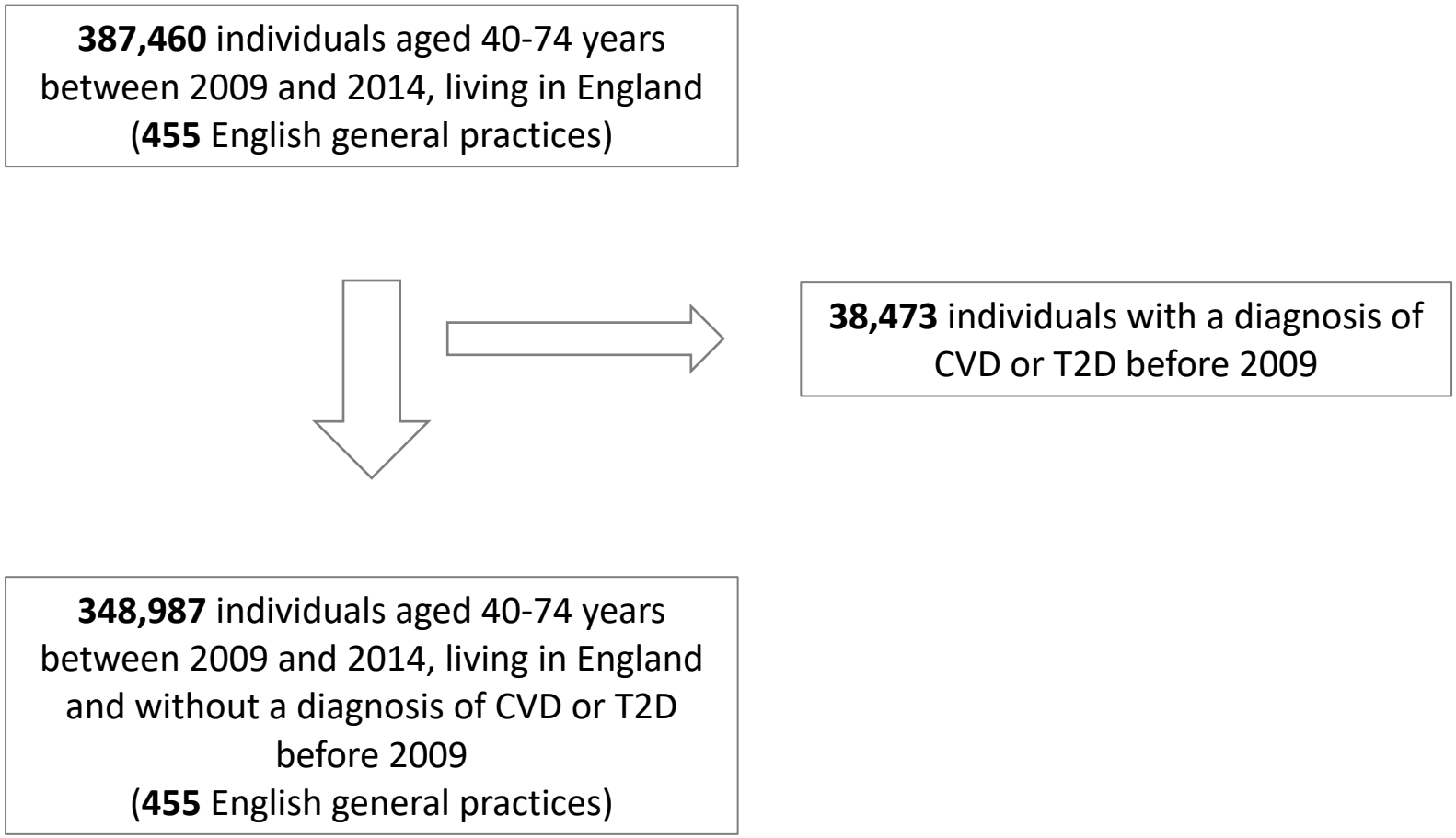
7.3.1 Study design

This is a retrospective cohort study that compared selected health outcomes of individuals registered with general practices with different levels of programme coverage (tertiles). Analyses were controlled for individuals' likelihood of accessing the programme using propensity score regression adjustment. Individuals were included in the analyses irrespective of their participation in the programme, similarly to an intention-to-screen design (249).

7.3.2 Data Source and Study Population

As explained in Chapter 3 I used data from the CPRD, which were linked to hospital admission and mortality data (253). Briefly, I obtained data for a computer-selected random sample of 387,460 individuals aged 40-74 years who were continuously registered with 455 CPRD general practices in England between 1 January 2009 and 31 December 2014. After excluding individuals with a diagnosis of CVD and T2D before 1 January 2009, 348,987 individuals eligible for the NHS Health Check programme were included in this study (Figure 14). To allow a longer follow-up of the study population, I obtained an update of CPRD data that capture study outcomes up to 31 May 2016.

Figure 14. Study tree showing final sample included in the current study.



Notes: adapted from Palladino R, Vamos EP, Chang KC, Khunti K, Majeed A, Millett C. Evaluation of the Diabetes Screening Component of a National Cardiovascular Risk Assessment Programme in England: a Retrospective Cohort Study. Sci Rep. 2020;10(1):1231

7.3.3 NHS Health Check programme coverage

I defined practice-level Health Check coverage during the first three years of the programme (2009-2011) as the number of attendees divided by the number of Health Check eligible individuals registered with the practice. I identified Health Check attendance using an established algorithm (195, 198) because the coding system in general practice electronic records for Health Check attendance was poorly implemented during early phase of the programme (195). I considered programme coverage in the first three years as the exposure to allow sufficient follow-up time to detect changes in the outcome measures following programme implementation. I divided general practices into tertiles based on their Health Check coverage during the first three years of the programme. Individuals were therefore categorised into 3 groups according to their registered practices' tertile of Health Check coverage.

7.3.4 Diabetes risk score

I used 'QDiabetes' (254), a validated diabetes risk assessment tool (180) to compute individuals' diabetes risk score (DRS) on the 1st January 2009. Individuals with a DRS ≥ 10 were considered at high risk of T2D (180, 254).

7.3.5 Outcomes

The diagnosis of NDH was based on Read codes (Appendix Table 10) or laboratory blood tests following the WHO diagnostic laboratory criteria for NDH (FPG: 6.1-6.9 mmol (111 mg/dl and 125 mg/dl) or OGTT 7.8-11.1 mmol/L or HbA1c: 42 to 47 mmol/mol (6.0-6.4%)). New T2D diagnoses were determined using both primary care (Read codes) and hospital admission records data (International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes), as previously recommended (209). Only a

small proportion (3%) of individuals at high risk of T2D at baseline had data on OGTT recorded, therefore, I present FPG and HbA1c as glycaemic outcome measures in this study.

Data on study outcomes obtained for each cohort year included SBP, DBP, BMI, smoking status, and 10-year modelled CVD risk score. Smoking status was defined as smoker, non-smoker or ex-smoker. CVD risk score was estimated based on the 'QRISK2' algorithm, as recommended by the National Institute for Health and Care Excellence (255).

Data on FPG, HbA1c, total cholesterol and prescription of oral anti-diabetic medications and statins, were obtained for each cohort year for people at high risk of T2D at baseline, and for individuals with newly detected T2D and NDH for each year following detection. Given that the use of HbA1c was introduced as a diagnostic test in UK national clinical guidelines in 2012, FPG was more widely available in the study, with a high proportion of missing data for HbA1c (254). Therefore, I constructed an additional binary variable for a combined measure of blood glucose as follows: NDH: FPG mmol/L 6.1-6.9 mmol/L or HbA1c 42 to 47 mmol/mol (6.0-6.4%; T2D: FPG ≥ 7.0 mmol/L or HbA1c ≥ 48 mmol/m (6.5%)) (254). The binary variable was coded as '1' if blood glucose levels were below the clinical criteria to define NDH or T2D (e.g. for individuals at high risk of T2D and with incident NDH: FPG < 6.1 mmol/L and HbA1c < 42 mmol/m; for those with incident T2D: FPG < 7.0 mmol/L and HbA1c < 48 mmol/m).

7.3.6 Study covariates

Study covariates included practice and patient characteristics. Practice characteristics included English geographic region, IMD, and case-load (defined as the number of individuals eligible for the Health Check programme within the practice). Individual characteristics included age, sex, ethnicity (white, non-white or missing), number of co-morbidities (using a previously published list of comorbidities (225)), and prescription of anti-hypertensive, antidiabetic, lipid lowering and steroid medications.

7.3.7 Statistical analysis

I aimed to compare study outcomes between individuals registered with general practices with different levels of participation (defined as the tertiles of practice coverage of eligible individuals) in the Health Check programme. I adopted a propensity score regression adjustment in order to reduce selection bias (256). I estimated three sets of propensity scores using logistic regression models. Each model generated propensity scores based on the probability of individuals being registered with a practice with a specific level of programme coverage compared with the other groups (low coverage vs. medium coverage; low coverage vs. high coverage; medium coverage vs. high coverage). All logistic regression models were adjusted for baseline variables that may be associated with programme coverage, this included age, sex, ethnicity, BMI, SBP and DBP, IMD, case-load and geographical region.

To reduce individuals' missing data at baseline, in line with previous research part of this doctoral thesis (Chapter 5 and 6) I used the latest clinical data for each individual within 5 years before the start of the study period (198). I then used multiple imputation by chained equations (10 copies) to estimate missing data for BMI and blood pressure at baseline because these variables were needed to calculate the baseline DRS and the propensity scores. I included the following covariates in the imputation model: age, gender, ethnicity, smoking status, number of co-morbidities, anti-hypertensive medication, lipid-lowering medication, steroid medication, practice IMD and region. Estimates were combined using Rubin's rule. Individuals with missing data on smoking were classified as non-smokers if there was no indication in the past of the patient being a smoker (257).

I assessed the unadjusted differences in the population characteristics between individuals registered with low, medium and high programme coverage practices using Chi-square, t-

test and ANOVA, as appropriate. Cox Proportional Hazards regression models were used to estimate the hazard ratios for the detection of NDH and T2D among the three groups, using the low coverage group as reference. These analyses were conducted on different sub-populations: i) total sample ii) individuals at high risk of T2D (DRS at baseline ≥ 10). Individuals were considered at risk for the entire study period and censored in case of death. The assumption of parallel hazard functions over time was met. To test this assumption I examined plots of log(−log survival time) against log survival time and Schoenfeld residuals against survival time. In addition, I used linear regression of Schoenfeld residuals on time to test for independence between residuals and time. I examined whether the programme was associated with improved risk factor control by comparing individuals' outcome data between low, medium, high programme coverage groups during the study period (1 January 2009-31 May 2016). I used multilevel mixed-effect regression models to account for the hierarchical structure of the data when computing standard errors. I calculated the interclass correlation coefficient (ICC) to test for interdependence of clusters within my study population.(258). The ICC expresses the proportion of variance in the outcome variable that can be explained by grouping structure of the hierarchical model. (258). In multilevel modelling, failing to account for correlated structure of the observations might lead to smaller estimated standard errors, which might lead to incorrect inference. Specifically, I compared a two-level model, accounting for repeated measures within each individual, and a three-level model, accounting for multiple individuals registered with same general practices. Considering that all ICC for the three-level model were either below or around 0.1, which can be considered as a modest indicator of correlation within the cluster, in line with previous research evaluating the NHS Health Check programme using similar CPRD data extractions (195, 251, 259), I analysed the data employing two-level mixed-effect

regression models. Specifically, I used mixed-effects linear regression models for continuous outcomes and mixed-effects logistic regression models for binary outcomes. For continuous outcomes, including FPG, HbA1c, SBP, DBP, BMI, total cholesterol, and QRISK2, I calculated the annual mean value of the outcome in case of multiple measurements within a year for each individual. For binary outcomes including blood glucose targets, smoking status and prescription of antidiabetic medication, I considered the latest data recorded within a year for each individual. The mixed-effect analyses were conducted on different sub-populations: i) total sample ii) individuals at high risk of T2D (DRS at baseline ≥ 10) iii) individuals with newly detected NDH iv) individuals with newly diagnosed T2D. For the third and fourth models, the time period was defined as the time between the year of diagnosis and the end of the study period (31 May 2016). Analyses on FPG, HbA1c, and total cholesterol were only performed on individuals at high risk of T2D and with newly detected NDH and T2D because monitoring of these parameters is only recommended by national guidance for people at high risk of T2D or diagnosed T2D (254). Similarly, prescription of anti-diabetic medications and statins were only analysed in sub-populations 2, 3, and 4 in order to assess differences in pharmaceutical approach in individuals at high risk or with incident NDH or T2D. Assumptions of the mixed-effect linear regression models were tested graphically for the violations against normality of random effects and homogeneity of residual variance. No evidence of violations against assumptions and no apparent outliers were identified. These models were adjusted for year (of the outcome recorded), and for baseline covariates including a combination of both practice (region and IMD) and individual (age, gender, ethnicity, smoking status, BMI, and anti-hypertensive medication) characteristics. All models were further adjusted for the three propensity scores generated.

Sensitivity analyses were performed using regression models without adjustment for propensity scores. Considering the percentage of missing data for the FPG, HbA1c, and total cholesterol outcomes (13.6% for total cholesterol, 28.5% for fasting plasma glucose, and 67.6% for HbA1c in individuals at high risk of T2D), I performed complete-case analysis. Percentages of missing data are reported in Appendix Table 11.

7.4 RESULTS

Coverage of the Health Check programme between 2009 and 2011 ranged from 0.5 to 61.6% with median values (interquartile range) of: i) 8.5% (6.3 to 10.2%); ii) 15.4% (13.6 to 17.5%); and iii) 26.3% (22.8 to 34.6%) among low, medium, and high programme coverage practices, respectively. The three groups were largely similar in terms of sex and mean age at baseline, while they differed in ethnicity, smoking status, BMI, and prescription of anti-hypertensive treatment (Table 5). At baseline, the mean diabetes risk score was 5.9 in the total study population with 17.7% of the individuals being at high risk of T2D (DRS≥10). Mean DRS and percentage of individuals at high risk of T2D varied significantly between groups (Table 6).

7.4.1 Incident cases of NDH and T2D

Mean follow-up of the entire study population was 7.8 ± 0.9 years, while for those at high risk of T2D at baseline mean follow-up was 6.8 ± 1.6 years. 0.8% of the study population met the diagnostic criteria for NDH at baseline, while 7,126 cases (2.3%) were detected during the study period corresponding to an incidence of newly detected NDH of 0.23 per 1000 person-years. Incidence rates were 15% and 19% higher for the medium and high coverage practices, respectively (medium coverage practices: HR 1.15, 95%CI (1.08-1.22); high coverage practices: 1.19 (1.11-1.27)), compared with the low coverage practices. Among patients at high risk of T2D at baseline, incidence rate of newly detected NDH in high

coverage practices was 23% higher than in low coverage practices (HR 1.23 (1.11-1.37)).

Over the study period, 12,171 new cases of T2D were diagnosed, corresponding to an incident rate of 0.64 per 1000 person-years. Incident rates were 10% and 9% higher in the medium and high coverage practices respectively (medium coverage practices: 1.10 (1.05 – 1.15); high coverage practices: 1.09 (1.03 – 1.14), compared with low coverage practices. Further increase in rates of new T2D diagnoses was evident when restricting the analyses to individuals at high risk of diabetes (Table 6, Figure 15).

Table 5. Characteristics of study population at baseline according to the general practices' coverage of the NHS Health Check programme and individuals' diabetes risk score.

Notes: Results are reported as proportion for categorical variables and mean and standard deviation for continuous variables. Baseline differences between individuals registered with a practice with low, medium, and high programme coverage ('total column' for each group) were tested using Chi-square, T-test, and analysis of covariance, as appropriate. Results are shown as p-value in the last column. Legend: *Tertiles of general practices' coverage of the NHS Health Check Programme were defined based on programme coverage during the first three years after its implementation (2009-11). Adapted from Palladino R, Vamos EP, Chang KC, Khunti K, Majeed A, Millett C. Evaluation of the Diabetes Screening Component of a National Cardiovascular Risk Assessment Programme in England: a Retrospective Cohort Study. Sci Rep. 2020;10(1):1231

	Low Coverage*		Medium Coverage*		High Coverage*		Total		
	DRS ≥ 10	**TOTAL**	**DRS ≥ 10**	**TOTAL**	**DRS ≥ 10**	**TOTAL**	**DRS ≥ 10**	**TOTAL**	**P VALUE**
N	22860 17.4%	131160 100.0%	21624 17.5%	123716 100.0%	17299 18.4%	94111 100.0%	61783 17.7%	348987 100.0%	
GENDER									
Female	39.8%	49.8%	41.4%	49.8%	42.4%	49.8%	41.1%	49.7%	0.849
AGE (years)	58.7 (9.8)	50.4 (10.7)	58.1 (10.3)	49.9 (10.6)	57.8 (9.2)	49.8 (8.7)	58.2 (9.9)	50.1 (10.6)	p<0.001
ETHNICITY									
White	50.1%	47.5%	52.1%	48.7%	60.0%	54.4%	54.6%	49.8%	p<0.001
Non white	2.3%	3.7%	4.8%	7.3%	5.9%	8.8%	4.2%	6.4%	
Missing ethnicity	47.6%	48.8%	43.1%	44.0%	34.1%	36.8%	42.2%	43.9%	p<0.001
PRACTICE IMD									
1Q – least deprived	17.5%	20.0%	17.4%	22.2%	11.0%	12.7%	15.6%	18.8%	p<0.001
2Q	22.1%	23.8%	19.9%	20.7%	19.2%	20.5%	20.5%	21.8%	
3Q	28.7%	28.1%	21.0%	20.9%	13.8%	14.4%	21.8%	21.8%	
4Q	19.2%	17.5%	22.7%	20.3%	24.1%	23.7%	21.8%	20.2%	p<0.001
5Q – most deprived	12.4%	10.6%	19.0%	15.9%	31.9%	28.7%	20.2%	17.4%	
SMOKING STATUS									
Non-smoker	50.9%	60.0%	48.8%	59.0%	46.6%	56.0%	48.9%	58.6%	p<0.001
Ex-smoker	28.00%	18.1%	27.3%	17.4%	27.0%	17.5%	27.5%	17.7%	p<0.001
Current smoker	21.16%	21.9%	23.9%	23.6%	26.4%	26.5%	23.6%	23.7%	p<0.001
BMI (kg/m2)	32.6 (5.2)	27.0 (6.5)	32.6 (5.4)	27.1 (6.9)	32.7 (5.4)	27.3 (5.7)	32.8 (5.9)	27.1 (5.9)	
ANTHYPERTENSIVE TREATMENT	36.5%	11.6%	34.6%	11.0%	36.7%	12.3%	35.8%	15.6%	p<0.001
DIABETES RISK SCORE	17.3 (8.6)	5.8 (7.2)	17.5 (9.6)	5.8 (7.0)	17.9 (8.7)	6.2 (7.7)	17.6 (9.1)	5.9 (8.2)	p<0.001

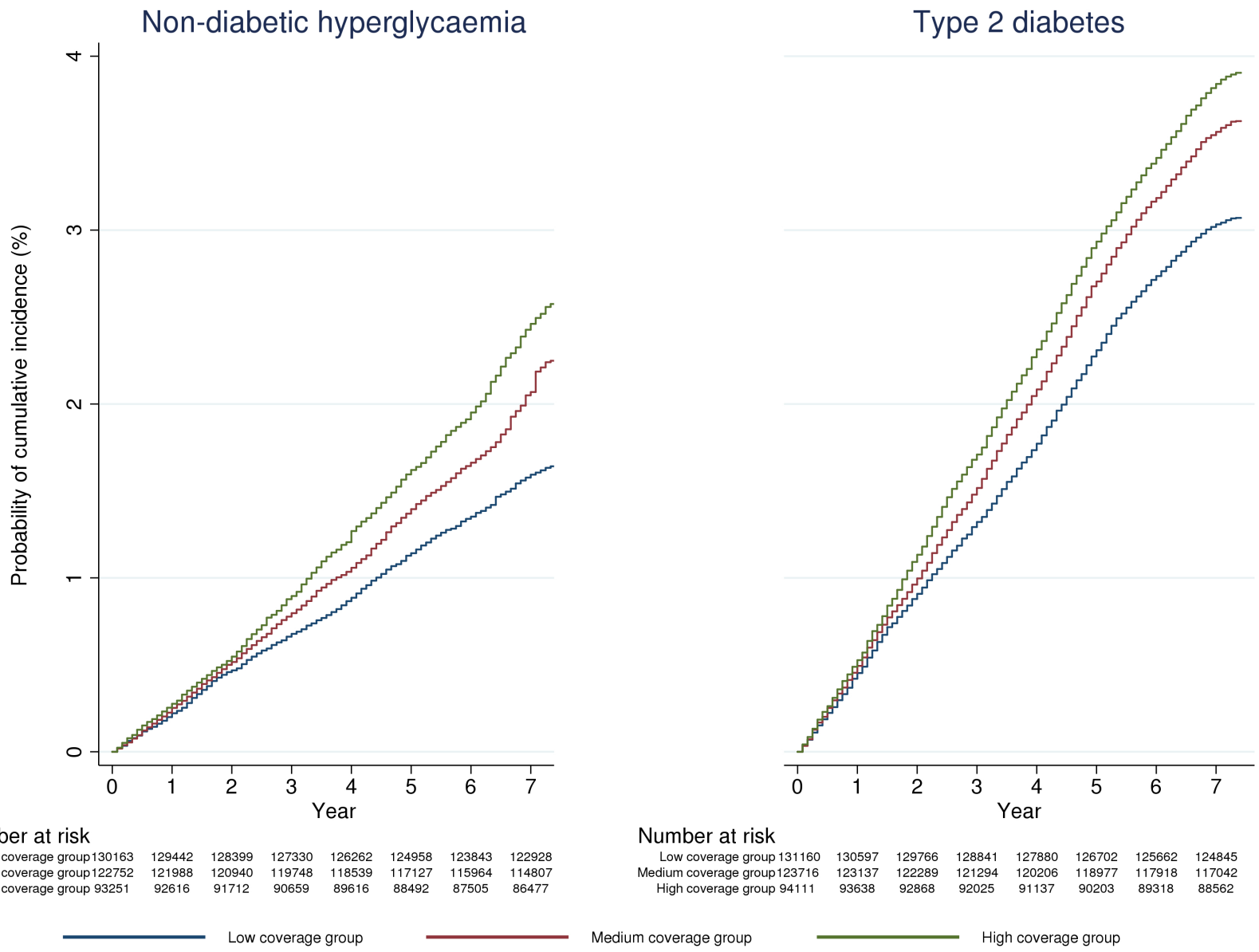
Table 6. Differences in incidence rates of diagnoses of non-diabetic hyperglycaemia and type 2 diabetes by general practices' coverage of the NHS Health Check Programme and patients' baseline diabetes risk score. Time period was Jan 2009-May 2016.

