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Disease burden of diabetes, diabetic retinopathy and their future projections

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Key words

Diabetes Mellitus, Diabetic Retinopathy, Current Disease Burden, Future Projections

Abstract

Objectives

To estimate the current disease burden, trends and future projections for Diabetes Mellitus (DM) and Diabetic Retinopathy in IQVIA Medical Research Data (IMRD).

Participants / Design / Setting

We performed a cross-sectional study of patients aged 12 and above to determine the prevalence of Diabetes Mellitus and Diabetic Retinopathy from IMRD database (primary care database) in January 2017. We also carried out a series of cross-sectional studies to look into prevalence trends, and then applied a double exponential smoothing model to forecast the future burden of Diabetes Mellitus and Diabetic Retinopathy in UK.

Results

The crude Diabetes Mellitus or Diabetic Retinopathy prevalence in 2017 was 5.2%. The Diabetic Retinopathy, Sight Threatening Retinopathy (STR) and Diabetic Maculopathy prevalence figures in 2017 were 33.78%, 12.28% and 7.86% respectively in our IMRD cross-sectional study. There are upward trends in the prevalence of Diabetes Mellitus, Diabetic Retinopathy, and Sight-threatening retinopathy, most marked and accelerating in Sight-threatening retinopathy in type 1 Diabetes Mellitus (T1DM) but slowing in type 2 Diabetes Mellitus (T2DM), and in the overall prevalence of Diabetic Retinopathy.

Conclusion

Our results suggest differential rising trends in the prevalence of Diabetes Mellitus and diabetic retinopathy. Preventive strategies, as well as treatment services

planning, can be based on these projected prevalence estimates. Improvements that are necessary for the optimisation of care pathways, and preparations to meet demand and capacity challenges, can also be based on this information. The limitations of the study can be overcome by a future collaborative study linking Diabetic Retinopathy (DR) screening and hospital eye services data.

Article Summary: Strengths and limitations of this study

- This is an up to date study to give DM and Diabetic Retinopathy prevalence trends from 1998 to 2018.
- This study forecasts the future Diabetic Retinopathy disease burden up to 2030 to enable preparation for impending challenges.
- Current prevalence of age 12 and over, diagnosed DM, DR, STR, Diabetic Macular Oedema disease and treatment burden in United Kingdom
- This study has not however been adjusted for the risk factors for the incidence/prevalence of Diabetes Mellitus or Diabetic Retinopathy
- A possible impact of coding errors and subjectivity in documentation cannot be precluded

Introduction

DR is the fourth most common cause of blindness and visual impairment in high-income countries (1). Services are overburdened and optimisation requires accurate estimates of disease and the expected treatment burden (2). A recent systematic review of studies estimating the incidence of DR (3) highlighted the paucity of contemporary evidence from developed countries on the disease burden and recommended that estimates should be based on populations with Diabetes Mellitus (DM) rather than the general population so as not to dilute the estimates. A recent attempt to forecast the UK-wide disease burden of DR was hindered by the need for reliable data (4).

Previous studies have been conducted on the prevalence of DR (5-9), with the most recent UK-wide study being performed in 2014 based on Clinical Practice Research Datalink (CPRD). Two of these studies also explored trends in DR incidence and prevalence (6, 9). A significant amount of heterogeneity in the populations studied, the classification of DR, and the definition of its presence and severity was present in these studies. Studies of the forecasts of the future disease burden of DR would be useful both for preparing health care delivery systems for the future, and in preventing blindness in patients with DM. There is a Europe wide forecast study with UK component based on pre 2009 data dealing with DR only (10). The disease burden estimate of DR will not be complete without a similar estimate for the diabetes burden. A UK wide upto date study dealing with DM, DR and STR is needed.