Notes: Results are shown from multivariable Cox regression models. All models have been adjusted for the baseline values of the following independent variables: age, gender, ethnicity, smoking status, body mass index, antihypertensive medication, general practice deprivation score, and region. Models have also been adjusted for propensity score based on patients' probability of being registered with a practice with low, medium or high coverage of the Health Check Programme. Abbreviations: DRS = diabetes risk score, HR = Hazard ratio. Legends: *p<0.05, **p<0.01, *** p<0.001, § Tertiles of general practices coverage of the NHS Health Check Programme were defined based on programme coverage during the first three years after its implementation (2009-11). Adapted from Palladino R, Vamos EP, Chang KC, Khunti K, Majeed A, Millett C. Evaluation of the Diabetes Screening Component of a National Cardiovascular Risk Assessment Programme in England: a Retrospective Cohort Study. Sci Rep. 2020;10(1):1231

		TOTAL SAMPLE			DRS ≥ 10		
	INCIDENCE RATE	HR	95% CI		HR	95% CI	
NON-DIABETIC HYPERGLYCAEMIA							
PROGRAMME COVERAGE§							
Low	**0.19 per 1000 person-years (N = 2,096)**		ref			ref	
Medium	**0.25 per 1000 person-years (N = 2,693)**	1.15***	1.08	1.22	1.15**	1.04	1.27
High	**0.29 per 1000 person-years (N = 2,337)**	1.19***	1.11	1.27	1.23***	1.11	1.37
TYPE 2 DIABETES	**CRUDE RATES**	**HR**	**95% CI**		**HR**	**95% CI**	
PROGRAMME COVERAGE§							
Low	**0.35 per 1000 person-years (N = 4,018)**		ref			ref	
Medium	**0.42 per 1000 person-years (N = 4,482)**	1.10***	1.05	1.15	1.13**	1.05	1.21
High	**0.45 per 1000 person-years (N = 3,671)**	1.09***	1.03	1.14	1.10*	1.02	1.19

Figure 15. Kaplan Meier curves showing estimated rates of newly detected Non-diabetic Hyperglycaemia and newly diagnosed Type 2 Diabetes between Jan 2009 and May 2016 by general practices' coverage of the NHS Health Check.

Notes: In the calculation of individuals at risk of being detected with non-diabetic-hyperglycaemia(NDH), those meeting diagnostic criteria for NDH before 2009 were excluded at baseline and those with incident type 2 diabetes were progressively excluded. Adapted from Palladino R, Vamos EP, Chang KC, Khunti K, Majeed A, Millett C. Evaluation of the Diabetes Screening Component of a National Cardiovascular Risk Assessment Programme in England: a Retrospective Cohort Study. Sci Rep. 2020;10(1):1231


Non-diabetic hyperglycaemia
Type 2 diabetes
Probability of cumulative incidence (%)
0
1
2
3
4
0 1 2 3 4 5 6 7
Year
Number at risk
Low coverage group 130163 129442 128399 127330 126262 124958 123843 122928
Medium coverage group 122752 121988 120940 119748 118539 117127 115964 114807
High coverage group 93251 92616 91712 90659 89616 88492 87505 86477
Low coverage group 131160 130597 129766 128841 127880 126702 125662 124845
Medium coverage group 123716 123137 122289 121294 120206 118977 117918 117042
High coverage group 94111 93638 92868 92025 91137 90203 89318 88562
Low coverage group
Medium coverage group
High coverage group

7.4.2 Management of blood glucose

Compared with individuals at high risk of T2D registered with low coverage practices, those at high risk registered with high coverage practice had 0.1 mmol/L lower mean FPG and 48% greater likelihood of having blood glucose levels below the diagnostic criteria for NDH (FPG: β coefficient (95% CI) -0.09 (-0.12, -0.05); blood glucose levels below diagnostic criteria: OR 1.48 (1.43, 1.53)), over the study period.

Among incident NDH cases, those registered with high coverage practices had a 0.2 mmol/L lower mean FPG (-0.16(-0.27 – -0.04)) over the follow-up period compared with patients registered with low coverage practices. Among individuals with incident T2D, those registered with high coverage practice had a 0.3 mmol/L lower mean FPG (-0.34 (-0.54 –- 0.13). Detailed results are presented in Figure 16.

No differences were found between groups for the likelihood of receiving anti-diabetic medications among individuals with incident T2D following the diagnosis.

7.4.3 Cardiovascular risk factor management

7.4.3.1 Blood pressure

Over the study period, compared with those registered with a low coverage practice, individuals registered with medium and high coverage practices had a mean SBP 0.3 and 0.4 mm Hg lower (β coefficient (95% CI) -0.25 (-0.35 - -0.15); -0.43 (-0.54 - -0.32), repectively). Difference was more pronounced among individuals at high risk of T2D, with a 0.4 and 0.6 mm Hg lower mean in the medium and high coverage tertiles (medium coverage practices:– 0.38 (-0.65 - -0.11); high coverage practices: -0.59 (-0.87 - -0.30)), respectively. Individuals with newly diagnosed T2D registered with high coverage practices had 0.9 mmHg lower SBP

mean (-0.87 (-1.50 - -0.25)). Results for the mean DBP were qualitatively similar (Figure 4).

7.4.3.2 Body Mass Index

Among those at high risk of T2D, individuals registered with high coverage practices had 0.3 kg/m^2 higher mean BMI (β coefficient (95% CI) 0.25 (0.19 - 0.32)), compared with the low coverage group. No differences were found at follow-up among individuals meeting the diagnostic criteria for NDH and with newly diagnosed T2D (Figure 17).

7.4.3.3 Smoking prevalence

Individuals registered with a high coverage practice had 6% greater likelihood of being smoker (OR (95% CI) 1.06 (1.02 – 1.11)), compared with low coverage practices. For incident cases of T2D the likelihood of being smoker over the follow-up period was 34% and 40% greater for those registered with medium and high coverage practices, compared with those registered with low coverage practices (Figure 17).

7.4.3.4 Total cholesterol

Individuals with incident NDH registered with high coverage practices had a 0.1 mmol/L lower mean total cholesterol (β coefficient (95% CI) -0.10 (-0.17 - -0.04)), compared with those registered with low coverage practices (Figure 17). No difference between the two groups were found in prescribing of statins following the detection of NDH.

7.4.3.5 Modelled CVD risk

Compared with those registered with low coverage practices, individuals registered with medium and high coverage practices had a 0.1% lower modelled CVD risk score. Differences were more pronounced among individuals meeting diagnostic criteria for NDH which, on

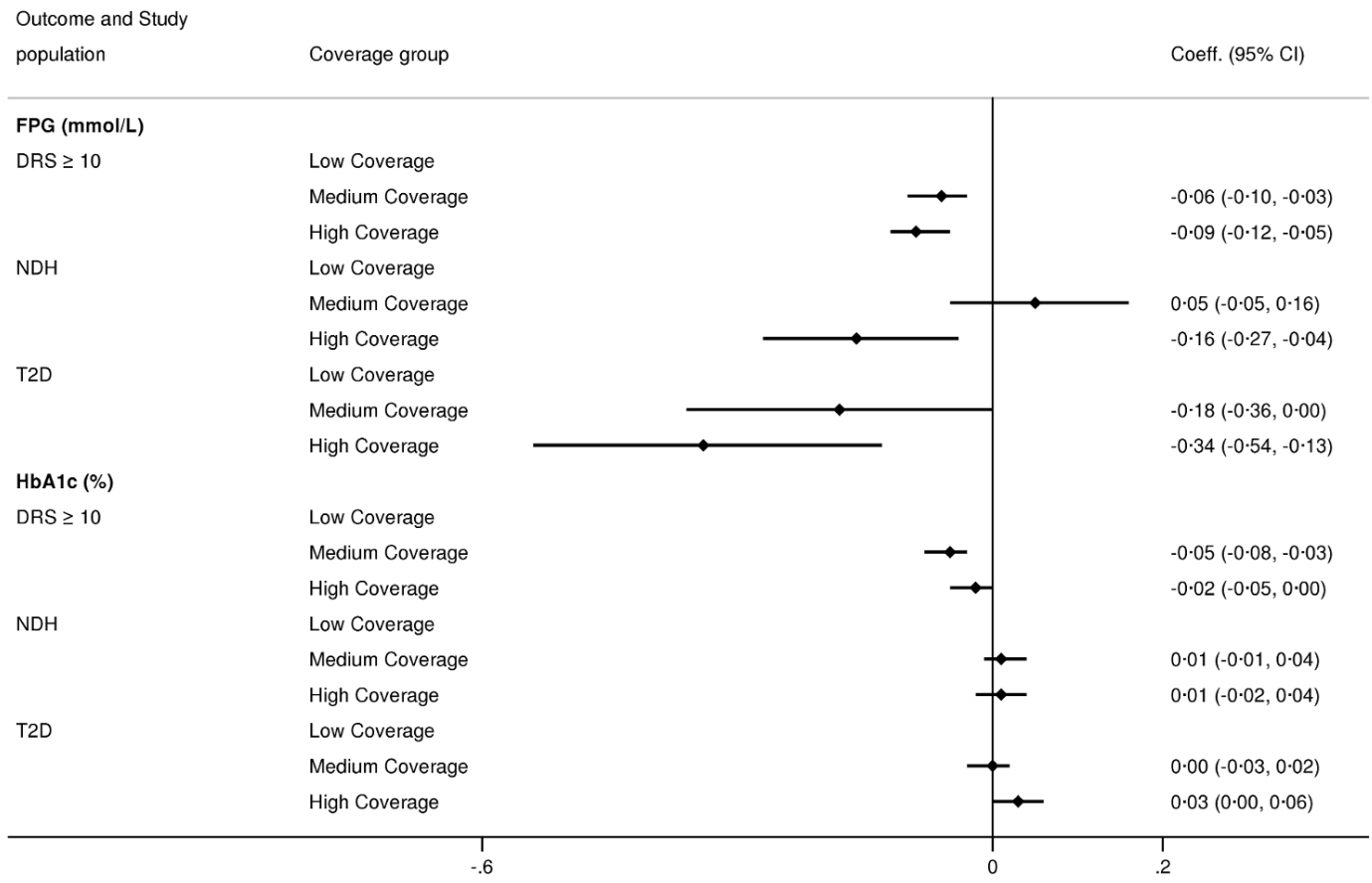
average, had a 0.9% lower cardiovascular risk score after the detection (β coefficient (95% CI -0.85 (-1.35 - -0.35)).

7.4.4 Sensitivity analyses

Results of the regression analyses without propensity score adjustment were largely similar to the main findings and are presented in Appendix Table 13-Table 16.

Figure 16. Differences in fasting plasma glucose levels and prescription of anti-diabetic medications according to general practices' coverage of the Health Check programme, patients' baseline diabetes risk score, and new diagnoses of non-diabetic hyperglycaemia and type 2 diabetes between 2009 and 2016 in England.

Notes: Time period was from 1 January 2009 to 31 May 2016. Tertiles of general practices coverage of the NHS Health Check Programme were defined based on programme coverage during the first three years after its implementation (2009-11). Results are shown from mixed-effect linear regression models for continuous outcomes and mixed-effect logistic regression models for binary outcomes. In both models 'Low Coverage' group has been used as referent category. Independent variables included in the model are the following: practices' early programme coverage of the NHS Health Check programme, year, and baseline age, gender, ethnicity, smoking status, BMI, antihypertensive medication, presence of cardiovascular disease, general practice IMD, and region. Models have also been adjusted for propensity score based on patients' probability of being registered with a practice with low, medium or high coverage of the Health Check Programme. Abbreviations: DRS = diabetes risk score, NDH = non-diabetic hyperglycaemia, OR = Odds Ratio. Adapted from Palladino R, Vamos EP, Chang KC, Khunti K, Majeed A, Millett C. Evaluation of the Diabetes Screening Component of a National Cardiovascular Risk Assessment Programme in England: a Retrospective Cohort Study. Sci Rep. 2020;10(1):1231


Outcome and Study population
Coverage group
Coeff. (95% CI)
FPG (mmol/L)
DRS ≥ 10
Low Coverage
Medium Coverage
-0·06 (-0·10, -0·03)
High Coverage
-0·09 (-0·12, -0·05)
NDH
Low Coverage
Medium Coverage
0·05 (-0·05, 0·16)
High Coverage
-0·16 (-0·27, -0·04)
T2D
Low Coverage
Medium Coverage
-0·18 (-0·36, 0·00)
High Coverage
-0·34 (-0·54, -0·13)
HbA1c (%)
DRS ≥ 10
Low Coverage
Medium Coverage
-0·05 (-0·08, -0·03)
High Coverage
-0·02 (-0·05, 0·00)
NDH
Low Coverage
Medium Coverage
0·01 (-0·01, 0·04)
High Coverage
0·01 (-0·02, 0·04)
T2D
Low Coverage
Medium Coverage
0·00 (-0·03, 0·02)
High Coverage
0·03 (0·00, 0·06)
-.6
0
.2

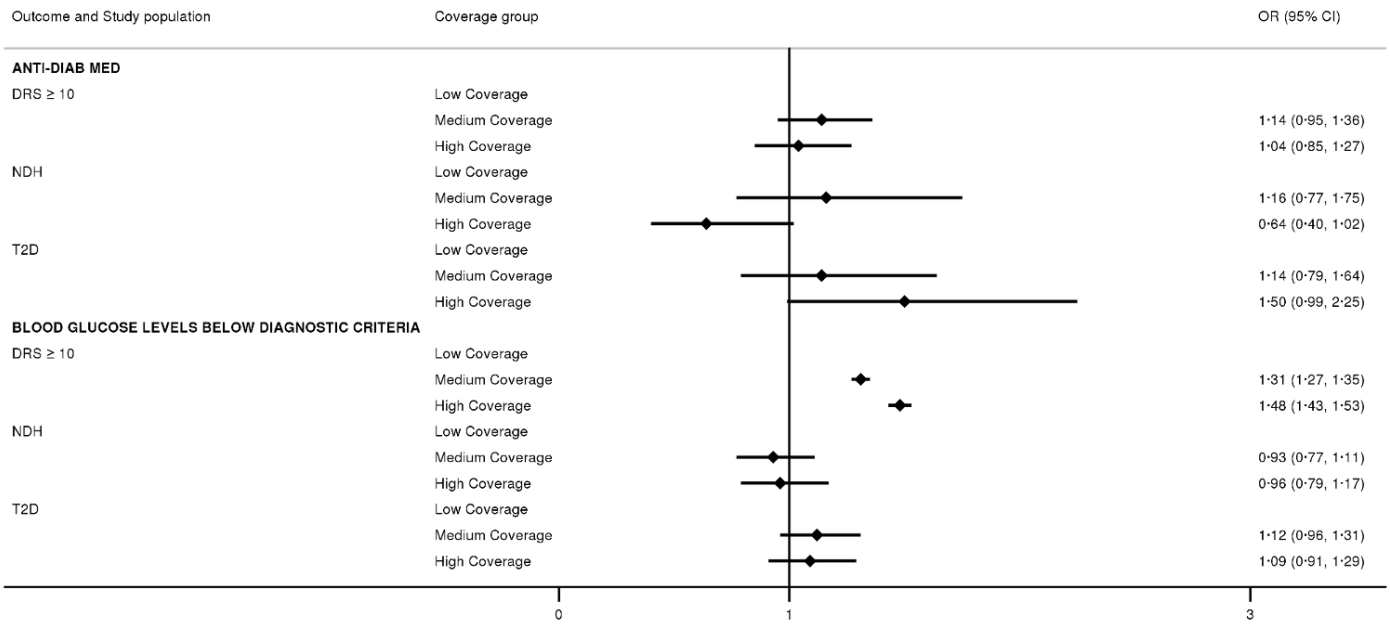
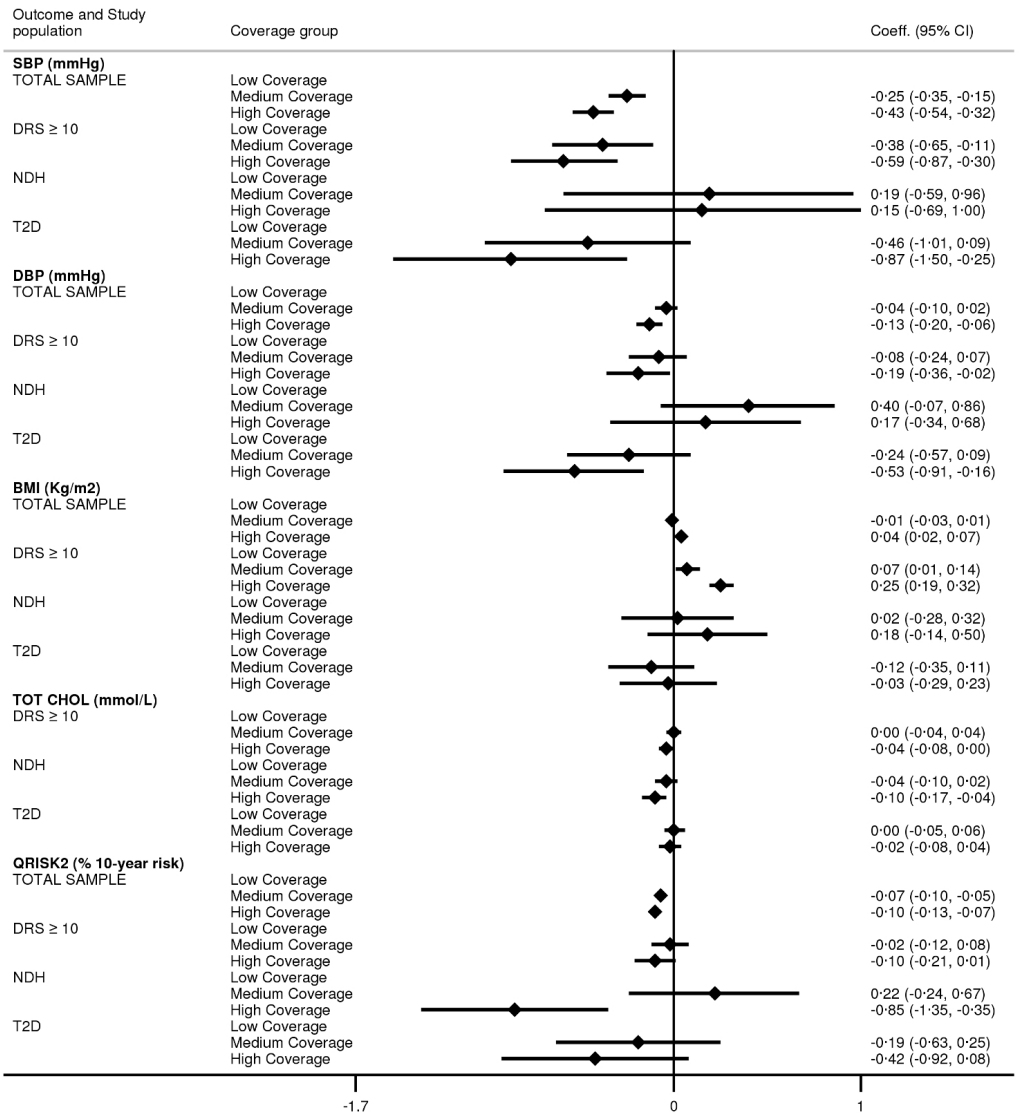

Outcome and Study population
Coverage group
OR (95% CI)
ANTI-DIAB MED
DRS ≥ 10
Low Coverage
Medium Coverage
1·14 (0·95, 1·36)
High Coverage
1·04 (0·85, 1·27)
NDH
Low Coverage
Medium Coverage
1·16 (0·77, 1·75)
High Coverage
0·64 (0·40, 1·02)
T2D
Low Coverage
Medium Coverage
1·14 (0·79, 1·64)
High Coverage
1·50 (0·99, 2·25)
BLOOD GLUCOSE LEVELS BELOW DIAGNOSTIC CRITERIA
DRS ≥ 10
Low Coverage
Medium Coverage
1·31 (1·27, 1·35)
High Coverage
1·48 (1·43, 1·53)
NDH
Low Coverage
Medium Coverage
0·93 (0·77, 1·11)
High Coverage
0·96 (0·79, 1·17)
T2D
Low Coverage
Medium Coverage
1·12 (0·96, 1·31)
High Coverage
1·09 (0·91, 1·29)
0
1
3

Figure 17. Differences in cardiovascular risk factors between 2009 and 2016 by general practices' coverage of the NHS Health Check programme and individuals' baseline diabetes risk.

***Notes*:** Time period was from 1 January 2009 to 31 May 2016. Tertiles of general practices coverage of the NHS Health Check Programme were defined based on programme coverage during the first three years after its implementation (2009-11). Results are shown from mixed-effect linear regression models for continuous outcomes and mixed-effect logistic regression models for binary outcomes. In both models 'Low Coverage' group has been used as referent category. Independent variables included in the model are the following: practices' early programme coverage of the NHS Health Check programme, year, and baseline age, gender, ethnicity, smoking status, BMI, antihypertensive medication, presence of cardiovascular disease, general practice IMD, and region. To calculate estimates for individuals with a DRS ≥ 10 an interaction term between early programme coverage and DRS has also been included. Differences in total cholesterol levels and statins prescription have been restricted to only those with a DRS ≥ 10 at baseline. Models have also been adjusted for propensity score based on patients' probability of being registered with a practice with low, medium or high coverage of the Health Check Programme. Abbreviations: DRS = diabetes risk score, NDH = non-diabetic hyperglycaemia, T2D = type 2 diabetes, OR = Odds Ratio. Adapted from Palladino R, Vamos EP, Chang KC, Khunti K, Majeed A, Millett C. Evaluation of the Diabetes Screening Component of a National Cardiovascular Risk Assessment Programme in England: a Retrospective Cohort Study. Sci Rep. 2020;10(1):1231


Outcome and Study population
Coverage group
Coeff. (95% CI)
SBP (mmHg)
TOTAL SAMPLE
Low Coverage
Medium Coverage
-0·25 (-0·35, -0·15)
High Coverage
-0·43 (-0·54, -0·32)
DRS ≥ 10
Low Coverage
Medium Coverage
-0·38 (-0·65, -0·11)
High Coverage
-0·59 (-0·87, -0·30)
NDH
Low Coverage
Medium Coverage
0·19 (-0·59, 0·96)
High Coverage
0·15 (-0·69, 1·00)
T2D
Low Coverage
Medium Coverage
-0·46 (-1·01, 0·09)
High Coverage
-0·87 (-1·50, -0·25)
DBP (mmHg)
TOTAL SAMPLE
Low Coverage
Medium Coverage
-0·04 (-0·10, 0·02)
High Coverage
-0·13 (-0·20, -0·06)
DRS ≥ 10
Low Coverage
Medium Coverage
-0·08 (-0·24, 0·07)
High Coverage
-0·19 (-0·36, -0·02)
NDH
Low Coverage
Medium Coverage
0·40 (-0·07, 0·86)
High Coverage
0·17 (-0·34, 0·68)
T2D
Low Coverage
Medium Coverage
-0·24 (-0·57, 0·09)
High Coverage
-0·53 (-0·91, -0·16)
BMI (Kg/m2)
TOTAL SAMPLE
Low Coverage
Medium Coverage
-0·01 (-0·03, 0·01)
High Coverage
0·04 (0·02, 0·07)
DRS ≥ 10
Low Coverage
Medium Coverage
0·07 (0·01, 0·14)
High Coverage
0·25 (0·19, 0·32)
NDH
Low Coverage
Medium Coverage
0·02 (-0·28, 0·32)
High Coverage
0·18 (-0·14, 0·50)
T2D
Low Coverage
Medium Coverage
-0·12 (-0·35, 0·11)
High Coverage
-0·03 (-0·29, 0·23)
TOT CHOL (mmol/L)
DRS ≥ 10
Low Coverage
Medium Coverage
0·00 (-0·04, 0·04)
High Coverage
-0·04 (-0·08, 0·00)
NDH
Low Coverage
Medium Coverage
-0·04 (-0·10, 0·02)
High Coverage
-0·10 (-0·17, -0·04)
T2D
Low Coverage
Medium Coverage
0·00 (-0·05, 0·06)
High Coverage
-0·02 (-0·08, 0·04)
QRISK2 (% 10-year risk)
TOTAL SAMPLE
Low Coverage
Medium Coverage
-0·07 (-0·10, -0·05)
High Coverage
-0·10 (-0·13, -0·07)
DRS ≥ 10
Low Coverage
Medium Coverage
-0·02 (-0·12, 0·08)
High Coverage
-0·10 (-0·21, 0·01)
NDH
Low Coverage
Medium Coverage
0·22 (-0·24, 0·67)
High Coverage
-0·85 (-1·35, -0·35)
T2D
Low Coverage
Medium Coverage
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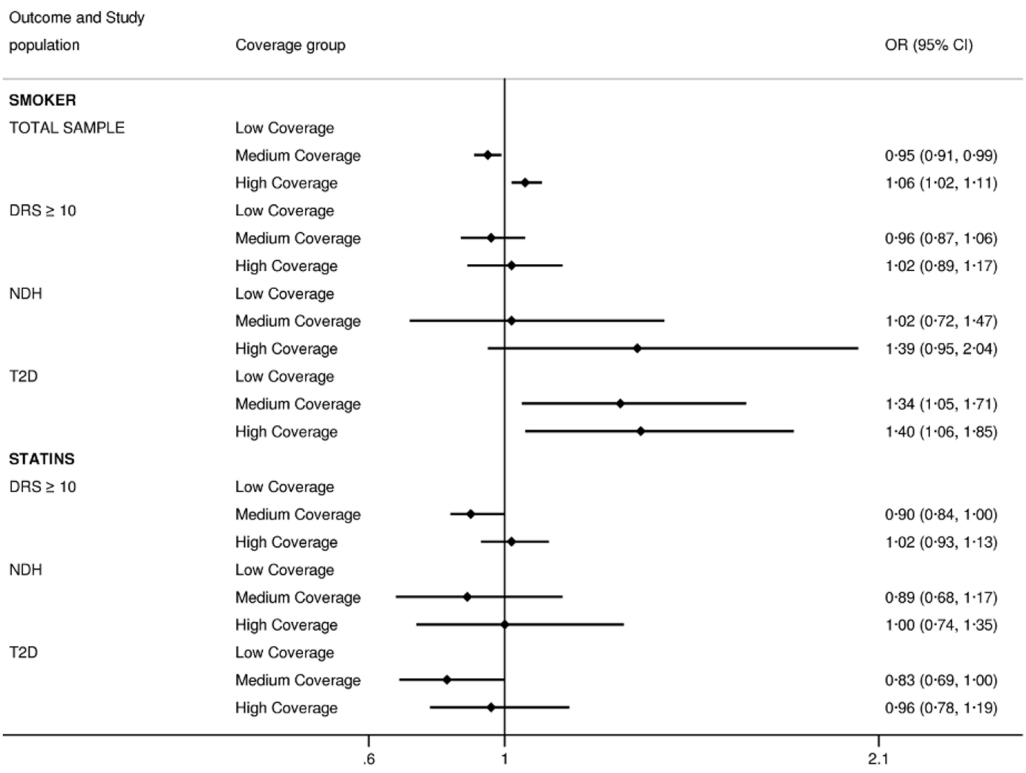
High Coverage
-0·42 (-0·92, 0·08)
-1.7
0
1


Outcome and Study population
Coverage group
OR (95% CI)
SMOKER
TOTAL SAMPLE
Low Coverage
Medium Coverage
0·95 (0·91, 0·99)
High Coverage
1·06 (1·02, 1·11)
DRS ≥ 10
Low Coverage
Medium Coverage
0·96 (0·87, 1·06)
High Coverage
1·02 (0·89, 1·17)
NDH
Low Coverage
Medium Coverage
1·02 (0·72, 1·47)
High Coverage
1·39 (0·95, 2·04)
T2D
Low Coverage
Medium Coverage
1·34 (1·05, 1·71)
High Coverage
1·40 (1·06, 1·85)
STATINS
DRS ≥ 10
Low Coverage
Medium Coverage
0·90 (0·84, 1·00)
High Coverage
1·02 (0·93, 1·13)
NDH
Low Coverage
Medium Coverage
0·89 (0·68, 1·17)
High Coverage
1·00 (0·74, 1·35)
T2D
Low Coverage
Medium Coverage
0·83 (0·69, 1·00)
High Coverage
0·96 (0·78, 1·19)
.6
1
2.1

7.5 DISCUSSION

In this retrospective analysis of prospectively collected data using a representative sample of the English population, I assessed the impact of the diabetes risk assessment and screening component of the NHS Health Check programme on the detection of NDH and T2D and levels of blood glucose and cardiovascular risk factors among individuals at high risk of T2D and newly diagnosed cases. I found that general practices with the highest programme coverage had 19% and 9% higher detection rates of NDH and T2D respectively, compared with practices with the lowest coverage. Compared with counterparts registered with low coverage practices, individuals with incident NDH registered with high coverage practices had lower levels of fasting plasma glucose and cholesterol over the study period but similar blood pressure and BMI levels. Individuals newly diagnosed with T2D in high coverage practices had lower levels of blood pressure, and fasting plasma glucose, but similar levels of cholesterol, and BMI. Furthermore, individuals with NDH registered with practices with higher coverage had a 0.9% lower modelled 10-year cardiovascular risk score compared with individuals in low coverage practices.

The impact of the NHS Health Check programme on cardiovascular risk factor control was greater in those newly detected with NDH and T2D than in those at high risk of T2D. Within the latter group those registered with medium and high coverage practices had on average lower blood pressure levels over the study period, as compared with the counterpart registered with low coverage practices. However, those differences were statistically significant but not clinically meaningful, and this was more evident for diastolic than systolic blood pressure. Furthermore, there were no differences in the modelled 10-year cardiovascular risk score between the groups of individuals at high risk of T2D registered with

general practices with different level of programme coverage over the study period. This might be explained by the small differences observed in blood pressure levels together with the increase in BMI levels and the absence of difference in smoking status and total cholesterol levels

The clinical benefits of large-scale programmes directed at the identification and management of individuals at high risk of diabetes remain unclear (114, 165-168). Evidence from randomised trials suggests that early detection of abnormal glucose metabolism through screening and subsequent intensive management reduce cardiovascular risk among individuals with NDH and newly diagnosed T2D (166, 172). The results of the ADDITION-Denmark study suggest that diabetes screening was associated with a significant reduction in risk of all-cause mortality and CVD events in those diagnosed with diabetes (260). However, criticisms have been raised on the interpretation of these findings due to selection of non-randomised control population for the study (167, 168).

Results on the benefit of diabetes screening in reducing CVD risk were also confirmed by a modelling study using data from randomised trials (166). Although it is difficult to make direct comparisons with other studies due to differences in design and settings, these results also indicate better cardiovascular risk factor control in individuals with newly detected NDH and newly diagnosed T2D who were registered with practices that more widely adopted diabetes screening as part of Health Check. Findings from this research also suggest that the intensity of control of cardiovascular risk factors is aligned with increased clinical risk, and this appears to be more evident among practices that adopt systematic risk assessment and management strategies.

Similarly, individuals at high risk of T2D, and patients with newly detected NDH and T2D

registered with high coverage practices had lower fasting plasma glucose levels than those registered with low coverage practices. This finding is also in line with previous studies reporting lower blood glucose levels among individuals with screen-detected T2D compared with patients detected in routine clinical care (171).

7.5.1 Strengths and limitations

Data on the impact of diabetes risk assessment and screening programmes in real world settings are scarce. The NHS Health Check is one of the largest such programmes globally and its delivery in a universal health system with high penetration of electronic health records provides a unique opportunity for evaluation. I employed a robust study design using a representative sample of the English population (261). I used general practice coverage of the Health Check programme as exposure, which arguably captures whether practices adopt a pro-active approach to prevention, including identifying individuals at high risk of T2D. This design may also reduce possible selection bias, such as the 'healthy screenee bias', that might occur when directly comparing those who attend and those who do not attend a screening programme. My findings, therefore, cannot be directly attributable to programme attendance because they also capture differences between practices in their approach to pro-actively perform more opportunistic screenings as well as better embed national guidelines into clinical practice.

Several caveats merit discussion. In line with what I found, it has been reported that the coverage of the NHS Health Check in the first years of the programme was low, with considerable practice-level variations (195). In England, variations in the coverage of national programmes (195, 197) have been attributed to differences in the organisation of general practices, socio-economic deprivation and patient health status and preferences (195, 197, 262). In the present study the three coverage groups differed in socio-demographic and

clinical characteristics at baseline, and I sought to reduce this possible source of bias by adjusting analyses for the propensity of being registered with a general practice with a specific level of programme coverage. Although the analysis only included individuals without cardiovascular disease and diabetes at baseline, I reported baseline diabetes prevalence across tertiles of programme coverage, which was higher in the high coverage group. Similarly, for individuals included in the analysis the baseline DRS was slightly higher in the high coverage group as compared with the low coverage. This might partially attenuate my findings, which might also reflect proportionality in diabetes risk and greater underlying diabetes incidence in high coverage groups. Other limitations include missing values at baseline for blood pressure and BMI records, variables required for the estimation of baseline risk of T2D and propensity scores. I addressed this by using multiple imputation and including a wide range of clinical and socio-demographic variables that may be predictive of the missing data. I conducted complete-case analyses for the FPG, HbA1c, and total cholesterol study outcomes due to presence of missing data. Finally, when using routinely collected data concerns have been raised about miscoding, misclassification and misdiagnosis. However, CPRD is a reliable widely used data source and is subject to regular quality checks (253).

7.5.2 Policy implications

The English National Health Service has invested considerable resources in improving the early detection and management of diabetes through the NHS Health Checks and the recently introduced NHS Diabetes Prevention Programme, which involves intensive lifestyle interventions among CVD risk management in individuals with NDH. My findings show that general practices that actively participated in the NHS Health Check programme had not only

detected larger number of previously undiagnosed NDH and T2D cases, but achieved better glucose and cardiovascular risk management among individuals identified with high T2D risk and newly diagnosed T2D. This is particularly important, considering the currently existing variations in programme delivery across general practices regarding coverage and uptake of interventions offered through the programme that have the potential to improve health. These findings are encouraging given that patients with NDH or T2D have an increased risk for cardiovascular morbidity and mortality. However, the long-term effects of diabetes risk assessment programmes on hard clinical outcomes and the burden of T2D warrant further research. Furthermore, it is still unclear at what scale would diabetes risk assessment programmes generate population-level impacts while remaining cost-effective. Such person-centred interventions require a higher level of engagement from individuals and their impact on health inequalities require rigorous evaluation. Besides focusing on early detection of diabetes and assessment of individuals at high risk, it is important that policy interventions include approaches which reduce T2D risk factors across the entire population, regardless of person-level risk.

7.5.3 Conclusions

I found that general practices' actively participating in the NHS Health Check programme had higher detection of NDH and T2D and better management of cardiovascular disease risk in newly diagnosed cases. However, further evaluation is required on long-term population-level health impacts and cost-effectiveness combined with information on effects on health inequalities before widespread implementation of similar programmes can be recommended, especially in settings with limited healthcare resources.

8 Overall Discussion and Conclusions

As part of preventive strategies to reduce the burden of diabetes there has been an increasing focus on identifying individuals with NDH for early management. NDH is a considered to be a major risk factor for progression to T2D and has also been associated with increased risk of macrovascular disease and all-cause mortality, while evidence linking NDH to microvascular disease is growing but not entirely consistent. As majority of the evidence on NDH comes from studies based on all individuals with the condition, little is known about what is the association between NDH and risk of vascular condition for individuals who progress to T2D.

Furthermore, evidence on how individuals with NDH and with newly diagnosed T2D are managed optimally in routine primary care settings in the UK is still lacking. The NHS Health Check programme, launched in 2009 in England and rolled out nationally, is one of the world's largest cardiovascular risk assessment and management programmes. Although its primary focus is cardiovascular risk assessment, the programme also includes a T2D risk assessment and screening component. To date, no previous studies have reported the evaluation of the diabetes screening component of the Health Check programme.

The main aim of this PhD was to examine whether the detection and management of NDH before diagnosis of T2D is associated with the risk of vascular disease and all-cause mortality following the diagnosis of T2D. A secondary aim of this PhD was to assess whether the NHS Health Check programme increased the detection of T2D and NDH, and improved control of blood glucose and cardiovascular risk factors among newly diagnosed cases.

8.1 Summary of main findings

Analysing data from a retrospective cohort of individuals newly diagnosed with T2D in England between 2004 and 2017, I found that the half of the study population (49.9%) had at least one microvascular or macrovascular disease at the time of T2D diagnosis. The proportion of individuals having at least one microvascular disease at time of T2D diagnosis varied substantially by glycaemic status before the T2D diagnosis, ranging from 42.4% for individuals with NDH detected to 30.7% for individuals with glycaemic values within the normal range before the T2D diagnosis. Adjusted analyses found that individuals with prior NDH and those without glycaemic testing were significantly more likely to have retinopathy and nephropathy at the time of T2D diagnosis, as compared with individuals with glycaemic values within the normal range. Detection of NDH before the diagnosis of T2D was also more likely associated with previous diagnosis of coronary heart disease at the time of T2D diagnosis. Conversely, individuals with prior NDH were less likely to have cerebrovascular and peripheral arterial disease compared with those who had glycaemic values within the normal range before T2D diagnosis. There were only small variations in these findings across various NDH diagnostic criteria including the WHO/IEC, ADA and NICE. Assigning a diagnostic label for NDH to those tested and detected with NDH was less likely associated with presence of microvascular and macrovascular diseases at time of T2D diagnosis, as compared with those with NDH without a diagnostic code. Individuals with prior NDH of non-White ethnic groups were also more likely to have microvascular disease at time of diagnosis of T2D as compared with the White counterpart.

Analysing data from the same population I found that differences in the hazards of incident microvascular disease according to glycaemic status in the three years before the diagnosis of T2D persisted up to 7.5 years following the diagnosis of T2D. As compared with individuals with glycaemic status within the normal range in the three years before the diagnosis of T2D,

those detected with prior NDH had increased hazard of incident retinopathy in the first 7.5 years following the diagnosis of T2D, while increased hazard of incident nephropathy was observed within the first 5 years. Estimated differences were wider for retinopathy than nephropathy, although in both cases they progressively attenuated over the study period. In the 10 years following the diagnosis of T2D the only difference in the hazard of macrovascular disease was observed for those detected with prior NDH in the first 2.5 years following the diagnosis, as compared with those with prior normoglycaemic status. Individuals detected with NDH in the three years before the diagnosis of T2D had also lower hazard of mortality than those with prior normoglycaemic status in the 5 years following the diagnosis of T2D. In line with findings for microvascular disease, differences progressively attenuated over the study period.

Conducting a retrospective cohort study using a representative sample of the English population without CVD at baseline, I assessed the impact of the diabetes risk assessment and screening component of the NHS Health Check programme on the detection of NDH and T2D and levels of blood glucose and cardiovascular risk factors among individuals at high risk of T2D and newly diagnosed cases. I found that general practices with the highest programme coverage had 19% and 9% higher detection rates of NDH and T2D respectively, compared with practices with the lowest coverage. Compared with counterparts registered with low coverage practices, individuals with incident NDH registered with high coverage practices had lower levels of FPG and cholesterol over the study period but similar blood pressure and BMI levels. Individuals newly diagnosed with T2D in high coverage practices had lower levels of blood pressure, and FPG, but similar levels of cholesterol, and BMI. Furthermore, individuals with NDH registered with practices with higher coverage had a 0.9% lower modelled 10-year cardiovascular risk score compared with individuals in low coverage

practices.

8.2 Strengths and Limitations of this work

The strengths and limitations of the study design and methodologies have been thoroughly discussed in each analysis chapters, but here I shall discuss the general strengths and limitations of this thesis. First, the main strength of this work was the use of a nationally representative primary care database for all the analyses. Most of the evidence on the management of individuals at increased risk of T2D comes from trial and modelling study. Therefore, the use of routinely collected primary and secondary care data representative of the English population allowed to better understand the association between testing, detection, management of NDH, and T2D related outcomes in real world settings. Furthermore, to my knowledge this is the first study evaluating the diabetes screening component of a national cardiovascular and diabetes risk assessment and management programme. Data on the impact of diabetes risk assessment and screening programmes in real world settings are scarce. Therefore, the evaluation of this programme might provide important information for countries with similar Health Systems or for modelling studies assessing the impact of similar programmes in different settings i.e. Health Systems with limited resources available.

Whilst the use of population-level real-world data can be considered as one of the main strengths of this doctoral thesis, this can also be also seen as a limitation. Although CPRD is a reliable data source, which is subject to regular quality checks (253), the use of routinely collected data means that due to miscoding, misclassification, or misdiagnosis, individuals might have been wrongly categorised or important data might have been excluded. Furthermore, the national roll-out of the NHS Health Check programme did not allow to

select an external control, therefore, similarly to previous research papers (251, 259) an internal control group was selected, obtained stratifying programme coverage in tertiles. However, differences in programme coverage might be attributed not only to adherence to national guideline but also to differences in the organisation of general practices, socio-economic deprivation and patient health status and preferences (195, 197, 262). Therefore, I employed a robust design based on the propensity-score adjustment method to reduce the selection bias due to these additional factors.

8.3 Comparison with Existing Literature

Findings about the high burden of vascular disease among newly diagnosed T2D cases are in line with previous studies (230-232). For instance, a study by Kostev and colleagues conducted on 12,524 individuals in UK primary care settings found that the prevalence of retinopathy at time of T2D was 19% (230). Although my research used data from similar settings, the prevalence I estimated in this doctoral thesis is slightly higher and one of the reasons might be that I used a more comprehensive approach to define retinopathy (Appendix Table 1), which included not only primary care but also secondary care diagnoses. Additionally, a study by Koopman and colleagues using representative data of the US population found a very similar prevalence of nephropathy in diagnosed T2D cases (232).

Results from this doctoral thesis also support the body of evidence suggesting that NDH is associated with an excess risk for the development of both macrovascular and microvascular diseases considering the continuum of risk across the glycaemic range, including the NDH range (130, 132, 233). Notably, available literature on the association between NDH and microvascular disease was not entirely consistent (130). Previous reviews by Tabak and colleagues and by Fagg and colleagues questioned whether the excess of risk seen for

individuals with previous NDH was, at least partially, attributable to the progression to T2D. On the contrary, my findings show a clear association between NDH and microvascular disease. I found that prior NDH was associated with increased odds of retinopathy and nephropathy already present at time of diagnosis of T2D and also with an increased risk of these microvascular diseases following the diagnosis of T2D. Remarkably, this association appeared to be stronger for retinopathy then for nephropathy, suggesting that that the associated risk of the latter condition might be less dependent on prolonged exposure to mild hyperglycaemia. This is in line with the findings of a recent meta-analysis that concluded that the association between NDH and nephropathy was significant but modest, and this might be partially explained by underlying confounding or common causes contributing to both hyperglycaemia and kidney disease (130, 143).

Previous studies demonstrated that chronic hyperglycaemia contributes to the pathogenesis of macrovascular dysfunction (130-133). However, findings from this doctoral thesis confirm only partially previous literature. I found that individuals with NDH detected before the diagnosis of T2D had increased odds of having a previous diagnosis of coronary heart disease but had also lower odds of having cerebrovascular and peripheral arterial disease at time of T2D diagnosis. Furthermore, those with prior NDH had also lower risk of incident macrovascular disease. Several explanations might contribute to explain these findings. First, while the association between hyperglycaemia and increased risk of coronary heart disease is supported by a consistent body of evidence (130, 237), the association with cerebrovascular disease appears to be less clear (238). Second, these findings might be compatible with a potential surveillance bias as individuals with any cardiovascular disease are more likely to be screened for diabetes and intermediate hyperglycaemia compared with the general population and thus have a higher chance of earlier diagnosis of diabetes.

I found small variations in findings about the prevalence of vascular complications at time of T2D diagnosis across NDH sub-groups defined by the WHO/IEC, NICE, and ADA. However, when analysing differences in risk of vascular outcomes and mortality following the diagnosis of T2D differences were more pronounced but still limited. This is in contrast with previous literature that found that different diagnostic criteria identify different groups of individuals who differ in progression rates to T2D and risk of associated vascular morbidity and mortality (96, 131, 216, 217). For instance, Huang and colleagues in a recent meta-analysis found that while the mortality risk for individuals with NDH defined by different diagnostic criteria was similar, differences in the risk of composite cardiovascular events were found, with those detected with NDH adopting the FPG/WHO criterion or the IGT criterion having a higher risk then those detected adopting the FPG/ADA criterion. Findings from my doctoral thesis cannot directly compare with previous findings as I focused on a different population considering that in my studies I did not include the whole NDH population but a sub-population who effectively progressed to T2D.

No previous study specifically evaluated the association between NDH, ethnic groups, and the odds of having vascular disease at time of T2D diagnosis. However, findings from my doctoral thesis are in line with previous studies suggesting that the risk of microvascular disease is higher for South Asians and other ethnic minorities (63, 88). Furthermore, findings about the odds of macrovascular disease at time of T2D diagnosis being lower for non-White ethnic groups with prior NDH then the counterpart of other ethnic groups are also in line with a recent study that found that CVD risk is greater for White ethnic groups then South Asians (52).

To my knowledge my research is the first evaluating the diabetes screening component of the

NHS Health Check. In a previous research Chang and colleagues found that attendance to this cardiovascular risk assessment and management programme was associated with increased diabetes diagnosis (251), which is in line with my findings. However, the aim of that research paper was to evaluate the entire programme without a specific focus on the evaluation of the diabetic screening component, that constitutes part of the programme, or on the management of NDH detected cases. I found that increased coverage of the programme was associated with increased detection of NDH and T2D cases and improvement in their cardiovascular risk profile. Although my study used real-world data, my findings are comparable with trial and modelling evidence suggesting that early detection of abnormal glucose metabolism through screening and subsequent intensive management reduce cardiovascular risk among individuals with NDH and newly diagnosed T2D (166, 172). Specifically in relation to glucose management, I found that individuals with newly detected NDH and T2D registered with high coverage practices had lower fasting plasma glucose levels than those registered with low coverage practices. This finding is also in line with previous studies reporting lower blood glucose levels among individuals with screen-detected T2D compared with patients detected in routine clinical care (171).

8.4 Policy Implications

Half of the study population (49.9%) had vascular disease at the time of T2D diagnosis. Additionally, almost 60% of the newly diagnosed T2D did not have glycaemic measurements recorded within three years before their diagnosis. These findings suggest that despite continuous efforts to improve detection of individuals at increased risk of T2D in England, for example with the introduction of specific guidelines for the management of individuals at

increased risk of T2D or with the implementation of a diabetes screening component within a national cardiovascular risk assessment and management programme, a great proportion of those at high risk might still be undetected or detected late. While there are many unanswered questions regarding factors contributing to NDH detection, NDH has significant clinical implications for microvascular and macrovascular diseases and T2D outcomes, and similarly to T2D the risk might be greater for individuals from ethnic minorities. Consistent findings from this doctoral thesis show that prolonged exposure to mild hyperglycaemia is associated with increased risk of developing microvascular disease that persists even after the diagnosis of T2D. A major consideration is whether targeted preventive strategies identify individuals who would benefit the most from risk assessment and, where appropriate, early management. Furthermore, it is also questioned whether these interventions would provide appropriate management for vascular risk reduction in those identified at high risk (220, 233), considering that major benefits are likely to occur from early diagnosis and treatment (166). While discussions on the pathophysiological differences between NDH subtypes continue, there have been calls to move away from a glucocentric definition towards a multifactorial detection strategy for NDH that reflects the presence of other risk factors for T2D as well as early manifestation of vascular disease (130, 240).

My findings also show that general practices that actively participated in the NHS Health Check programme had not only detected larger number of previously undiagnosed NDH and T2D cases, but achieved better glucose and cardiovascular risk management among individuals identified with high T2D risk and newly diagnosed T2D. These findings are encouraging given that official data shows that programme coverage has further improved over the past five years (193), implying that recently a greater proportion of those at high risk

of T2D might be effectively detected and managed earlier. However, the long-term effects of diabetes risk assessment programmes on hard clinical outcomes and the burden of T2D warrant further research.