A previous study on future projections of DM in the United Kingdom was found to underestimate prevalence (11). Moreover, evidence suggests that the rate of

increase is not constant or uniform across DM subtypes (namely T2DM and T1DM, especially in children (12). The incidence rate of T1DM (pooled estimate of European centres, UK included) in children is expected to continue to rise at a rate of 3.4% per annum (13). Gonzalez et al (14) reported an increasing prevalence of DM for the 10 years up to 2005. Public Health England (PHE) figures are available for 2019, based on the Quality Outcome Framework, except in Scotland where they are based on Scottish Diabetes Survey (15). However, these figures are limited to those over 17 years old. We aimed to estimate recent trends in the disease burden of DM, and to use this as a base on which to estimate the current disease burden for DR and STR in the UK. We then wanted to design, train and validate a forecasting model to support future projections of these disease burdens. Since DR screening is offered after age 12 only, the population of interest to us was age 12 or over only.

Methods

Study design and data source

To study the trend, and to forecast the future burden of diagnosed DM, DR and STR, we used the IMRD database to conduct a series of yearly cross-sectional analyses on the 1st of each year from 1998 to 2018. In addition, a detailed cross sectional study was carried out on the 1st of January 2017 to estimate the prevalence of T1DM and T2DM in the whole UK population, and of DR in patients with T1DM and T2DM.

IMRD is a large UK general practice electronic database containing anonymised patient records from 787 general practices, with over 15 million patient records, of which around 3.7 million are active at a given time point (6.2% of the UK population). IMRD provides information on demographics, lifestyle, diagnoses, and prescriptions,

and is quality checked (16). Based on the demographics distribution observed in IMRD, it is considered generalizable to the UK population (17). IMRD has previously been used and validated to estimate prevalence trends of DM and DR, and to identify risk factors for DR (14, 18-21).

Study population

To ensure that only high quality data was included, and that all important covariates were documented, general practices were eligible only if they showed acceptable mortality rates one year before the cross-sectional study date (16), and had been using the electronic medical record system for at least a year. Patients from eligible general practices must have been registered with their practice for at least one year and must be aged 12 years or above to be included in the study to match the Diabetic Eye Screening Programme criteria (DESP). For estimation of the prevalence of T1DM and T2DM, the whole registered population was included as the denominator population (per 1000). For estimation of STR and DR prevalence, patients with DM served as the denominator (per 100). Estimates are stratified by type of diabetes. There was no patient and public involvement in this research project.

Case definition of diagnoses of DM and DR

Clinical diagnosis and symptoms in the IMRD database are recorded using the Read code classification system (22). Read codes were selected using a rigorous seven step process and selected search terms (Appendix 1, 2). Read codes are given in Appendix 3. Patients with a Read code record of DM before the study entry date were identified. Patients with a record of DM specified as type 1 were categorised as

type 1 if they had at least one prescription record for insulin and no record for any oral glucose-lowering medication other than metformin in the database. The remaining patients with diabetes were categorized as type 2. Prevalence estimates calculated were verified against PHE estimates of DM (23).

The most severe DR Read code recorded before study entry was used to classify their DR or STR status. Stages of DR among those patients identified with DM were classified using the Royal College of Ophthalmology modified classification (24). However, patients with a retinopathy record were stratified into mutually exclusive categories of 1) Pre-STR including no retinopathy and background retinopathy, 2) STR and 3) Retinopathy unspecified as either pre-STR (background retinopathy) or STR. Pre-STR was further categorized into mutually exclusive categories: 1) R0 or 2) R1. STR was further categorized into mutually exclusive categories of 1) STR based on diagnostic codes and 2) STR that needed treatment or resulted in vision loss. Within STR we categorised pre-proliferative DR (R2) and proliferative DR (R3) as mutually exclusive groups. STR was further stratified into overlapping categories based on the presence of STR (R2/3) and maculopathy (M1). Treatment and vision loss codes included: (i) laser therapy, (ii) vitreous injection and other vitreous procedures, (iii) low vision or blindness.