The English National Health Service has recently rolled-out the NHS Diabetes Prevention Programme nationally, which involves intensive lifestyle interventions among CVD risk management in individuals with NDH. The programme is currently being evaluated but its integration within the NHS Health Check programme might have contributed to increasing efficiency of the programme in managing individuals at increased risk of T2D. Furthermore, it is still unclear at what scale would diabetes risk assessment programmes generate population-level impacts while remaining cost-effective, especially considering that such programmes have started to be implemented also in different settings with limited available resources (179). Such person-centred interventions require a higher level of engagement from individuals and their impact on health inequalities require rigorous evaluation. Besides focusing on early detection of diabetes and assessment of individuals at high risk, it is important that policy interventions include approaches, which reduce T2D risk factors across the entire population, regardless of person-level risk.

8.5 Unanswered Questions and Future Research

Over the past decade, many position papers from experts in the field have encouraged to move away from a glucocentric approach to define individuals at high risk of T2D, adopting a multifactorial detection strategy for NDH that reflects the presence of other risk factors for T2D as well as early manifestation of vascular disease (130, 240). In line with this position, in my results (Chapter 5 and 6) the currently available definitions for NDH do not seem to fully

explain differences in vascular risk across groups with different glycaemic testing and detection status before the progression to T2D. Whilst the association between mild hyperglycaemia and the risk of microvascular disease seems to be quite well explained by the current available diagnostic criteria for NDH (with very good level of overlap between them), this is not the case when considering the risk of macrovascular disease, considering that these conditions are preventable but often already present at time of T2D diagnosis. Important vascular risk factors like BMI and blood pressure, which might explain part of this variability, are not currently included as contributing factors for the definition of NDH. Furthermore, individuals from non-White ethnic groups with NDH appear to have increased odds of having vascular complications already present at time of T2D diagnosis and, although ethnicity is a well-established risk factor for T2D progression and is included in diabetes filters commonly used in clinical practice (Chapter 2), it is not taken into consideration in the current NDH definition.

Thus, a future research project might aim to profile individuals at high risk of T2D and vascular disease considering a wider range of cardiovascular risk factors, beyond the glycaemic measures, as well as the time to progression to T2D. Statistical approaches part of the structural equation modelling family like latent class analysis or latent transition analysis might be employed to answer this research question using an updated version of the current CPRD dataset which I used to answer objectives 1-3.

With the last research chapter of this doctoral thesis I evaluated the diabetes screening component of the NHS Health Check programme. However, this research project aimed at evaluating the impact of the diabetes screening component on the whole eligible population without exploring whether the programme helped narrowing inequalities across different socio-economic groups. Similarly to what Chang and colleagues did for the evaluation of the

whole programme (259), I might repeat analyses stratifying by sex, age groups, ethnic groups, and deprivation quintiles.

The NHS Diabetes Prevention Programme has started its national roll-out in June 2016, with the process expected to be completed in 2019 (188, 194). The programme offers tailored interventions to individuals with NDH, including diet and lifestyle advices, support for weight loss, and physical exercise programmes. Although general practitioners have the possibility to directly refer individuals to the NHS Diabetes Prevention Programme, the programme has now become part of the Health Check framework as well (193). Whilst the national evaluation of the NHS Diabetes Prevention Programme is currently being performed (194), this implementation might have had a positive impact on the NHS Health Check performance as well, which might warrant further evaluation. Finally, the NHS Health Check programme was rolled out nationally in 2009, therefore, it is now possible to evaluate the long-term impact of the programme using more then 10-year follow-up data for those who attended the programme in its first years. Analyses might be fully powered to evaluate long-term outcomes like CVD mortality, which might offer important information for modelling studies evaluating the impact of the implementation of diabetes screening programmes and their cost-effectiveness in different real-world settings, where limited resources might be available.

8.6 Conclusions

With this doctoral thesis using a large representative extraction of the English population I have found that both microvascular and macrovascular diseases were frequently detected at the time of T2D diagnosis. As compared with individuals with glycaemic values within the

normal range in the three years before the diagnosis of T2D, those detected with NDH were more likely to have microvascular disease already present at time of T2D diagnosis. Among those previously detected with NDH the prevalence of microvascular disease at time of T2D diagnosis was greater for those of non-White ethnic groups. Furthermore, the increased risk of developing microvascular disease associated with prior NDH persisted up to 7.5 years following the diagnosis of T2D. The association with NDH appeared to be stronger for retinopathy then nephropathy. Considering the increased vascular risk for individuals with NDH, a glucocentric approach to manage this high-risk status might not be sufficient. Timely identification of NDH and specific clustering of NDH with other risk factors for T2D might prompt earlier assessment for risk factors and tailored cardiovascular risk reduction strategies during the NDH phase to reduce the burden of vascular disease.

I also found that general practices actively participating in the NHS Health Check programme had higher detection of NDH and T2D, and better management of cardiovascular disease risk in newly diagnosed cases. Compared with counterparts registered with low coverage practices, individuals with incident NDH registered with high coverage practices had lower levels of fasting plasma glucose, cholesterol, and 10-year cardiovascular risk score over the study period. Individuals newly diagnosed with T2D in high coverage practices had lower levels of blood pressure, and fasting plasma glucose. However, further evaluation is required on long-term population-level health impacts and cost-effectiveness combined with information on effects on health inequalities before widespread implementation of similar programmes can be recommended, especially in settings with limited healthcare resources.

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10 Appendix: Additional Tables and Figures

Appendix Table 1. Definition of Non-diabetic Hyperglycaemia and study outcomes

Detection of Non-diabetic hyperglycaemia	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 Non-diabetic Hyperglycaemia, Impaired Glucose Tolerance, Impaired Glucose Metabolism, Intermediate Hyperglycaemia, and pre-diabetes
Microvascular disease present at time of diagnosis of Type 2 diabetes (diagnosed in the five years before and fifteen months after the diagnosis of Type 2 diabetes)	
Diabetic retinopathy	Diagnostic codes for diabetic retinopathy (including codes 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 m^2 ICD-10 (N18.3; N18.4; N18.5) OPCS-4 (M01; X40)
Macrovascular disease at time of diagnosis of Type 2 diabetes (diagnosed before 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)
Coronary heart disease Acute Myocardial Infarction (AMI), Coronary Artery Disease (CAD), Coronary Revascularisation Procedures	**AMI** Diagnostic codes for acute myocardial infarction ICD-10 (I21; I22) **CAD** Diagnostic codes for CAD ICD-10 (I20; I25) **Coronary Revascularisation Procedures** OPCS-4.6: K49; K50; K75; K40-K46)
Peripheral Arterial disease Peripheral arterial	**PAD** Diagnostic codes for peripheral arterial disease ICD-10 (E11.5; I70.2/7; I70.92) **AMPUTATION**

disease (PAD), non-traumatic 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)

Appendix Table 2. 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 Non-diabetic Hyperglycaemia before the diagnosis of Type 2 diabetes. Results are presented using NICE and ADA criteria for the definition of Non-diabetic Hyperglycaemia.

Notes: Clinical data within three years before the diagnosis of Type 2 diabetes were used to define the detection of non-diabetic hyperglycaemia. 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 non-diabetic hyperglycaemia. Abbreviations: FPG: fasting plasma glucose, OGTT: glucose tolerance test (2-hour after 75 g glucose load), ACEi: Angiotensin-converting-enzyme inhibitor, ARBs: Angiotensin II receptor blockers.

NICE criteria to define non-diabetic hyperglycaemia: 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 non-diabetic hyperglycaemia: 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 measures recorded before the diagnosis of Type 2 diabetes	NICE DIAGNOSTIC CRITERIA[2]			ADA DIAGNOSTIC CRITERIA[3]		
			Glycaemic values within the normal range before the diagnosis of T2D	Non-diabetic hyperglycaemia detected before the diagnosis of T2D	p-values	Glycaemic values within the normal range before the diagnosis of T2D	Non-diabetic hyperglycaemia 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		3.2	2.7	
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		44.9	51.2	
Current smoker	16.1	19.8	18.6	16.3		18.2	16.3	

(continued)

	Total	No glycaemic measures recorded before the diagnosis of Type 2 diabetes	NICE DIAGNOSTIC CRITERIA[2]			ADA DIAGNOSTIC CRITERIA[3]		
			Glycaemic values within the normal range before the diagnosis of T2D	Non-diabetic hyperglycaemia detected before the diagnosis of T2D	p-values	Glycaemic values within the normal range before the diagnosis of T2D	Non-diabetic hyperglycaemia 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)	<0.001Ω	16.9 (13.6)	15.0 (11.9)	<0.001Ω
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		23.1	24.3	
5 Q - most deprived	25.6	25.8	27.3	24.6		27.4	24.6	

Appendix Table 3. Characteristics of individuals with Non-diabetic Hyperglycaemia stratified by having a diagnostic code for Non-diabetic Hyperglycaemia recorded. Results are presented using WHO/IEC, NICE, and ADA criteria for the definition of Non-diabetic Hyperglycaemia.

Notes: Clinical data within three years before the diagnosis of Type 2 diabetes were used to define the detection of non-diabetic hyperglycaemia. 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 non-diabetic hyperglycaemia and non-diabetic hyperglycaemia without a diagnostic label recorded for non-diabetic hyperglycaemia.

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 non-diabetic hyperglycaemia: 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 non-diabetic hyperglycaemia: 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 non-diabetic hyperglycaemia: 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 non-diabetic hyperglycaemia

§ ANOVA test for the comparison of groups with and without a diagnostic label recorded for non-diabetic hyperglycaemia

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 DIAGNOSTIC CRITERIA[1]			NICE DIAGNOSTIC CRITERIA[2]			ADA DIAGNOSTIC CRITERIA[3]		
	Tested before the diagnosis of T2D (NDH without diagnostic code assigned)	Tested before the diagnosis of T2D (NDH detected and diagnostic code assigned)	p-values	Tested before the diagnosis of T2D (NDH without diagnostic code assigned)	Tested before the diagnosis of T2D (NDH detected and diagnostic code assigned)	p-values	Tested before the diagnosis of T2D (NDH without diagnostic code assigned)	Tested before the diagnosis of T2D (NDH detected and diagnostic code assigned)	p-values
N	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)	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[§]
Ethnicity (%)									
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		3.4	3.2		3.4	3.2	
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	
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;	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[§]

mean (SD)
(continued)

	WHO/IEC DIAGNOSTIC CRITERIA[1]			NICE DIAGNOSTIC CRITERIA[2]			ADA DIAGNOSTIC CRITERIA[3]		
	Tested before the diagnosis of Type 2 diabetes (NDH without diagnostic code assigned)	Tested before the diagnosis of Type 2 diabetes (NDH detected and diagnostic code assigned)	p-values	Tested before the diagnosis of Type 2 diabetes (NDH without diagnostic code assigned)	Tested before the diagnosis of Type 2 diabetes (NDH detected and diagnostic code assigned)	p-values	Tested before the diagnosis of Type 2 diabetes (NDH without diagnostic code assigned)	Tested before the diagnosis of Type 2 diabetes (NDH detected and diagnostic code assigned)	p-values
Number of chronic diseases; mean (SD)	3.1 (2.0)	3.1 (2.0)	0.006$^{\Omega}$	3.1 (2.1)	3.1 (2.0)	0.883$^{\Omega}$	3.1 (2.1)	3.1 (2.0)	0.831$^{\Omega}$
Medications (%)									
Anti-hypertensive	67.6	67.5	0.689$^{¥}$	66.9	67.5	0.203$^{¥}$	66.4	67.5	0.015$^{¥}$
ACEi/ARBs	50	50.5	0.306$^{¥}$	49.5	50.4	0.035$^{¥}$	49	50.5	0.001$^{¥}$
Anti-lipid medications	62.7	64	0.007$^{¥}$	61.6	64	<0.001$^{¥}$	61	64	<0.001$^{¥}$
Anti-diabetic*	33.5	35.5	<0.001$^{¥}$	32.8	35.5	<0.001$^{¥}$	32.1	35.4	<0.001$^{¥}$
Biguanides	31.5	33.2	0.001$^{¥}$	30.6	33.2	<0.001$^{¥}$	29.9	33.2	<0.001$^{¥}$
Sulphonylureas	4.3	4.7	0.052$^{¥}$	4.7	4.7	0.914$^{¥}$	4.5	4.7	0.237$^{¥}$
Insulin	1.2	1.3	0.123$^{¥}$	1.5	1.3	0.050$^{¥}$	1.4	1.3	0.415$^{¥}$
Other	0.1	0.2	0.100$^{¥}$	0.1	0.2	0.055$^{¥}$	0.15	0.21	0.147$^{¥}$
Anti-platelet	33.0	33.3	0.524	33.0	33.3	0.491	32.5	33.3	0.064
Number of primary care visits in the year before T2D diagnosis; mean (SD)	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§
Index of Multiple Deprivation 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		17.7	19		17.8	19	
3 Q	19.7	19.2	<0.001$^{¥}$	19.5	19.2	<0.001$^{¥}$	19.4	19.2	<0.001$^{¥}$
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	

Appendix Table 4. 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 non-diabetic hyperglycaemia. 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 non-diabetic hyperglycaemia.

WHO/IEC criteria to define non-diabetic hyperglycaemia: 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 non-diabetic hyperglycaemia: 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 non-diabetic hyperglycaemia: 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%

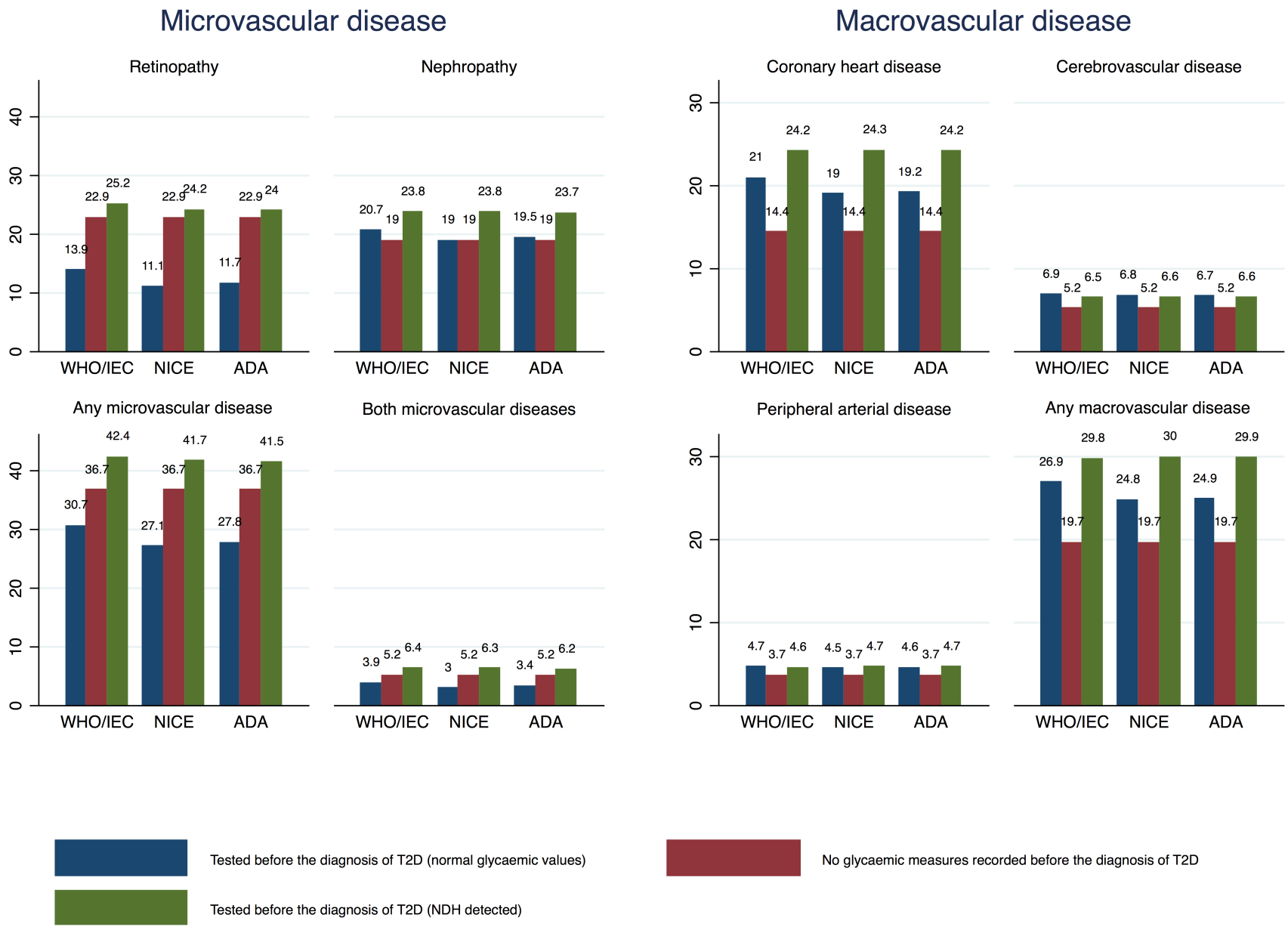
Abbreviations: T2D: Type 2 diabetes FPG: fasting plasma glucose, OGTT: glucose tolerance test (2-hour after 75 g glucose load).

	Glycaemic values within the normal range before the diagnosis of T2D			Non-diabetic hyperglycaemia detected before the diagnosis of T2D		
	DIAGNOSTIC CRITERIA			DIAGNOSTIC CRITERIA		
	WHO/IEC[1]	NICE[2]	ADA[3]	WHO/IEC[1]	NICE[2]	ADA[3]
Type 2 diabetes diagnosed from 2004 to 2011						
N	11,567	7,086	7,695	27,121	31,602	30,993
TYPE OF GLYCAEMIC MEASURES RECORDED BEFORE THE DIAGNOSIS OF T2D (%)						
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 T2D (%)						
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						
N	21,902	14,431	14,317	43,885	51,356	51,470
TYPE OF GLYCAEMIC MEASURES RECORDED BEFORE THE DIAGNOSIS OF T2D (%)						
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%
OGTT	4.5%	2.0%	3.0%	22.6%	20.6%	20.3%

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

Appendix Figure 1. Prevalence of microvascular (retinopathy and nephropathy) and macrovascular (coronary heart disease, cerebrovascular, and peripheral arterial disease) disease present at time of the diagnosis of Type 2 diabetes according to Non-diabetic Hyperglycaemia 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%.

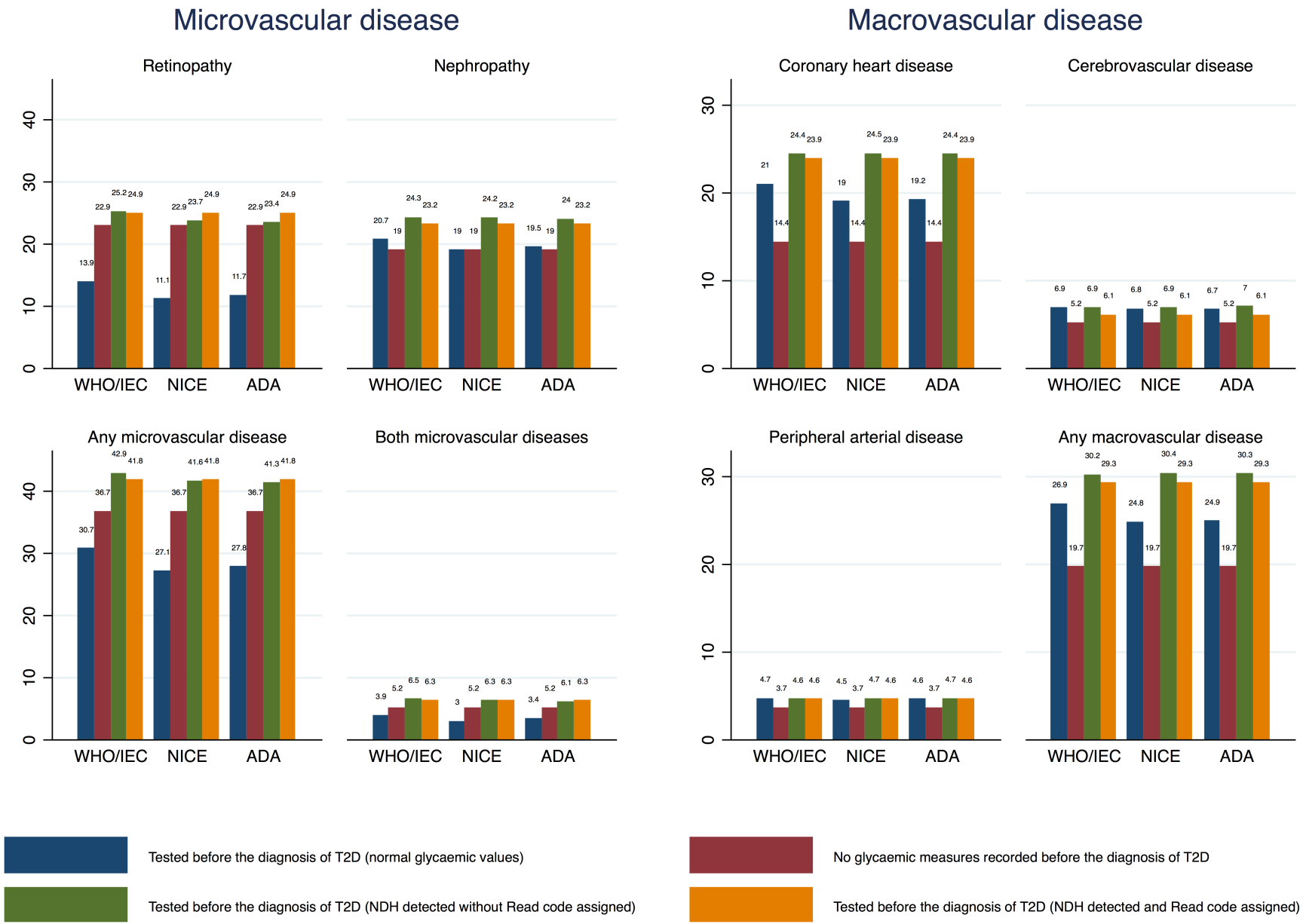

Microvascular disease
Macrovascular disease
Retinopathy
Nephropathy
Coronary heart disease
Cerebrovascular disease
Any microvascular disease
Both microvascular diseases
Peripheral arterial disease
Any macrovascular disease
WHO/IEC
NICE
ADA
Tested before the diagnosis of T2D (normal glycaemic values)
Tested before the diagnosis of T2D (NDH detected)
No glycaemic measures recorded before the diagnosis of T2D

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

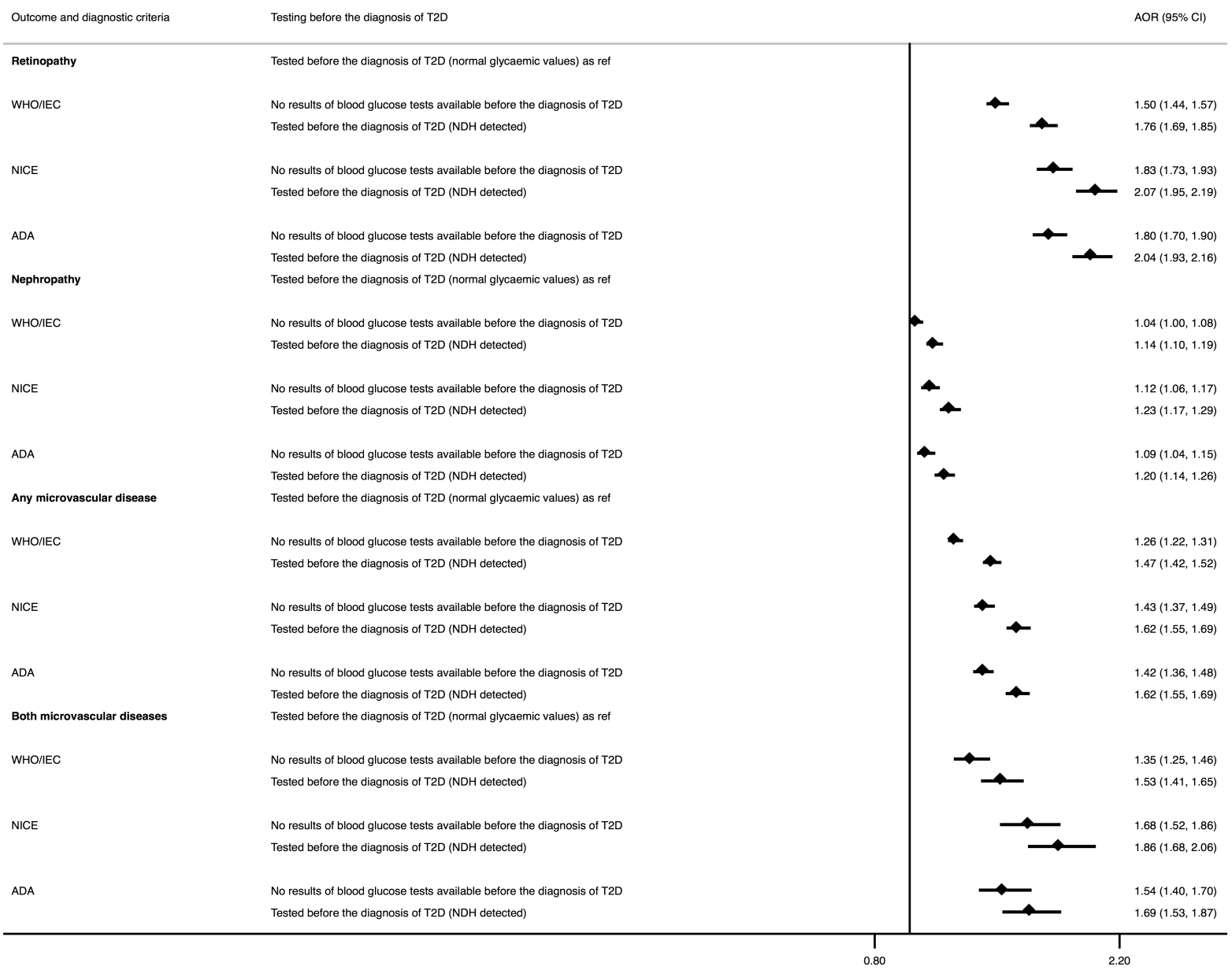
2) NICE criteria: 5.5-6.9 mmol/L, OGTT 7.8-11.1 mmol/L, HbA1c 42 to 47 mmol/mol or 6.0-6.4%;

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
Coronary heart disease
Cerebrovascular disease
Any microvascular disease
Both microvascular diseases
Peripheral arterial disease
Any macrovascular disease
WHO/IEC
NICE
ADA
Tested before the diagnosis of T2D (normal glycaemic values)
No glycaemic measures recorded before the diagnosis of T2D
Tested before the diagnosis of T2D (NDH detected without Read code assigned)
Tested before the diagnosis of T2D (NDH detected and Read code assigned)

Appendix Figure 3. Association between glycaemic testing and detection of Non-diabetic Hyperglycaemia 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, NDH: non-diabetic hyperglycaemia.


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 (NDH 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 (NDH 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 (NDH 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 (NDH 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 (NDH 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 (NDH 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 (NDH 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 (NDH 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 (NDH detected)
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 (NDH 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 (NDH detected)
1.86 (1.68, 2.06)
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 (NDH detected)
1.69 (1.53, 1.87)
0.80
2.20

Appendix Figure 4. Association between glycaemic testing and detection of non-diabetic hyperglycaemia 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, NDH: non-diabetic hyperglycaemia

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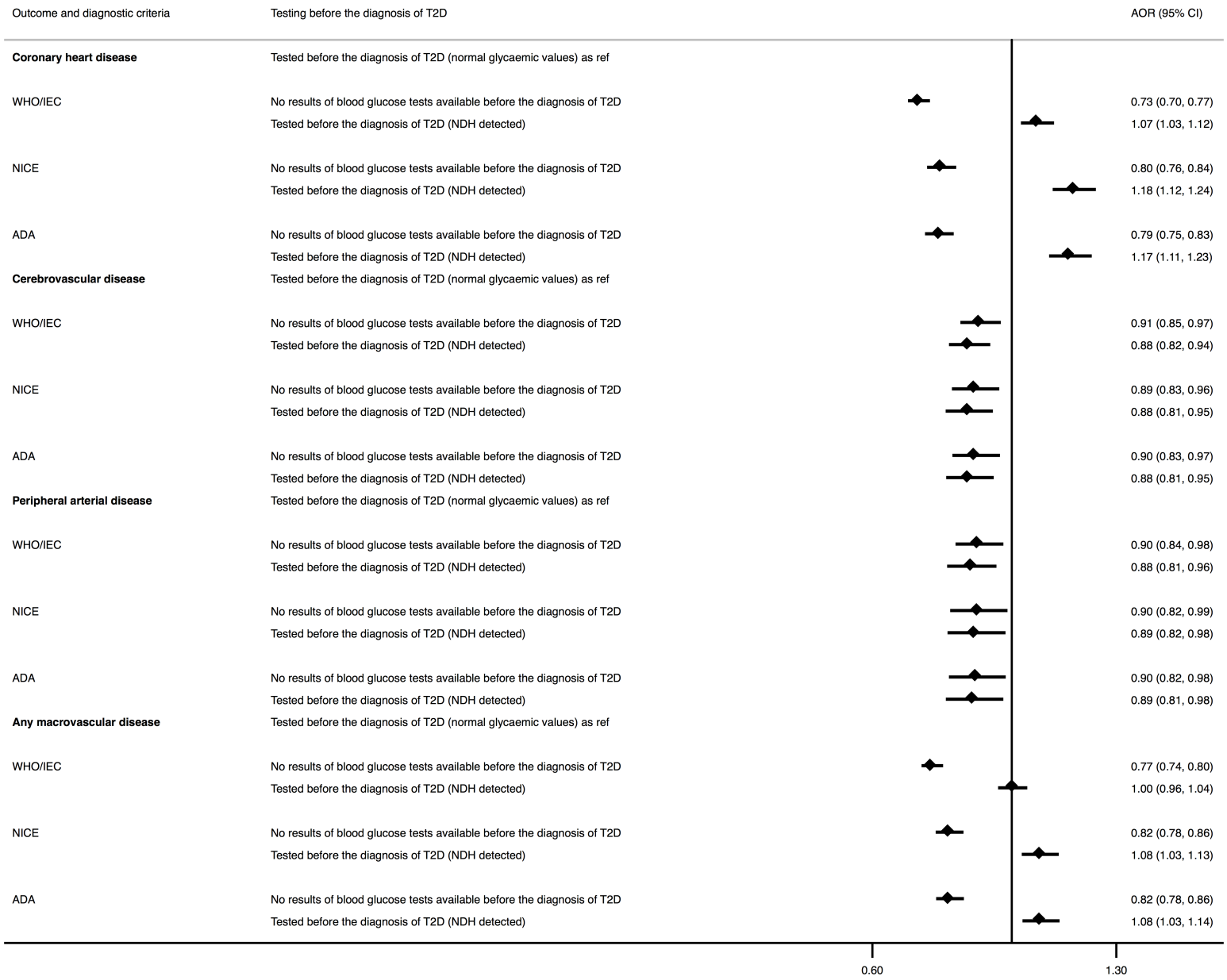

Outcome and diagnostic criteria
Testing before the diagnosis of T2D
AOR (95% CI)
Coronary heart disease
Tested before the diagnosis of T2D (normal glycaemic values) as ref
WHO/IEC
No results of blood glucose tests available before the diagnosis of T2D
0.73 (0.70, 0.77)
Tested before the diagnosis of T2D (NDH detected)
1.07 (1.03, 1.12)
NICE
No results of blood glucose tests available before the diagnosis of T2D
0.80 (0.76, 0.84)
Tested before the diagnosis of T2D (NDH detected)
1.18 (1.12, 1.24)
ADA
No results of blood glucose tests available before the diagnosis of T2D
0.79 (0.75, 0.83)
Tested before the diagnosis of T2D (NDH 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, 0.97)
Tested before the diagnosis of T2D (NDH detected)
0.88 (0.82, 0.94)
NICE
No results of blood glucose tests available before the diagnosis of T2D
0.89 (0.83, 0.96)
Tested before the diagnosis of T2D (NDH detected)
0.88 (0.81, 0.95)
ADA
No results of blood glucose tests available before the diagnosis of T2D
0.90 (0.83, 0.97)
Tested before the diagnosis of T2D (NDH detected)
0.88 (0.81, 0.95)
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, 0.98)
Tested before the diagnosis of T2D (NDH detected)
0.88 (0.81, 0.96)
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 (NDH detected)
0.89 (0.82, 0.98)
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 (NDH detected)
0.89 (0.81, 0.98)
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 (NDH detected)
1.00 (0.96, 1.04)
NICE
No results of blood glucose tests available before the diagnosis of T2D
0.82 (0.78, 0.86)
Tested before the diagnosis of T2D (NDH 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 (NDH detected)
1.08 (1.03, 1.14)
0.60
1.30

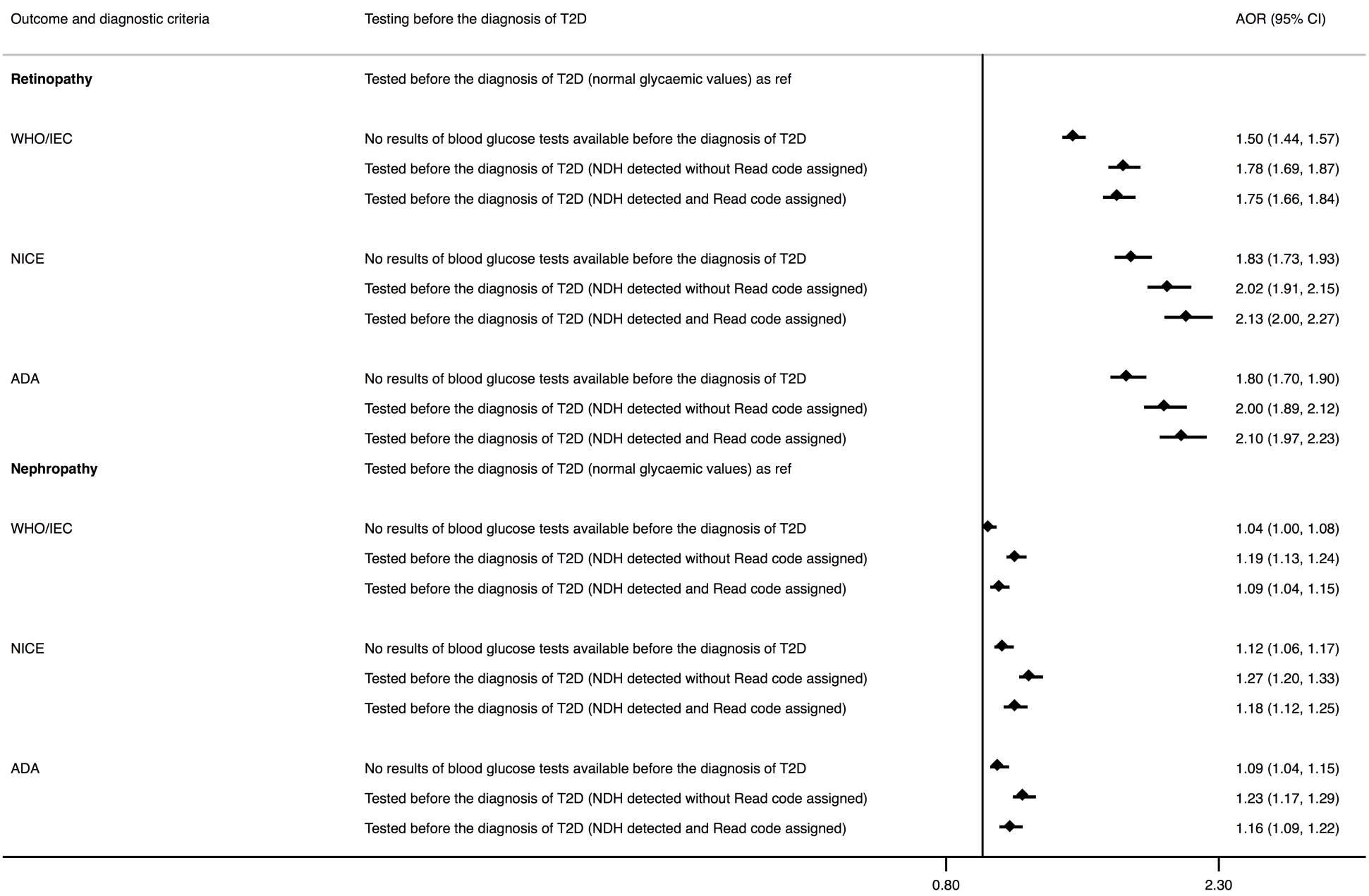
Appendix Figure 5. Association between glycaemic testing and detection of non-diabetic hyperglycaemia and the presence of microvascular disease at the time of diagnosis of Type 2 diabetes.

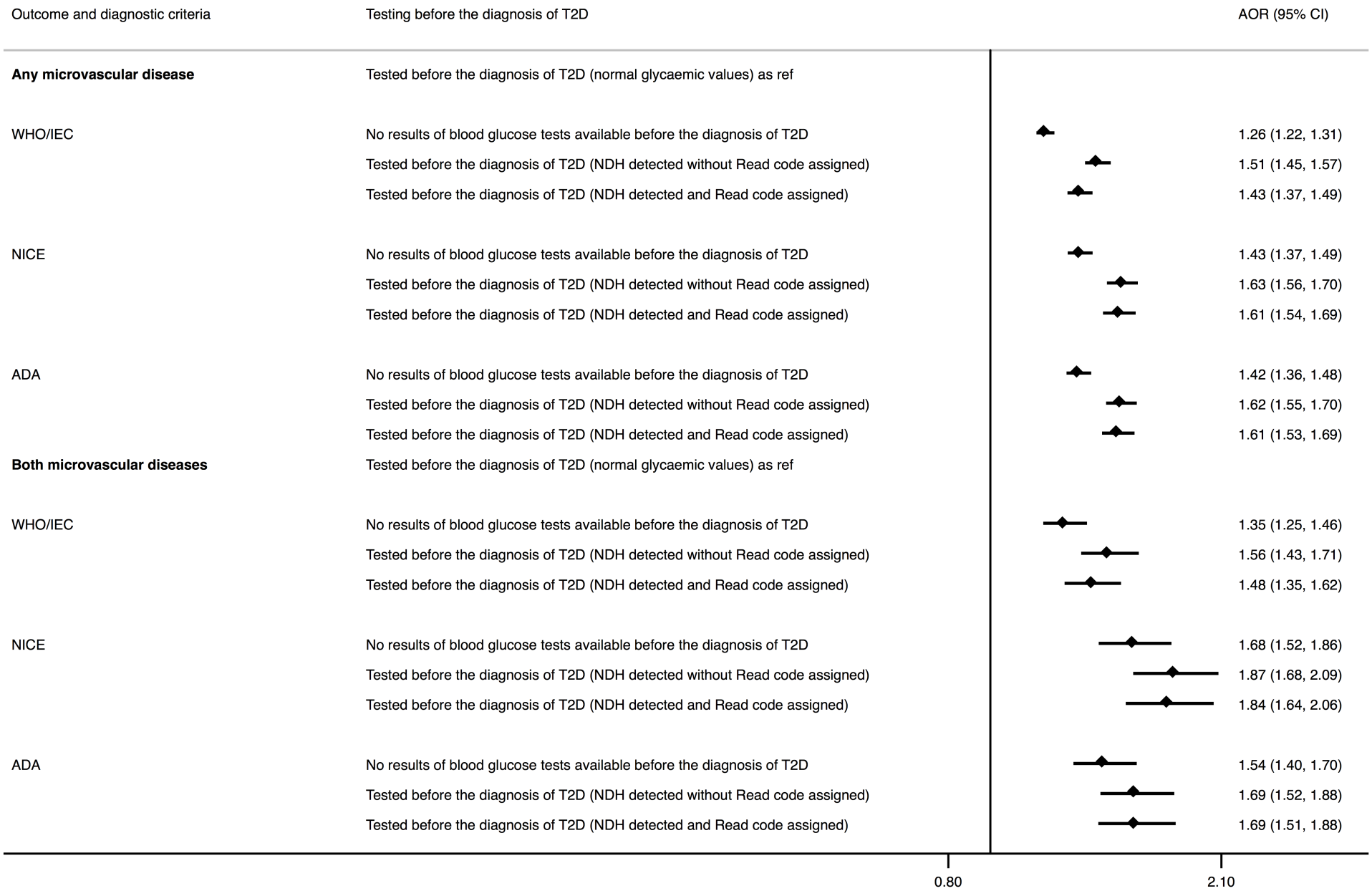
Notes: Adjusted Odds Ratios (AOR) and 95% confidence intervals (95% CI) have been estimated employing multivariable logistic regression models adjusted for age, sex, ethnicity (White, South Asian, Black, Other, Unknown), smoking status (non-smoker, ex-smoker, smoker), total cholesterol, systolic and 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, NDH: non-diabetic hyperglycaemia.

WHO/IEC criteria to define non-diabetic hyperglycaemia: 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 non-diabetic hyperglycaemia: 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 non-diabetic hyperglycaemia: 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)
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 (NDH detected without Read code assigned)
1.78 (1.69, 1.87)
Tested before the diagnosis of T2D (NDH detected and Read code assigned)
1.75 (1.66, 1.84)
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 (NDH detected without Read code assigned)
2.02 (1.91, 2.15)
Tested before the diagnosis of T2D (NDH detected and Read code assigned)
2.13 (2.00, 2.27)
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 (NDH detected without Read code assigned)
2.00 (1.89, 2.12)
Tested before the diagnosis of T2D (NDH detected and Read code assigned)
2.10 (1.97, 2.23)
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 (NDH detected without Read code assigned)
1.19 (1.13, 1.24)
Tested before the diagnosis of T2D (NDH detected and Read code assigned)
1.09 (1.04, 1.15)
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 (NDH detected without Read code assigned)
1.27 (1.20, 1.33)
Tested before the diagnosis of T2D (NDH detected and Read code assigned)
1.18 (1.12, 1.25)
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 (NDH detected without Read code assigned)
1.23 (1.17, 1.29)
Tested before the diagnosis of T2D (NDH detected and Read code assigned)
1.16 (1.09, 1.22)
0.80
2.30


Outcome and diagnostic criteria
Testing before the diagnosis of T2D
AOR (95% CI)
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 (NDH detected without Read code assigned)
1.51 (1.45, 1.57)
Tested before the diagnosis of T2D (NDH detected and Read code assigned)
1.43 (1.37, 1.49)
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 (NDH detected without Read code assigned)
1.63 (1.56, 1.70)
Tested before the diagnosis of T2D (NDH detected and Read code assigned)
1.61 (1.54, 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 (NDH detected without Read code assigned)
1.62 (1.55, 1.70)
Tested before the diagnosis of T2D (NDH detected and Read code assigned)
1.61 (1.53, 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 (NDH detected without Read code assigned)
1.56 (1.43, 1.71)
Tested before the diagnosis of T2D (NDH detected and Read code assigned)
1.48 (1.35, 1.62)
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 (NDH detected without Read code assigned)
1.87 (1.68, 2.09)
Tested before the diagnosis of T2D (NDH detected and Read code assigned)
1.84 (1.64, 2.06)
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 (NDH detected without Read code assigned)
1.69 (1.52, 1.88)
Tested before the diagnosis of T2D (NDH detected and Read code assigned)
1.69 (1.51, 1.88)
0.80
2.10

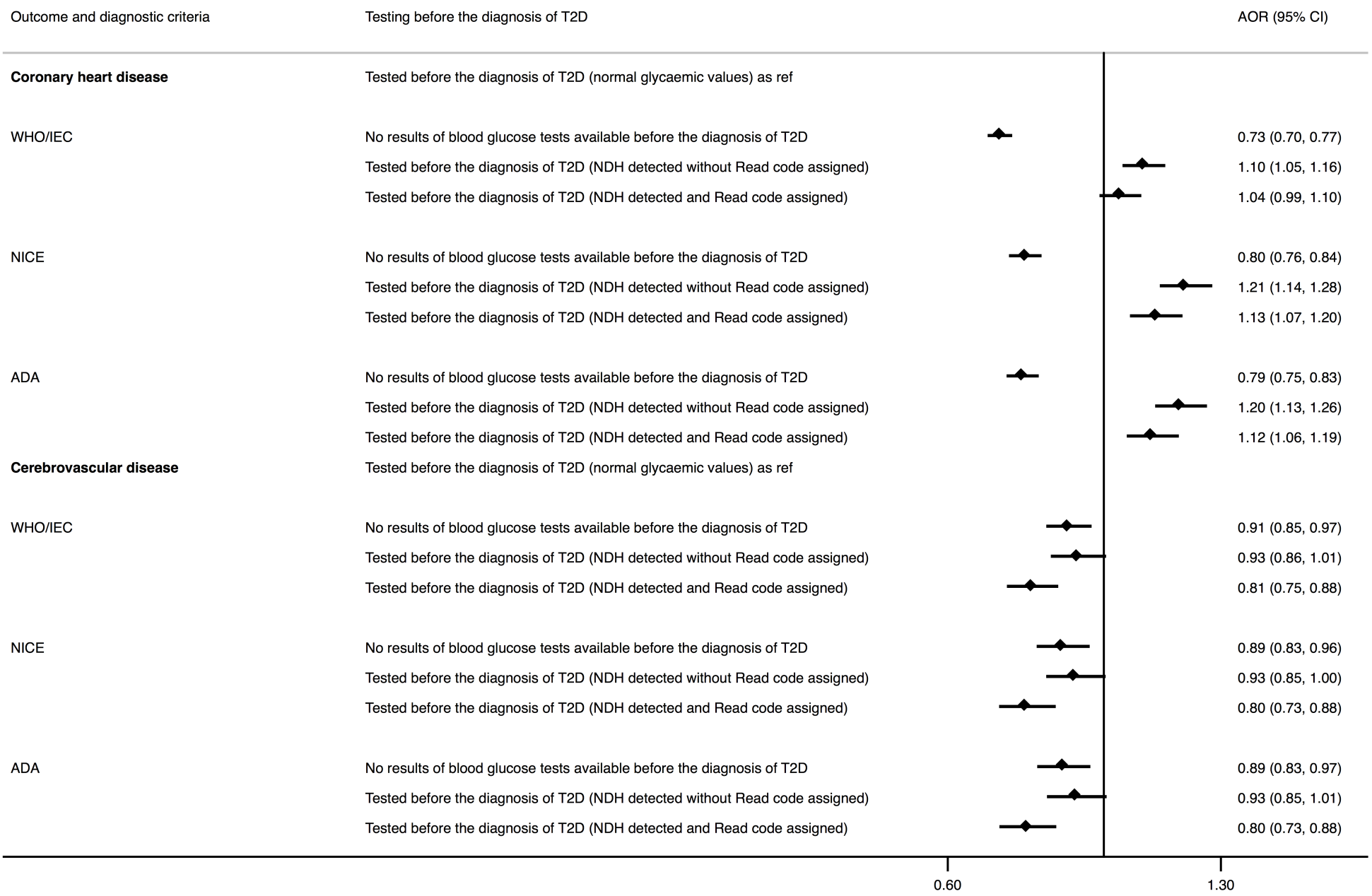
Appendix Figure 6. Association between testing and detection of Non-diabetic Hyperglycaemia and presence of macrovascular disease at the time of diagnosis of Type 2 diabetes. For individuals with non-diabetic hyperglycaemia detected a further stratification has been considered according to whether a corresponding diagnostic code was assigned at time of Non-diabetic Hyperglycaemia detection.