Time trend analysis and forecasting models

A double exponential smoothing model was chosen to cover the level and trend, as this was yearly cross-sectional data with no seasonal / cyclical variation expected or observed (25) not unlike Adams et al published model (26). The IMRD serial cross-sectional data for the prevalence of DM and DR (STR and any retinopathy) were split into two portions - 1998 to 2013 (training data) and 2014 to 2018 (test data). The

model was fitted to the training data and then prediction was carried out from 2014 to 2018. This was then compared with the test data for validation. Thereafter, the yearly prevalence of DR and STR were projected up to 2030 using the same model with 95% prediction intervals. This was done using the statistical software R (2019) (27). Prevalence rates were then converted into patient numbers, using projected population figures from the Office of National Statistics (28).

IMRD data analysis for annual prevalence of DM and DR.

Prevalence trends between the two decades before and after 2008 were compared for trend analysis. Patients identified as T1DM or T2DM on or before 1st of January in each year analysed were identified as the numerators for calculating the prevalence of T1DM and T2DM. The prevalence was estimated by dividing the numerator population by the eligible registered population aged above 12 years (denominator) on 1st of January for the corresponding year. Among these patients, those diagnosed with any retinopathy and those with STR were numerators for calculating the prevalence of DR and STR respectively. Prevalence estimates are provided for patients with T1DM and T2DM separately with 95% confidence intervals A description of patients aged 12 or above with a diagnosis of DM is also given for the year 2017. Baseline characteristics such as age, and age at diagnosis of diabetes were summarized as the mean (SD), and as frequency (percentage) for sex, Townsend deprivation quintile and ethnicity. These characteristics were also reported as stratified by type of DM. A detailed description of the proportion of DM patients (T1DM and T2DM aged 12 or above) with DR in the year 2017 categorized by DR severity is also presented.

Estimates from IMRD were compared to estimates obtained from data from UK studies (5-7, 9, 30) for verification and comparison in Appendices 6 and 7.

Ethical approvals:

The study protocols were submitted to both the Scientific Review Committee and the Science, Technology, Engineering and Mathematics Ethical Review Committee at the University of Birmingham for review and approval, which were granted. Consent was not required.

Results

Figure 1 gives the Patients flow and case selection algorithm. As of 1st January 2017, 2,813,916 people were eligible to be included in the primary cross-sectional analysis. The demography characteristics of the sample are given in Table 1. The mean age of patients with T1DM and T2DM as of 1st January 2017 was 42.5 (17.2) and 66.3 (13.0) respectively. The mean age at diagnosis of T1DM and T2DM were 21.4 (14.3) and 57.0 (13.1) respectively. Nearly 80% and 55% of patients respectively had their Townsend deprivation and ethnicity recorded in IMRD.

Prevalence trends

The results in figures 2 and 3 show an almost a global upward trend in the prevalence of both types of diabetes (T1DM and T2DM) and in DR (all types of DR / STR). The highest rise was seen in STR in those with T1DM (3.7 times increase in two decades). The second highest rise was in all types of DR in the T2DM population (2.8 times). Splitting this data by the decades (1998 to 2007 versus 2009 to 2018), the end of the first decade showed a higher increase in every category (diabetes as well as diabetic retinopathy) as compared to the second decade, except in T1DM

where it was higher in second decade (Appendix 4). T2DM increased more than T1DM between 1998 and 2018, but while the increase in T2DM prevalence slowed recently, the increase in T1DM prevalence accelerated significantly in the recent decade.