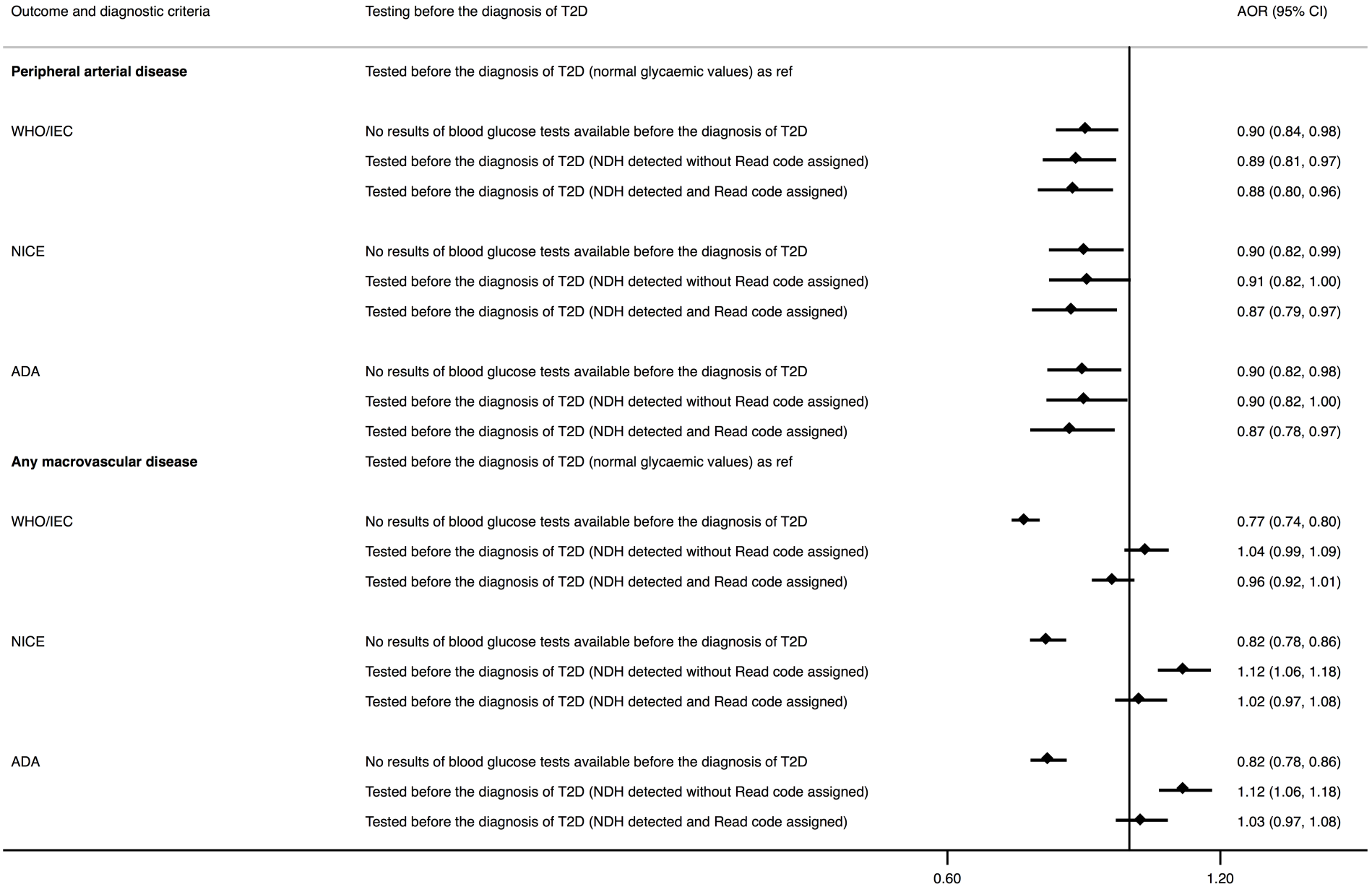
Notes: Adjusted Odds Ratios (AOR) and 95% confidence intervals (95% CI) have been estimated employing multivariable logistic regression models adjusted for age, sex, ethnicity (White, South Asian, Black, Other, Unknown), smoking status (non-smoker, ex-smoker, smoker), total cholesterol, systolic and 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, NDH: non-diabetic hyperglycaemia.

WHO/IEC criteria to define non-diabetic hyperglycaemia: 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 non-diabetic hyperglycaemia: 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 non-diabetic hyperglycaemia: 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)
Coronary heart 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)
Tested before the diagnosis of T2D (NDH detected without Read code assigned)
1.10 (1.05, 1.16)
Tested before the diagnosis of T2D (NDH detected and Read code assigned)
1.04 (0.99, 1.10)
NICE
No results of blood glucose tests available before the diagnosis of T2D
0.80 (0.76, 0.84)
Tested before the diagnosis of T2D (NDH detected without Read code assigned)
1.21 (1.14, 1.28)
Tested before the diagnosis of T2D (NDH detected and Read code assigned)
1.13 (1.07, 1.20)
ADA
No results of blood glucose tests available before the diagnosis of T2D
0.79 (0.75, 0.83)
Tested before the diagnosis of T2D (NDH detected without Read code assigned)
1.20 (1.13, 1.26)
Tested before the diagnosis of T2D (NDH detected and Read code assigned)
1.12 (1.06, 1.19)
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, 0.97)
Tested before the diagnosis of T2D (NDH detected without Read code assigned)
0.93 (0.86, 1.01)
Tested before the diagnosis of T2D (NDH detected and Read code assigned)
0.81 (0.75, 0.88)
NICE
No results of blood glucose tests available before the diagnosis of T2D
0.89 (0.83, 0.96)
Tested before the diagnosis of T2D (NDH detected without Read code assigned)
0.93 (0.85, 1.00)
Tested before the diagnosis of T2D (NDH detected and Read code assigned)
0.80 (0.73, 0.88)
ADA
No results of blood glucose tests available before the diagnosis of T2D
0.89 (0.83, 0.97)
Tested before the diagnosis of T2D (NDH detected without Read code assigned)
0.93 (0.85, 1.01)
Tested before the diagnosis of T2D (NDH detected and Read code assigned)
0.80 (0.73, 0.88)
0.60
1.30


Outcome and diagnostic criteria
Testing before the diagnosis of T2D
AOR (95% CI)
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, 0.98)
Tested before the diagnosis of T2D (NDH detected without Read code assigned)
0.89 (0.81, 0.97)
Tested before the diagnosis of T2D (NDH detected and Read code assigned)
0.88 (0.80, 0.96)
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 (NDH detected without Read code assigned)
0.91 (0.82, 1.00)
Tested before the diagnosis of T2D (NDH detected and Read code assigned)
0.87 (0.79, 0.97)
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 (NDH detected without Read code assigned)
0.90 (0.82, 1.00)
Tested before the diagnosis of T2D (NDH detected and Read code assigned)
0.87 (0.78, 0.97)
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 (NDH detected without Read code assigned)
1.04 (0.99, 1.09)
Tested before the diagnosis of T2D (NDH detected and Read code assigned)
0.96 (0.92, 1.01)
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 (NDH detected without Read code assigned)
1.12 (1.06, 1.18)
Tested before the diagnosis of T2D (NDH detected and Read code assigned)
1.02 (0.97, 1.08)
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 (NDH detected without Read code assigned)
1.12 (1.06, 1.18)
Tested before the diagnosis of T2D (NDH detected and Read code assigned)
1.03 (0.97, 1.08)
0.60
1.20

Appendix Table 5. Characteristics of the study population in the year following the diagnosis of Type 2 diabetes stratified by ethnical group and by whether individuals were tested and reached detection thresholds for NDH before the diagnosis of Type 2 diabetes.

Notes: Results are presented using World Health Organization/International Expert Committee criteria for the definition of Non-diabetic Hyperglycaemia. Clinical data within three years before the diagnosis of Type 2 diabetes were used to define the detection of pre-diabetes. P-values from Chi-square and ANOVA tests, as appropriate, are reported for comparison between the three groups defined by testing and detection of pre-diabetes. Abbreviations: NDH: non-diabetic hyperglycaemia, 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/ International Expert Committee criteria to define NDH: 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%

¥ Chi-square test was performed to assess the unadjusted difference between groups

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

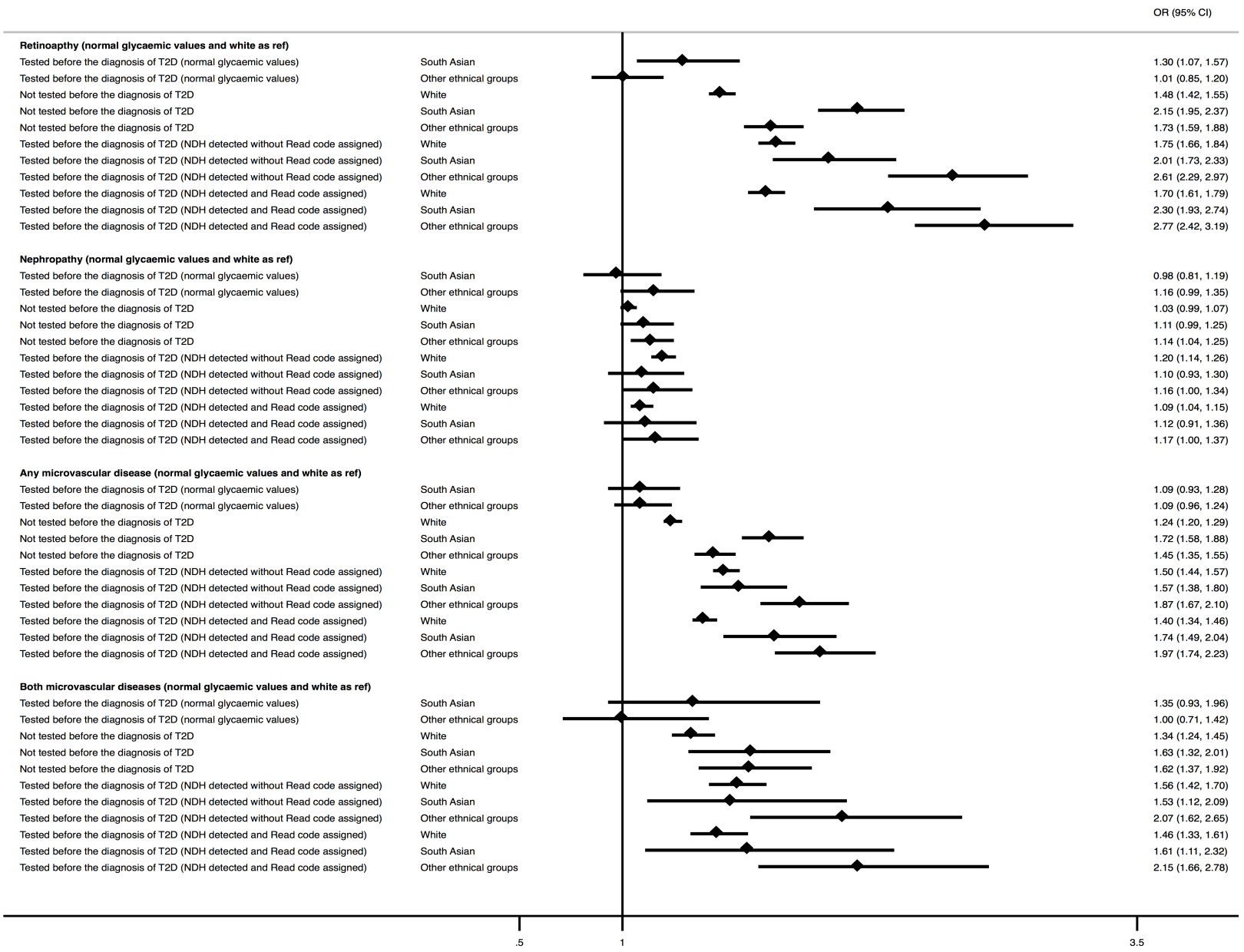
*If an individual was prescribed multiple medications from different anti-diabetic classes, each class was considered (e.g. for an individual who was prescribed biguanides and sulphonylureas in the year following the diagnosis of Type 2 diabetes, data were recorded as follows: anti-diabetic YES; biguanides YES; sulphonylureas YES; insulin NO; other anti-diabetic NO).

	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 (NDH detected)		
	White	**South-Asian**	**Others**	**White**	**South-Asian**	**Others**	**White**	**South-Asian**	**Others**
N	19,533	948	1,421	86,303	2,883	4,763	39,381	1,904	2,600
%	89.2	4.3	6.5	91.9	3.1	5.1	89.7	4.3	5.9
FEMALE (%)	55.2	58.5	53.4	48.6	48.1	52.2	46.3	49.4	51.4
AGE (years; mean (SD))	62.3 (14.7)	52.3 (13.9)	53.7 (13.4)	61.0 (14.7)	50.8 (12.9)	51.7 (12.9)	65.2 (12.3)	55.3 (12.4)	56.9 (12.2)
SMOKING STATUS (%)									
Non-smoker	32.9	62.5	57.8	34.9	64.1	54.8	29.6	60.9	52.1
Ex-smoker	48.4	26.6	30.2	44.9	22.2	29.1	53.9	26.7	34.3
Current smoker	18.7	10.9	12	20.2	13.7	16.1	16.5	12.3	13.6
HbA1c at diagnosis (mmol/mol; mean(SD))	50.7 (16.4)	53.2 (21.1)	52.2 (18.9)	67.7 (22.2)	70.4 (23.2)	68.8 (25.7)	58.3 (16.4)	58.4 (16.8)	58.2 (17.3)
BMI (kg/m2; mean (SD))	29.7 (7.1)	28.0 (5.5)	29.5 (6.3)	30.1 (6.8)	28.2 (5.4)	29.2 (6.1)	31.5 (6.5)	29.1 (5.3)	30.3 (6.1)
SYSTOLIC BLOOD PRESSURE (mm Hg; mean (SD))	134.5 (15.6)	128.0 (15.3)	131.4 (15.4)	136.8 (16.5)	130.7 (16.5)	131.9 (16.7)	137.9 (14.3)	131.8 (14.3)	134.4 (14.4)
DIASTOLIC BLOOD PRESSURE (mm Hg; mean (SD))	78.6 (9.3)	78.5 (8.9)	79.6 (9.3)	80.1 (9.6)	80.1 (9.7)	80.5 (9.8)	79.3 (8.8)	79.9 (8.7)	80.8 (8.7)
TOTAL CHOLESTEROL (mmol/L; mean (SD))	5.0 (1.1)	5.0 (1.0)	5.0 (1.1)	5.2 (1.1)	5.1 (1.0)	5.1 (1.1)	4.9 (1.1)	5.0 (1.0)	5.0 (1.0)
NUMBER OF CHRONIC DISEASES (mean (SD))	3.3 (2.1)	2.4 (1.9)	2.3 (1.8)	2.5 (2.0)	1.8 (1.7)	1.8 (1.7)	3.2 (2.)	2.5 (1.9)	2.4 (1.8)
MEDICATIONS IN THE YEAR FOLLOWING T2D diagnosis (%)									
Anti-hypertensive	54.7	38.2	42.9	48.6	33.4	35.3	69.4	48.5	54
Ace/Arb	39	28.5	28	34.9	25.3	24.5	51.8	37.2	36.2
Anti-lipids	46.4	37.3	33.2	45	37.4	33.6	64.7	52.7	49.8
Anti-diabetic*	16.9	23.1	23.9	39.6	47.3	45.3	29.1	38.1	38.9
Biguanides	14.5	20.7	21	34.8	42.6	40	27.1	36.2	36.9
Sulphonylureas	2.9	4.2	4.5	8.9	9.3	10.3	3.3	3.7	4.2
Insulin	1.8	1.8	3.8	3	2.7	4.6	1	1	1.5
Other anti-diabetic	0.1	0.1	0	0.1	0.1	0.1	0.2	0	0
Anti-platelet	27.4	18.8	16.5	25	17.3	13.7	34.4	24.4	20.4
NUMBER PRIMARY CARE VISITS IN THE YEAR BEFORE DIAGOSIS of T2D (mean (SD))	22.5 (14.9)	20.4 (13.1)	19.5 (12.5)	19.2 (12.7)	16.8 (11.2)	16.7 (11.0)	21.0 (12.8)	19.4 (11.1)	18.8 (10.7)
GENERAL PRACTICE INDEX OF MULTI-DEPRIVATION (%)									
1 Q - least deprived	13	11.9	8.2	15.1	10.8	8.5	14.2	10.8	8

2 Q	19.6	17.5	12.5	19.8	17.2	15	18.8	13	12.9
3 Q	17.5	19.8	21.4	19.1	18.1	18.9	19.4	20.9	19.2
4 Q	23.1	25.3	30.9	20.6	26.7	26.4	23.7	27.6	28.6
5 Q - most deprived	26.7	25.4	27	25.5	27.1	31.1	23.9	27.7	31.3

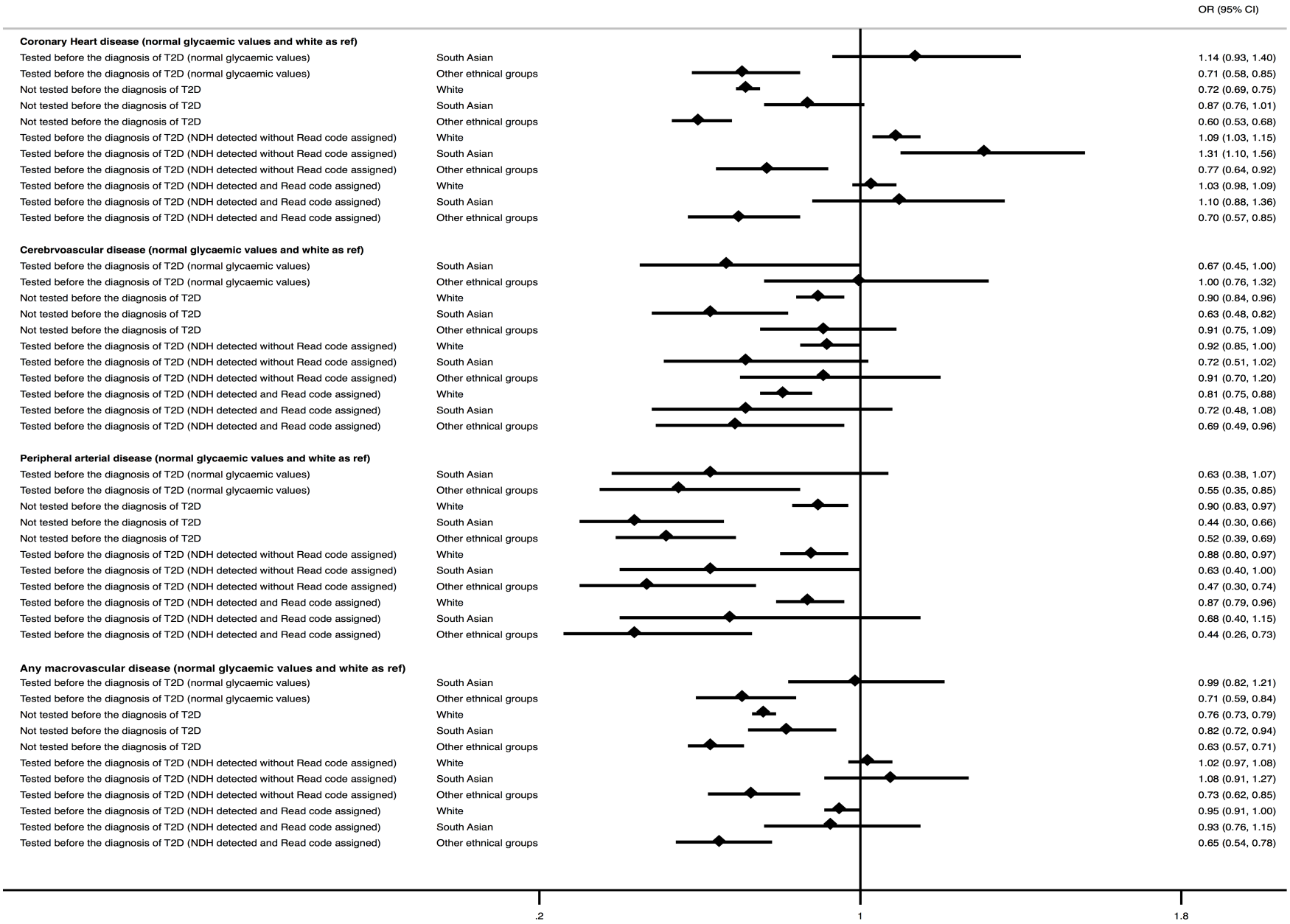
Appendix Figure 7. Association between glycaemic testing and detection of Non-diabetic Hyperglycaemia, ethnicity, and presence of microvascular disease at the time of diagnosis of Type 2 diabetes. Individuals with Non-diabetic Hyperglycaemia were further classified into two groups based on whether a diagnostic code for Non-diabetic Hyperglycaemia was recorded in their health records.

Notes: Adjusted Odds Ratios (AOR) and 95% confidence intervals (95% CI) have been estimated employing multivariable logistic regression models. An interaction term between NDH status before the diagnosis of Type 2 diabetes and ethnicity (White, South Asian, others) was fitted. Models were also adjusted for age, sex, 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: NDH: non-diabetic hyperglycaemia.


OR (95% CI)
Retinoapthy (normal glycaemic values and white as ref)
Tested before the diagnosis of T2D (normal glycaemic values) South Asian 1.30 (1.07, 1.57)
Tested before the diagnosis of T2D (normal glycaemic values) Other ethnical groups 1.01 (0.85, 1.20)
Not tested before the diagnosis of T2D White 1.48 (1.42, 1.55)
Not tested before the diagnosis of T2D South Asian 2.15 (1.95, 2.37)
Not tested before the diagnosis of T2D Other ethnical groups 1.73 (1.59, 1.88)
Tested before the diagnosis of T2D (NDH detected without Read code assigned) White 1.75 (1.66, 1.84)
Tested before the diagnosis of T2D (NDH detected without Read code assigned) South Asian 2.01 (1.73, 2.33)
Tested before the diagnosis of T2D (NDH detected without Read code assigned) Other ethnical groups 2.61 (2.29, 2.97)
Tested before the diagnosis of T2D (NDH detected and Read code assigned) White 1.70 (1.61, 1.79)
Tested before the diagnosis of T2D (NDH detected and Read code assigned) South Asian 2.30 (1.93, 2.74)
Tested before the diagnosis of T2D (NDH detected and Read code assigned) Other ethnical groups 2.77 (2.42, 3.19)
Nephropathy (normal glycaemic values and white as ref)
Tested before the diagnosis of T2D (normal glycaemic values) South Asian 0.98 (0.81, 1.19)
Tested before the diagnosis of T2D (normal glycaemic values) Other ethnical groups 1.16 (0.99, 1.35)
Not tested before the diagnosis of T2D White 1.03 (0.99, 1.07)
Not tested before the diagnosis of T2D South Asian 1.11 (0.99, 1.25)
Not tested before the diagnosis of T2D Other ethnical groups 1.14 (1.04, 1.25)
Tested before the diagnosis of T2D (NDH detected without Read code assigned) White 1.20 (1.14, 1.26)
Tested before the diagnosis of T2D (NDH detected without Read code assigned) South Asian 1.10 (0.93, 1.30)
Tested before the diagnosis of T2D (NDH detected without Read code assigned) Other ethnical groups 1.16 (1.00, 1.34)
Tested before the diagnosis of T2D (NDH detected and Read code assigned) White 1.09 (1.04, 1.15)
Tested before the diagnosis of T2D (NDH detected and Read code assigned) South Asian 1.12 (0.91, 1.36)
Tested before the diagnosis of T2D (NDH detected and Read code assigned) Other ethnical groups 1.17 (1.00, 1.37)
Any microvascular disease (normal glycaemic values and white as ref)
Tested before the diagnosis of T2D (normal glycaemic values) South Asian 1.09 (0.93, 1.28)
Tested before the diagnosis of T2D (normal glycaemic values) Other ethnical groups 1.09 (0.96, 1.24)
Not tested before the diagnosis of T2D White 1.24 (1.20, 1.29)
Not tested before the diagnosis of T2D South Asian 1.72 (1.58, 1.88)
Not tested before the diagnosis of T2D Other ethnical groups 1.45 (1.35, 1.55)
Tested before the diagnosis of T2D (NDH detected without Read code assigned) White 1.50 (1.44, 1.57)
Tested before the diagnosis of T2D (NDH detected without Read code assigned) South Asian 1.57 (1.38, 1.80)
Tested before the diagnosis of T2D (NDH detected without Read code assigned) Other ethnical groups 1.87 (1.67, 2.10)
Tested before the diagnosis of T2D (NDH detected and Read code assigned) White 1.40 (1.34, 1.46)
Tested before the diagnosis of T2D (NDH detected and Read code assigned) South Asian 1.74 (1.49, 2.04)
Tested before the diagnosis of T2D (NDH detected and Read code assigned) Other ethnical groups 1.97 (1.74, 2.23)
Both microvascular diseases (normal glycaemic values and white as ref)
Tested before the diagnosis of T2D (normal glycaemic values) South Asian 1.35 (0.93, 1.96)
Tested before the diagnosis of T2D (normal glycaemic values) Other ethnical groups 1.00 (0.71, 1.42)
Not tested before the diagnosis of T2D White 1.34 (1.24, 1.45)
Not tested before the diagnosis of T2D South Asian 1.63 (1.32, 2.01)
Not tested before the diagnosis of T2D Other ethnical groups 1.62 (1.37, 1.92)
Tested before the diagnosis of T2D (NDH detected without Read code assigned) White 1.56 (1.42, 1.70)
Tested before the diagnosis of T2D (NDH detected without Read code assigned) South Asian 1.53 (1.12, 2.09)
Tested before the diagnosis of T2D (NDH detected without Read code assigned) Other ethnical groups 2.07 (1.62, 2.65)
Tested before the diagnosis of T2D (NDH detected and Read code assigned) White 1.46 (1.33, 1.61)
Tested before the diagnosis of T2D (NDH detected and Read code assigned) South Asian 1.61 (1.11, 2.32)
Tested before the diagnosis of T2D (NDH detected and Read code assigned) Other ethnical groups 2.15 (1.66, 2.78)
.5
1
3.5

Appendix Figure 8. Association between glycaemic testing and detection of Non-diabetic Hyperglycaemia, ethnicity, and presence of macrovascular disease at the time of diagnosis of Type 2 diabetes. Individuals with Non-diabetic Hyperglycaemia were further classified into two groups based on whether a diagnostic code for Non-diabetic Hyperglycaemia was recorded in their health records.

Notes: Adjusted Odds Ratios (AOR) and 95% confidence intervals (95% CI) have been estimated employing multivariable logistic regression models. An interaction term between NDH status before the diagnosis of Type 2 diabetes and ethnicity (White, South Asian, others) was fitted. Models were also adjusted for age, sex, 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: NDH: non-diabetic hyperglycaemia.


OR (95% CI)
Coronary Heart disease (normal glycaemic values and white as ref)
Tested before the diagnosis of T2D (normal glycaemic values) South Asian 1.14 (0.93, 1.40)
Tested before the diagnosis of T2D (normal glycaemic values) Other ethnical groups 0.71 (0.58, 0.85)
Not tested before the diagnosis of T2D White 0.72 (0.69, 0.75)
Not tested before the diagnosis of T2D South Asian 0.87 (0.76, 1.01)
Not tested before the diagnosis of T2D Other ethnical groups 0.60 (0.53, 0.68)
Tested before the diagnosis of T2D (NDH detected without Read code assigned) White 1.09 (1.03, 1.15)
Tested before the diagnosis of T2D (NDH detected without Read code assigned) South Asian 1.31 (1.10, 1.56)
Tested before the diagnosis of T2D (NDH detected without Read code assigned) Other ethnical groups 0.77 (0.64, 0.92)
Tested before the diagnosis of T2D (NDH detected and Read code assigned) White 1.03 (0.98, 1.09)
Tested before the diagnosis of T2D (NDH detected and Read code assigned) South Asian 1.10 (0.88, 1.36)
Tested before the diagnosis of T2D (NDH detected and Read code assigned) Other ethnical groups 0.70 (0.57, 0.85)
Cerebrvoascular disease (normal glycaemic values and white as ref)
Tested before the diagnosis of T2D (normal glycaemic values) South Asian 0.67 (0.45, 1.00)
Tested before the diagnosis of T2D (normal glycaemic values) Other ethnical groups 1.00 (0.76, 1.32)
Not tested before the diagnosis of T2D White 0.90 (0.84, 0.96)
Not tested before the diagnosis of T2D South Asian 0.63 (0.48, 0.82)
Not tested before the diagnosis of T2D Other ethnical groups 0.91 (0.75, 1.09)
Tested before the diagnosis of T2D (NDH detected without Read code assigned) White 0.92 (0.85, 1.00)
Tested before the diagnosis of T2D (NDH detected without Read code assigned) South Asian 0.72 (0.51, 1.02)
Tested before the diagnosis of T2D (NDH detected without Read code assigned) Other ethnical groups 0.91 (0.70, 1.20)
Tested before the diagnosis of T2D (NDH detected and Read code assigned) White 0.81 (0.75, 0.88)
Tested before the diagnosis of T2D (NDH detected and Read code assigned) South Asian 0.72 (0.48, 1.08)
Tested before the diagnosis of T2D (NDH detected and Read code assigned) Other ethnical groups 0.69 (0.49, 0.96)
Peripheral arterial disease (normal glycaemic values and white as ref)
Tested before the diagnosis of T2D (normal glycaemic values) South Asian 0.63 (0.38, 1.07)
Tested before the diagnosis of T2D (normal glycaemic values) Other ethnical groups 0.55 (0.35, 0.85)
Not tested before the diagnosis of T2D White 0.90 (0.83, 0.97)
Not tested before the diagnosis of T2D South Asian 0.44 (0.30, 0.66)
Not tested before the diagnosis of T2D Other ethnical groups 0.52 (0.39, 0.69)
Tested before the diagnosis of T2D (NDH detected without Read code assigned) White 0.88 (0.80, 0.97)
Tested before the diagnosis of T2D (NDH detected without Read code assigned) South Asian 0.63 (0.40, 1.00)
Tested before the diagnosis of T2D (NDH detected without Read code assigned) Other ethnical groups 0.47 (0.30, 0.74)
Tested before the diagnosis of T2D (NDH detected and Read code assigned) White 0.87 (0.79, 0.96)
Tested before the diagnosis of T2D (NDH detected and Read code assigned) South Asian 0.68 (0.40, 1.15)
Tested before the diagnosis of T2D (NDH detected and Read code assigned) Other ethnical groups 0.44 (0.26, 0.73)
Any macrovascular disease (normal glycaemic values and white as ref)
Tested before the diagnosis of T2D (normal glycaemic values) South Asian 0.99 (0.82, 1.21)
Tested before the diagnosis of T2D (normal glycaemic values) Other ethnical groups 0.71 (0.59, 0.84)
Not tested before the diagnosis of T2D White 0.76 (0.73, 0.79)
Not tested before the diagnosis of T2D South Asian 0.82 (0.72, 0.94)
Not tested before the diagnosis of T2D Other ethnical groups 0.63 (0.57, 0.71)
Tested before the diagnosis of T2D (NDH detected without Read code assigned) White 1.02 (0.97, 1.08)
Tested before the diagnosis of T2D (NDH detected without Read code assigned) South Asian 1.08 (0.91, 1.27)
Tested before the diagnosis of T2D (NDH detected without Read code assigned) Other ethnical groups 0.73 (0.62, 0.85)
Tested before the diagnosis of T2D (NDH detected and Read code assigned) White 0.95 (0.91, 1.00)
Tested before the diagnosis of T2D (NDH detected and Read code assigned) South Asian 0.93 (0.76, 1.15)
Tested before the diagnosis of T2D (NDH detected and Read code assigned) Other ethnical groups 0.65 (0.54, 0.78)
.2
1
1.8

Appendix Table 6. Association between detection of NDH before the diagnosis of T2D and incident retinopathy following the diagnosis of T2D

Notes. Abbreviations: T2D = Type 2 diabetes, NDH = non-diabetic hyperglycaemia, IECC = International Expert Committee, ADA = American Diabetes Association.

[β] Hazard ratios were obtained from time-partitioned Cox regression model partitioning the 10-year follow-up into four equal segments. Models were adjusted for age, sex, ethnicity (White, South-Asian, Black, Other, and Unknown), smoking status (smoker, ex-smoker, non-smoker), body mass index, systolic and diastolic blood pressure, total cholesterol, baseline HbA1c, number of co-morbidites, medications (ACEi/ARB, other anti-hypertensive, lipid-lowering, biguanides, sulphonylureas, other anti-diabetic medications), number of primary care visits in the year prior the T2D diagnosis, and Index of Multiple Deprivation quintiles.

The definition of NDH was based on

[¥] WHO/IECC criteria to define NDH: 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 NDH: 5.5-6.9 mmol/L, OGTT 7.8-11.1 mmol/L, HbA1c 42 to 47 mmol/mol or 6.0-6.4%

[Σ] ADA criteria to define NDH: 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%

[£] Secondary analyses further stratified those detected with NDH in the three years before the diagnosis of T2D according to whether a diagnostic Read code for NDH was also recorded.

	Time							
	0-30 months		31-60 months		61-90 months		91-120 months	
	adjusted HR[β]	p-value	adjusted HR[β]	p-value	adjusted HR[β]	p-value	adjusted HR[β]	p-value
WHO criteria[¥]								
Glycaemic values within the normal range before diagnosis of T2D								
No glycaemic measures recorded before diagnosis of T2D	1.74 (1.60 - 1.91)	<0.001	1.45 (1.26 - 1.67)	<0.001	1.49 (1.18 - 1.89)	<0.001	1.03 (0.70 - 1.50)	0.889
NDH detected before diagnosis of T2D	1.86 (1.69 - 2.04)	<0.001	1.58 (1.37 - 1.84)	<0.001	1.42 (1.10 - 1.83)	0.010	0.89 (0.59 - 1.35)	0.591
NICE criteria[€]								
Glycaemic values within the normal range before diagnosis of T2D								
No glycaemic measures recorded before diagnosis of T2D	2.13 (1.88 - 2.41)	<0.001	1.83 (1.50 - 2.22)	<0.001	1.94 (1.37 - 2.73)	<0.001	1.94 (1.37 - 2.73)	<0.001
NDH detected before diagnosis of T2D	2.16 (1.90 - 2.45)	<0.001	1.94 (1.59 - 2.38)	<0.001	1.83 (1.28 - 2.60)	<0.001	1.17 (0.67 - 2.04)	0.586
ADA criteria[Σ]								
Glycaemic values within the normal range before diagnosis of T2D								
No glycaemic measures recorded before diagnosis of T2D	2.05 (1.83 - 2.31)	<0.001	1.74 (1.45 - 2.09)	<0.001	1.84 (1.34 - 2.53)	0.009	1.14 (0.70 - 1.85)	0.611
NDH detected before diagnosis of T2D	2.10 (1.86 - 2.36)	<0.001	1.87 (1.55 - 2.25)	<0.001	1.74 (1.25 - 2.42)	<0.001	1.02 (0.61 - 1.70)	0.948
Sensitivity analysis[£]								
WHO criteria[¥]								
Glycaemic values within the normal range before diagnosis of T2D								
No glycaemic measures recorded before diagnosis of T2D	1.74 (1.60 - 1.91)	<0.001	1.45 (1.26 - 1.67)	<0.001	1.49 (1.18 - 1.89)	<0.001	1.03 (0.70 - 1.50)	0.889
NDH detected before diagnosis of T2D	1.90 (1.72 - 2.10)	<0.001	1.63 (1.39 - 1.92)	<0.001	1.47 (1.11 - 1.94)	0.010	1.14 (0.73 - 1.78)	0.568
NDH detected before diagnosis of T2D (diagnostic code assigned)	1.81 (1.63 - 2.00)	<0.001	1.53 (1.30 - 1.81)	<0.001	1.37 (1.03 - 1.82)	0.030	0.66 (0.40 - 1.08)	0.097
NICE criteria[€]								
Glycaemic values within the normal range before diagnosis of T2D								
No glycaemic measures recorded before diagnosis of T2D	2.13 (1.88 - 2.41)	<0.001	1.83 (1.50 - 2.22)	<0.001	1.94 (1.37 - 2.73)	<0.001	1.28 (0.75 - 2.19)	0.365
NDH detected before diagnosis of T2D	2.13 (1.87 - 2.42)	<0.001	1.95 (1.58 - 2.40)	<0.001	1.86 (1.29 - 2.68)	<0.001	1.46 (0.82 - 2.59)	0.199
NDH detected before diagnosis of T2D (diagnostic code assigned)	2.21 (1.93 - 2.52)	<0.001	1.93 (1.56 - 2.40)	<0.001	1.78 (1.22 - 2.60)	<0.001	0.82 (0.44 - 1.53)	0.532
ADA criteria[Σ]								
Glycaemic values within the normal range before diagnosis of T2D								
No glycaemic measures recorded before diagnosis of T2D	2.05 (1.83 - 2.31)	<0.001	1.74 (1.45 - 2.09)	<0.001	1.84 (1.34 - 2.53)	<0.001	1.14 (0.70 - 1.85)	0.611
NDH detected before diagnosis of T2D	2.07 (1.83 - 2.35)	<0.001	1.88 (1.55 - 2.29)	<0.001	1.78 (1.26 - 2.51)	<0.001	1.26 (0.74 - 2.15)	0.389
NDH detected before diagnosis of T2D (diagnostic code assigned)	2.13 (1.87 - 2.42)	<0.001	1.85 (1.51 - 2.26)	<0.001	1.69 (1.19 - 2.41)	<0.001	0.73 (0.40 - 1.31)	0.285

Appendix Table 7. Association between detection of NDH before the diagnosis of T2D and incident nephropathy following the diagnosis of T2D

Notes. Abbreviations: T2D = Type 2 diabetes, NDH = non-diabetic hyperglycaemia, IECC = International Expert Committee, ADA = American Diabetes Association.

[β] Hazard ratios were obtained from time-partitioned Cox regression model partitioning the 10-year follow-up into four equal segments. Models were adjusted for age, sex, ethnicity (White, South-Asian, Black, Other, and Unknown), smoking status (smoker, ex-smoker, non-smoker), body mass index, systolic and diastolic blood pressure, total cholesterol, baseline HbA1c, number of co-morbidites, medications (ACEi/ARB, other anti-hypertensive, lipid-lowering, biguanides, sulphonylureas, other anti-diabetic medications), number of primary care visits in the year prior the T2D diagnosis, and Index of Multiple Deprivation quintiles.

The definition of NDH was based on

[¥] WHO/IECC criteria to define NDH: 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 NDH: 5.5-6.9 mmol/L, OGTT 7.8-11.1 mmol/L, HbA1c 42 to 47 mmol/mol or 6.0-6.4%

[Σ] ADA criteria to define NDH: 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%

[£] Secondary analyses further stratified those detected with NDH in the three years before the diagnosis of T2D according to whether a diagnostic Read code for NDH was also recorded.

	Time							
	0-30 months		31-60 months		61-90 months		91-120 months	
	adjusted HR[β]	p-value	adjusted HR[β]	p-value	adjusted HR[β]	p-value	adjusted HR[β]	p-value
WHO criteria[¥]								
Glycaemic values within the normal range before diagnosis of T2D								
No glycaemic measures recorded before diagnosis of T2D	1.18 (1.09 - 1.27)	<0.001	1.24 (1.10 - 1.40)	0.001	1.16 (0.96 - 1.40)	0.121	1.18 (0.83 - 1.68)	0.344
NDH detected before diagnosis of T2D	1.16 (1.07 - 1.26)	0.001	1.25 (1.09 - 1.42)	0.001	1.12 (0.91 - 1.37)	0.280	0.86 (0.58 - 1.26)	0.438
NICE criteria[€]								
Glycaemic values within the normal range before diagnosis of T2D								
No glycaemic measures recorded before diagnosis of T2D	1.19 (1.08 - 1.31)	<0.001	1.42 (1.21 - 1.67)	<0.001	1.31 (1.02 - 1.70)	0.037	1.17 (0.74 - 1.85)	0.512
NDH detected before diagnosis of T2D	1.16 (1.05 - 1.28)	0.004	1.42 (1.20 - 1.68)	<0.001	1.27 (0.98 - 1.66)	0.076	0.86 (0.53 - 1.39)	0.537
ADA criteria[Σ]								
Glycaemic values within the normal range before diagnosis of T2D								
No glycaemic measures recorded before diagnosis of T2D	1.17 (1.07 - 1.29)	0.001	1.45 (1.24 - 1.69)	<0.001	1.28 (1.00 - 1.62)	0.048	1.18 (0.75 - 1.86)	0.461
NDH detected before diagnosis of T2D	1.13 (1.03 - 1.25)	0.011	1.46 (1.25 - 1.72)	<0.001	1.23 (0.96 - 1.59)	0.100	0.87 (0.54 - 1.40)	0.572
Sensitivity analysis[£]								
WHO criteria[¥]								
Glycaemic values within the normal range before diagnosis of T2D								
No glycaemic measures recorded before diagnosis of T2D	1.18 (1.09 - 1.27)	<0.001	1.24 (1.10 - 1.40)	0.001	1.16 (0.96 - 1.40)	0.121	1.19 (0.83 - 1.68)	0.344
NDH detected before diagnosis of T2D	1.11 (1.01 - 1.22)	0.023	1.34 (1.16 - 1.55)	<0.001	1.10 (0.87 - 1.38)	0.420	0.88 (0.58 - 1.36)	0.574
NDH detected before diagnosis of T2D (diagnostic code assigned)	1.20 (1.10 - 1.32)	<0.001	1.14 (0.99 - 1.33)	0.075	1.14 (0.91 - 1.43)	0.256	0.83 (0.54 - 1.29)	0.404
NICE criteria[€]								
Glycaemic values within the normal range before diagnosis of T2D								
No glycaemic measures recorded before diagnosis of T2D	1.19 (1.08 - 1.31)	<0.001	1.42 (1.21 - 1.67)	<0.001	1.31 (1.02 - 1.70)	0.037	1.17 (0.74 - 1.85)	0.512
NDH detected before diagnosis of T2D	1.11 (1.00 - 1.23)	0.055	1.50 (1.26 - 1.78)	<0.001	1.26 (0.95 - 1.66)	0.106	0.89 (0.54 - 1.48)	0.652
NDH detected before diagnosis of T2D (diagnostic code assigned)	1.22 (1.10 - 1.37)	<0.001	1.31 (1.09 - 1.58)	0.004	1.29 (0.97 - 1.72)	0.080	0.82 (0.48 - 1.39)	0.455
ADA criteria[Σ]								
Glycaemic values within the normal range before diagnosis of T2D								
No glycaemic measures recorded before diagnosis of T2D	1.17 (1.07 - 1.29)	0.001	1.45 (1.24 - 1.69)	<0.001	1.28 (1.00 - 1.62)	0.048	1.18 (0.76 - 1.86)	0.461
NDH detected before diagnosis of T2D	1.08 (0.98 - 1.20)	0.123	1.56 (1.32 - 1.84)	<0.001	1.22 (0.94 - 1.59)	0.141	0.91 (0.55 - 1.49)	0.696
NDH detected before diagnosis of T2D (diagnostic code assigned)	1.20 (1.08 - 1.34)	0.001	1.34 (1.12 - 1.60)	0.001	1.25 (0.95 - 1.65)	0.104	0.83 (0.49 - 1.40)	0.482

Appendix Table 8. Association between detection of NDH before the diagnosis of T2D and incident macrovascular disease following the diagnosis of T2D

Notes. Abbreviations: T2D = Type 2 diabetes, NDH = non-diabetic hyperglycaemia, IECC = International Expert Committee, ADA = American Diabetes Association.

[β] Hazard ratios were obtained from time-partitioned Cox regression model partitioning the 10-year follow-up into four equal segments. Models were adjusted for age, sex, ethnicity (White, South-Asian, Black, Other, and Unknown), smoking status (smoker, ex-smoker, non-smoker), body mass index, systolic and diastolic blood pressure, total cholesterol, baseline HbA1c, number of co-morbidites, medications (ACEi/ARB, other anti-hypertensive, lipid-lowering, biguanides, sulphonylureas, other anti-diabetic medications), number of primary care visits in the year prior the T2D diagnosis, and Index of Multiple Deprivation quintiles.

The definition of NDH was based on

[¥] WHO/IECC criteria to define NDH: 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 NDH: 5.5-6.9 mmol/L, OGTT 7.8-11.1 mmol/L, HbA1c 42 to 47 mmol/mol or 6.0-6.4%

[Σ] ADA criteria to define NDH: 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%

[£] Secondary analyses further stratified those detected with NDH in the three years before the diagnosis of T2D according to whether a diagnostic Read code for NDH was also recorded.

	Time							
	0-30 months		31-60 months		61-90 months		91-120 months	
	adjusted HR[β]	p-value	adjusted HR[β]	p-value	adjusted HR[β]	p-value	adjusted HR[β]	p-value
WHO criteria[¥]								
Glycaemic values within the normal range before diagnosis of T2D								
No glycaemic measures recorded before diagnosis of T2D	1.00 (0.88 - 1.12)	0.940	1.00 (0.89 - 1.12)	0.980	0.91 (0.81 - 1.03)	0.150	0.91 (0.81 - 1.03)	0.150
NDH detected before diagnosis of T2D	0.81 (0.71 - 0.93)	<0.001	0.94 (0.83 - 1.06)	0.330	0.88 (0.77 - 1.01)	0.070	0.89 (0.75 - 1.05)	0.070
NICE criteria[€]								
Glycaemic values within the normal range before diagnosis of T2D								
No glycaemic measures recorded before diagnosis of T2D	1.03 (0.88 - 1.19)	0.740	0.97 (0.84 - 1.12)	0.650	0.85 (0.73 - 1.00)	0.040	0.90 (0.72 - 1.12)	0.354
NDH detected before diagnosis of T2D	0.87 (0.75 - 1.02)	0.090	0.91 (0.79 - 1.06)	0.230	0.83 (0.71 - 0.97)	0.020	0.96 (0.76 - 1.21)	0.714
ADA criteria[Σ]								
Glycaemic values within the normal range before diagnosis of T2D								
No glycaemic measures recorded before diagnosis of T2D	0.99 (0.85 - 1.14)	0.840	0.96 (0.84 - 1.10)	0.590	0.91 (0.78 - 1.06)	0.230	0.83 (0.67 - 1.02)	0.230
NDH detected before diagnosis of T2D	0.83 (0.71 - 0.97)	0.020	0.91 (0.79 - 1.05)	0.180	0.89 (0.76 - 1.05)	0.160	0.87 (0.70 - 1.08)	0.160
Sensitivity analysis[£]								
WHO criteria[¥]								
Glycaemic values within the normal range before diagnosis of T2D								
No glycaemic measures recorded before diagnosis of T2D	1.00 (0.88 - 1.12)	0.940	1.00 (0.89 - 1.12)	0.980	0.91 (0.81 - 1.03)	0.150	0.85 (0.72 - 1.00)	0.150
NDH detected before diagnosis of T2D	0.82 (0.71 - 0.96)	0.010	0.94 (0.82 - 1.08)	0.400	0.92 (0.79 - 1.06)	0.240	0.88 (0.73 - 1.06)	0.240
NDH detected before diagnosis of T2D (diagnostic code assigned)	0.81 (0.69 - 0.94)	0.010	0.94 (0.82 - 1.08)	0.380	0.85 (0.73 - 0.99)	0.040	0.89 (0.74 - 1.08)	0.040
NICE criteria[€]								
Glycaemic values within the normal range before diagnosis of T2D								
No glycaemic measures recorded before diagnosis of T2D	1.03 (0.88 - 1.19)	0.740	0.97 (0.84 - 1.12)	0.650	0.85 (0.73 - 1.00)	0.040	0.90 (0.72 - 1.12)	0.040
NDH detected before diagnosis of T2D	0.90 (0.76 - 1.07)	0.220	0.92 (0.78 - 1.07)	0.270	0.85 (0.72 - 1.01)	0.070	0.97 (0.76 - 1.23)	0.070
NDH detected before diagnosis of T2D (diagnostic code assigned)	0.83 (0.70 - 1.00)	0.050	0.91 (0.77 - 1.07)	0.260	0.80 (0.67 - 0.95)	0.010	0.95 (0.74 - 1.21)	0.010
ADA criteria[Σ]								
Glycaemic values within the normal range before diagnosis of T2D								
No glycaemic measures recorded before diagnosis of T2D	0.99 (0.85 - 1.14)	0.840	0.96 (0.84 - 1.10)	0.590	0.91 (0.78 - 1.06)	0.230	0.83 (0.67 - 1.02)	0.230
NDH detected before diagnosis of T2D	0.85 (0.72 - 1.00)	0.050	0.91 (0.78 - 1.06)	0.210	0.93 (0.78 - 1.10)	0.370	0.87 (0.70 - 1.09)	0.370
NDH detected before diagnosis of T2D (diagnostic code assigned)	0.80 (0.67 - 0.95)	0.010	0.91 (0.77 - 1.06)	0.230	0.85 (0.71 - 1.01)	0.070	0.87 (0.69 - 1.10)	0.070

Appendix Table 9. Association between detection of NDH before the diagnosis of T2D and mortality following the diagnosis of T2D

Notes. Abbreviations: T2D = Type 2 diabetes, NDH = non-diabetic hyperglycaemia, IECC = International Expert Committee, ADA = American Diabetes Association.

[β] Hazard ratios were obtained from time-partitioned Cox regression model partitioning the 10-year follow-up into four equal segments. Models were adjusted for age, sex, ethnicity (White, South-Asian, Black, Other, and Unknown), smoking status (smoker, ex-smoker, non-smoker), body mass index, systolic and diastolic blood pressure, total cholesterol, baseline HbA1c, number of co-morbidites, medications (ACEi/ARB, other anti-hypertensive, lipid-lowering, biguanides, sulphonylureas, other anti-diabetic medications), number of primary care visits in the year prior the T2D diagnosis, and Index of Multiple Deprivation quintiles.

The definition of NDH was based on

[¥] WHO/IECC criteria to define NDH: 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 NDH: 5.5-6.9 mmol/L, OGTT 7.8-11.1 mmol/L, HbA1c 42 to 47 mmol/mol or 6.0-6.4%

[Σ] ADA criteria to define NDH: 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%

[£] Secondary analyses further stratified those detected with NDH in the three years before the diagnosis of T2D according to whether a diagnostic Read code for NDH was also recorded.

	Time							
	0-30 months		31-60 months		61-90 months		91-120 months	
	adjusted HR[β]	p-value	adjusted HR[β]	p-value	adjusted HR[β]	p-value	adjusted HR[β]	p-value
WHO criteria[¥]								
Glycaemic values within the normal range before diagnosis of T2D								
No glycaemic measures recorded before diagnosis of T2D	1.05 (1.00 - 1.12)	0.070	0.95 (0.89 - 1.02)	0.145	1.00 (0.92 - 1.10)	0.945	1.06 (0.93 - 1.20)	0.393
NDH detected before diagnosis of T2D	0.70 (0.65 - 0.74)	<0.001	0.82 (0.76 - 0.88)	<0.001	0.91 (0.83 - 1.00)	0.053	1.00 (0.87 - 1.14)	0.988
NICE criteria[€]								
Glycaemic values within the normal range before diagnosis of T2D								
No glycaemic measures recorded before diagnosis of T2D	1.04 (0.97 - 1.12)	0.232	0.89 (0.82 - 0.97)	0.008	0.99 (0.88 - 1.11)	0.831	1.10 (0.93 - 1.31)	0.254
NDH detected before diagnosis of T2D	0.73 (0.68 - 0.79)	<0.001	0.78 (0.72 - 0.85)	<0.001	0.91 (0.81 - 1.02)	0.094	1.05 (0.88 - 1.25)	0.580
ADA criteria[Σ]								
Glycaemic values within the normal range before diagnosis of T2D								
No glycaemic measures recorded before diagnosis of T2D	1.04 (0.97 - 1.11)	0.281	0.94 (0.87 - 1.02)	0.147	0.97 (0.88 - 1.08)	0.637	1.03 (0.88 - 1.20)	0.752
NDH detected before diagnosis of T2D	0.73 (0.68 - 0.78)	<0.001	0.83 (0.76 - 0.91)	<0.001	0.89 (0.79 - 0.99)	0.038	0.97 (0.82 - 1.14)	0.687
Sensitivity analysis[£]								
WHO criteria[¥]								
Glycaemic values within the normal range before diagnosis of T2D								
No glycaemic measures recorded before diagnosis of T2D	1.05 (1.00 - 1.12)	0.070	0.95 (0.89 - 1.02)	0.144	1.00 (0.92 - 1.10)	0.946	1.06 (0.93 - 1.20)	0.393
NDH detected before diagnosis of T2D	0.75 (0.70 - 0.81)	<0.001	0.89 (0.82 - 0.97)	0.009	0.91 (0.82 - 1.01)	0.087	1.00 (0.87 - 1.16)	0.994
NDH detected before diagnosis of T2D (diagnostic code assigned)	0.63 (0.58 - 0.69)	<0.001	0.74 (0.67 - 0.81)	<0.001	0.91 (0.82 - 1.01)	0.084	1.00 (0.86 - 1.16)	0.971
NICE criteria[€]								
Glycaemic values within the normal range before diagnosis of T2D								
No glycaemic measures recorded before diagnosis of T2D	1.04 (0.97 - 1.12)	0.236	0.89 (0.82 - 0.97)	0.008	0.99 (0.88 - 1.11)	0.827	1.10 (0.93 - 1.31)	0.255
NDH detected before diagnosis of T2D	0.80 (0.74 - 0.86)	<0.001	0.84 (0.77 - 0.92)	<0.001	0.91 (0.81 - 1.03)	0.143	1.06 (0.88 - 1.27)	0.555
NDH detected before diagnosis of T2D (diagnostic code assigned)	0.63 (0.57 - 0.69)	<0.001	0.69 (0.63 - 0.77)	<0.001	0.90 (0.79 - 1.02)	0.092	1.04 (0.86 - 1.26)	0.662
ADA criteria[Σ]								
Glycaemic values within the normal range before diagnosis of T2D								
No glycaemic measures recorded before diagnosis of T2D	1.04 (0.97 - 1.11)	0.285	0.94 (0.87 - 1.02)	0.144	0.97 (0.88 - 1.08)	0.632	1.03 (0.87 - 1.20)	0.755
NDH detected before diagnosis of T2D	0.79 (0.73 - 0.85)	<0.001	0.90 (0.82 - 0.99)	0.029	0.89 (0.79 - 1.00)	0.060	0.96 (0.81 - 1.15)	0.683
NDH detected before diagnosis of T2D (diagnostic code assigned)	0.63 (0.57 - 0.68)	<0.001	0.73 (0.66 - 0.81)	<0.001	0.88 (0.78 - 1.00)	0.049	0.97 (0.81 - 1.16)	0.726

Appendix Table 10. List of Read codes used to identify individuals with non-diabetic hyperglycaemia

MEDCODE	READCODE	READTERM
11050	44Uz.11	Blood hyperglycaemia NOS
19781	44V2.00	Glucose tol. test impaired
22959	66AJ000	Chronic hyperglycaemia
102389	8HlS.00	Referral for management of impaired glucose tolerance
106220	9m9..00	Impaired glucose tolerance monitoring administration
106316	9m90.00	Impaired glucose tolerance monitoring invitation
106273	9m90000	Impaired glucose tolerance monitoring invitation 1st letter
106275	9m90100	Impaired glucose tolerance monitoring invitation 2nd letter
106323	9m90200	Impaired glucose tolerance monitoring invitation 3rd letter
102668	9NS0400	Referral for impaired glucose tolerance management offered
10921	C11y200	Impaired glucose tolerance
10983	C11y300	Impaired fasting glycaemia
105434	C11y400	Impaired glucose regulation
106604	C11y500	Pre-diabetes
3505	C313500	Glucose intolerance
11818	R102.00	[D]Glucose tolerance test abnormal
11149	R102.11	[D]Prediabetes
3295	R102.12	[D]Impaired glucose tolerance test
1789	R105712	[D]Hyperglycaemia
10791	R10D000	[D]Impaired fasting glycaemia
31161	R10D011	[D]Impaired fasting glucose
10042	R10E.00	[D]Impaired glucose tolerance
9310	Ryu8A00	[X]Hyperglycaemia, unspecified

Appendix Table 11. Percentage of missing data for sub-group analyses on fasting plasma glucose and total cholesterol

FASTING PLASMA GLUCOSE	DRS ≥ 10	INCIDENT NON-DIABETIC HYPERGLYCAEMIA	INCIDENT TYPE 2 DIABETES
PROGRAMME COVERAGE			
Low	16·6%	2·9%	3·7%
Medium	12·6%	2·0%	2·7%
High	10·9%	2·5%	3·4%
TOTAL	13·6%	2·4%	3·3%
HbA1c			
PROGRAMME COVERAGE			
Low	71·4%	23·8%	9·1%
Medium	66·0%	18·6%	6·5%
High	64·8%	17·6%	7·9%
TOTAL	67·6%	19·8%	7·8%
TOTAL CHOLESTEROL			
PROGRAMME COVERAGE			
Low	32·3%	2·6%	0·7%
Medium	27·3%	1·2%	0·4%
High	25·1%	1·3%	0·4%
TOTAL	28·5%	1·6%	0·5%

Appendix Table 12. Baseline values of the study outcomes by general practices' coverage of the NHS Health Check programme and individuals' baseline diabetes risk score.

	TOTAL SAMPLE	DRS ≥ 10
FASTING PLASMA GLUCOSE	**BASELINE VALUE (mmol/L)**	
PROGRAMME COVERAGE§		
Low		5·5 (1·7)
Medium		5·4 (1·7)
High		5·4 (1·6)
HbA1c	**BASELINE VALUE (%)**	
PROGRAMME COVERAGE§		
Low		4·6 (0·3)
Medium		4·3 (0·3)
High		4·5 (0·3)
ANTI-DIABETIC MEDICATIONS	**BASELINE VALUE (%)**	
PROGRAMME COVERAGE§		
Low		1·0
Medium		1·2
High		1·2
SYSTOLIC BLOOD PRESSURE	**BASELINE VALUE (mmHg)**	
PROGRAMME COVERAGE§		
Low	129·9 (17·0)	138·0 mmHg (17·8)
Medium	129·6 (16·6)	137·4 mmHg(19·3)
High	129·7 (17·6)	137·0 mmHg (17·1)
DIASTOLIC BLOOD PRESSURE	**BASELINE VALUE (mmHg)**	
PROGRAMME COVERAGE§		
Low	79·1 (10·1)	82·3 (11·4)
Medium	79·1 (10·8)	82·1 (11·6)
High	79·1 (11·3)	82·0 (10·5)
BODY MASS INDEX	**BASELINE VALUE (Kg/m²)**	
PROGRAMME COVERAGE§		
Low	27·2 (6·4)	32·6 (5·2)
Medium	27·2 (6·9)	32·6 (5·4)
High	27·4 (5·9)	32·7 (5·4)
SMOKING PREVALENCE	**BASELINE VALUE (%)**	
PROGRAMME COVERAGE§		
Low	21·7	20·6
Medium	23·5	23·1
High	26·4	26
TOTAL CHOLESTEROL¥	**BASELINE VALUE (mmol/L)**	
PROGRAMME COVERAGE§		
Low		5·2 (2·3)
Medium		5·2 (3·0)
High		5·1 (1·5)
STATINS¥	**BASELINE VALUE (%)**	
PROGRAMME COVERAGE§		
Low		29·2
Medium		30·2

High		33·3
QRISK2	BASELINE VALUE (% 10-year risk)	
PROGRAMME COVERAGE§		
Low	6·1 (6·6)	9·9 (9·8)
Medium	5·8 (6·6)	9·4 (9·7)
High	5·9 (6·6)	9·4 (9·2)

§ Tertiles of general practices coverage of the NHS Health Check Programme were defined based on programme coverage during the first three years after its implementation (2009-11).

¥ Changes in the mean total cholesterol has only been assessed for individuals at high risk of T2D at baseline because national guidelines do not recommend cholesterol monitoring for the whole population.

Appendix Table 13. Differences in incidence rates of diagnoses of non-diabetic hyperglycaemia and type 2 diabetes by general practices' coverage of the NHS Health Check Programme and patients' baseline diabetes risk score. Results obtained without adopting propensity score regression adjustment.

	TOTAL SAMPLE			DRS ≥ 10		
	HR	95% CI		HR	95% CI	
NON-DIABETIC HYPERGLYCAEMIA						
PROGRAMME COVERAGE§						
Low	Ref			ref		
Medium	1·18***	1·11	1·25	1·19***	1·08	1·31
High	1·18***	1·11	1·26	1·22***	1·10	1·36
TYPE 2 DIABETES	**HR**	**95% CI**		**HR**	**95% CI**	
PROGRAMME COVERAGE§						
Low	ref			ref		
Medium	1·12***	1·07	1·17	1·14***	1·06	1·23
High	1·09***	1·04	1·15	1·11*	1·02	1·20

Notes: Time period was Jan 2009-May 2016. Results are shown from multivariable Cox regression models. All models have been adjusted for the baseline values of the following independent variables: age, gender, ethnicity, smoking status, body mass index, antihypertensive medication, general practice deprivation score, and region. DRS = diabetes risk score, HR = Hazard ratio.

*p<0·05, **p<0·01, *** p<0·001.

§ Tertiles of general practices coverage of the NHS Health Check Programme were defined based on programme coverage during the first three years after its implementation (2009-11)

Appendix Table 14. Differences in fasting plasma glucose levels and prescription of anti-diabetic medications according to general practices' coverage of the Health Check programme, patients' baseline diabetes risk score, and new diagnoses of non-diabetic hyperglycaemia and type 2 diabetes between 2009 and 2016 in England. Results obtained without adopting propensity score regression adjustment.

	DRS ≥ 10			INCIDENT NON-DIABETIC HYPERGLYCAEMIA			INCIDENT TYPE 2 DIABETES		
FASTING PLASMA GLUCOSE	**Coeff.**	**95% CI**		**Coeff.**	**95% CI**		**Coeff.**	**95% CI**	
PROGRAMME COVERAGE§									
Low	ref			ref			ref		
Medium	-0·05**	-0·08	-0·01	0·04	-0·06	0·15	-0·17	-0·34	0·01
High	-0·08***	-0·11	-0·04	-0·18**	-0·29	-0·06	-0·37***	-0·57	-0·17
BLOOD GLUCOSE LEVELS BELOW DIAGNOSTIC CRITERIA	**OR**	**95% CI**		**OR**	**95% CI**		**OR**	**95% CI**	
PROGRAMME COVERAGE§									
Low	ref			ref			ref		
Medium	1·30***	1·26	1·33	0·91	0·76	1·1	1·11	0·95	1·29
High	1·47***	1·42	1·52	0·97	0·8	1·19	1·03	0·87	1·22
ANTI-DIABETIC MEDICATION	**OR**	**95% CI**		**OR**	**95% CI**		**OR**	**95% CI**	
PROGRAMME COVERAGE§									
Low	ref			ref			ref		
Medium	1·16	0·97	1·39	0·97	0·65	1·44	1·05	0·73	1·51
High	1·08	0·88	1·33	0·66	0·42	1·04	1·58*	1·05	2·37

Notes: Time period was from 1 January 2009 to 31 May 2016. Results are shown from mixed-effect linear regression models for continuous outcomes and mixed-effect logistic regression models for binary outcomes. Independent variables included in the model are the following: practices' early programme coverage of the NHS Health Check programme, year, and baseline age, gender, ethnicity, smoking status, BMI, antihypertensive medication, general practice IMD, and region.

DRS = diabetes risk score, NDH = non-diabetic hyperglycaemia, OR = Odds Ratio.

**p<0·01, *** p<0·001.

§ Tertiles of general practices coverage of the NHS Health Check Programme were defined based on programme coverage during the first three years after its implementation (2009-11).

Appendix Table 15. Differences in cardiovascular risk factors between 2009 and 2016 by general practices' coverage of the NHS Health Check programme and individuals' baseline diabetes risk score. Results obtained without adopting propensity score regression adjustment.

	TOTAL SAMPLE			DRS ≥ 10		
SYSTOLIC BLOOD PRESSURE	**Coeff.**	**95% CI**		**Coeff.**	**95% CI**	
PROGRAMME COVERAGE§						
Low		ref			ref	
Medium	-0·15**	-0·25	-0·06	-0·38*	-0·75	-0·01
High	-0·39***	-0·50	-0·28	-0·70***	-1·21	-0·40
DIASTOLIC BLOOD PRESSURE	**Coeff·**	**95% CI**		**Coeff·**	**95% CI**	
PROGRAMME COVERAGE§						
Low		ref			ref	
Medium	-0·08*	-0·14	-0·02	-0·20	-0·42	0·03
High	-0·09**	-0·16	-0·03	-0·29*	-0·54	-0·04
BODY MASS INDEX	**Coeff·**	**95% CI**		**Coeff·**	**95% CI**	
PROGRAMME COVERAGE§						
Low		ref			ref	
Medium	0·08***	0·04	0·12	-0·08	-0·22	0·05
High	0·25***	0·20	0·29	0·10	-0·06	0·25
SMOKING PREVALENCE	**OR**	**95% CI**		**OR**	**95% CI**	
PROGRAMME COVERAGE§						
Low		ref			ref	
Medium	0·96*	0·92	1·00	0·95	0·82	1·10
High	1·08***	1·04	1·13	0·97	0·80	1·16
TOTAL CHOLESTEROL¥				**Coeff·**	**95% CI**	
PROGRAMME COVERAGE§						
Low					ref	
Medium				-0·01	-0·05	0·02
High				-0·06**	-0·10	-0·02
STATINS¥				**OR**	**95% CI**	
PROGRAMME COVERAGE§						
Low					ref	
Medium				0·93	0·85	1·01
High				1·05	0·96	1·15
QRISK2	**Coeff·**	**95% CI**		**Coeff·**	**95% CI**	
PROGRAMME COVERAGE§						
Low		ref			ref	
Medium	-0·09***	-0·12	-0·06	-0·12*	-0·23	-0·01
High	-0·14***	-0·17	-0·10	-0·26***	-0·38	-0·15

Notes: Time period was from 1 January 2009 to 31 May 2016. Results are shown from mixed-effect linear regression models for continuous outcomes and mixed-effect logistic regression models for binary outcomes. Independent variables included in the model are the following: practices' early programme coverage of the NHS Health Check programme, year, and baseline age, gender, ethnicity, smoking status, BMI, antihypertensive medication, general practice IMD, and region. Change in total cholesterol has been restricted to only those with a DRS ≥ 10 at baseline. DRS = diabetes risk score, NDH = non-diabetic hyperglycaemia, T2D = type 2 diabetes, OR = Odds Ratio.

*p<0·05, **p<0·01, *** p<0·001.

§ Tertiles of general practices coverage of the NHS Health Check Programme were defined based on

programme coverage during the first three years after its implementation (2009-11).

¥ Differences in the mean total cholesterol and statins prescription have only been assessed for individuals at high risk of T2D at baseline because national guidelines do not recommend cholesterol monitoring for the whole population.

Appendix Table 16. Differences in cardiovascular disease risk factors in individuals with incident non-diabetic hyperglycaemia and type 2 diabetes after Jan 2009. Results obtained without adopting propensity score regression adjustment.

	INCIDENT NON-DIABETIC HYPERGLYCAEMIA			INCIDENT TYPE 2 DIABETES		
SYSTOLIC BLOOD PRESSURE	**Coeff.**	**95% CI**		**Coeff.**	**95% CI**	
PROGRAMME COVERAGE§						
Low		ref			ref	
Medium	0·26	-0·42	0·95	-0·51*	-1·01	-0·12
High	0·26	-0·48	1·01	-0·90***	-1·47	-0·33
DIASTOLIC BLOOD PRESSURE	**Coeff·**	**95% CI**		**Coeff·**	**95% CI**	
PROGRAMME COVERAGE§						
Low		ref			ref	
Medium	0·32	-0·09	0·73	-0·32*	-0·62	-0·02
High	0·21	-0·24	0·66	-0·56**	-0·90	-0·22
BODY MASS INDEX	**Coeff·**	**95% CI**		**Coeff·**	**95% CI**	
PROGRAMME COVERAGE§						
Low		ref			ref	
Medium	0·06	-0·20	0·33	-0·10	-0·31	0·12
High	0·19	-0·09	0·47	-0·01	-0·23	0·25
SMOKING PREVALENCE	**OR**	**95% CI**		**OR**	**95% CI**	
PROGRAMME COVERAGE§						
Low		ref			ref	
Medium	1·17	0·85	1·61	1·46**	1·17	1·83
High	1·36	0·96	1·92	1·43**	1·12	1·84
TOTAL CHOLESTEROL	**Coeff·**	**95% CI**		**Coeff·**	**95% CI**	
PROGRAMME COVERAGE§						
Low		ref			ref	
Medium	-0·03	-0·09	0·02	-0·02	-0·07	0·03
High	-0·10	-0·16	-0·04	-0·04	-0·10	0·01
STATINS	**OR**	**95% CI**		**OR**	**95% CI**	
PROGRAMME COVERAGE§						
Low		ref			ref	
Medium	0·84	0·64	1·09	0·85	0·71	1·02
High	1·01	0·76	1·36	0·96	0·79	1·20
QRISK2	**Coeff·**	**95% CI**	**Coeff·**	**95% CI**	**Coeff·**	**95% CI**
PROGRAMME COVERAGE§						
Low		ref				ref
Medium	-0·27	-0·71	0·17	-0·33	-0·77	0·10
High	-1·14***	-1·62	-0·65	-0·84**	-1·33	-0·35

Notes: For the analyses were considered only individuals with incident non-diabetic hyperglycaemia and type 2 diabetes after Jan 2009. Individuals included in the analyses were followed-up from the year of diagnosis until the end of the study (May 2016). Results are shown from mixed-effect linear regression models for continuous outcomes and mixed-effect logistic regression models for binary outcomes. Independent variables included in the model are the following: practices' early programme coverage of the NHS Health Check programme, year, and baseline age, gender, ethnicity, smoking status, BMI, antihypertensive medication, general practice IMD, and region. DRS = diabetes risk score, NDH = non-diabetic hyperglycaemia, T2D = type 2 diabetes, OR = Odds Ratio.

*p<0·05, **p<0·01, *** p<0·001.

§ Tertiles of general practices coverage of the NHS Health Check Programme were defined based on programme coverage during the first three years after its implementation (2009-11).