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Table 1: Demography of patients with DM in IMRD data on 1st of January 2017

	DM (N)	% / (SD)	T1DM (N)	% / (SD)	T2DM (N)	% / (SD)
Total	180,824	100.00%	12,434	6.88%	168,390	93.12%
Gender						
Male	101,628	56.20%	7,192	57.84%	94,436	56.08%
Female	79,196	43.80%	5,242	42.16%	73,954	43.92%
Age	180,824	64.7 (SD 14.7)	12,434	42.5 (SD 17.2)	168,390	66.3 (SD 13.0)
Age at diagnosis	180,788	54.6 (SD 16.0)	12,422	21.4 (SD 14.3)	168,366	57.0 (SD 13.1)
Townsend						
1	27,616	15.27%	2,037	16.38%	25,579	15.19%
2	30,011	16.60%	2,206	17.74%	27,805	16.51%
3	32,434	17.94%	2,222	17.87%	30,212	17.94%
4	31,332	17.33%	1,978	15.91%	29,354	17.43%
5	24,606	13.61%	1,568	12.61%	23,038	13.68%
Missing	34,825	19.26%	2,423	19.49%	32,402	19.24%
Ethnicity						
Caucasian	88,420	48.90%	6,584	52.95%	81,836	48.60%
Black afro Caribbean	2,738	1.51%	98	0.79%	2640	1.57%
Chinese/Middle eastern/ others	567	0.31%	45	0.36%	522	0.31%
South Asians	6,361	3.52%	124	1.00%	6237	3.70%
Mixed race	1243	0.69%	32	0.26%	1211	0.72%
Missing	81,495	45.07%	5551	44.64%	75944	45.10%

DM-Diabetes Mellitus; T2DM – Type 2 Diabetes Mellitus; T1DM – Type 1 Diabetes Mellitus Number; N, Standard deviation; (SD)

Forecasting model

The forecasted annual UK prevalence values of T1DM, T2DM, DR and STR, with their 95% prediction intervals (PI), are given in the Appendix 5. These suggest that the prevalence will increase by 24% (5 to 43%), 7% (-28 to 41%), 9% (-50 to 65%) and 17% (-21 to 54%) respectively by 2030. Corresponding estimates of the absolute numbers of people in the UK forecast to have these conditions are shown in Table 2. These correspond to 0.36 (.3 -.4), 4 (2.6 - 5.3), 1.6 (.7-2.5), and 0.64 (.42-.86) million people respectively having each condition respectively. We verified our UK forecast for 2019 and found the total figure (3,800,920) to be close to the Quality Outcome Framework provided estimate of diagnosed DM of 3,809,119.

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Table 2: Future Projections of Diabetes and DR disease Burden

Year	Projected Population	*T1DM	*T2DM	*Total DM	#DR	#STR
2019	66800000	280560	3520360	3800920	1311317	482717
2020	67200000	288960	3568320	3857280	1342333	497589
2021	67500000	297000	3604500	3901500	1369427	511097
2022	67800000	305100	3647640	3952740	1399270	525714
2023	68100000	306450	3684210	3990660	1420675	538739
2024	68400000	314640	3720960	4035600	1448780	552877
2025	68700000	322890	3764760	4087650	1479729	568183
2026	68900000	330720	3796390	4127110	1506395	581923
2027	69200000	339080	3833680	4172760	1535576	596705
2028	69400000	347000	3872520	4219520	1561222	611830
2029	69600000	354960	3904560	4259520	1588801	626149
2030	69800000	362960	3936720	4299680	1616680	640652

*The DR and STR forecast is actual IMRD based figures projected for the UK population (28). Formula used is Affected Population = Projected Prevalence X Projected Population. # In calculating projections for diabetic retinopathy we have applied the retinopathy rates of those aged 12 and above for the whole diabetes population rather than for those above 12 years old (age at which retinopathy screening commences and was one of our inclusion criteria). This approximately gives the projected total population, as breakdown for over 12 years is not available but the number of patients with DM below 12 years is negligibly small.

2017 Cross-sectional analysis

In the 2017 data analysis, 180,824 patients had a code for diabetes prior to this date of which 12,434 (6.9%) were identified as T1DM and 168,390 (93.1%) were identified as T2DM. Patients with DM were more likely to be men (56.2% vs 43.8%). The prevalence of DR in different stages of progression is given in Table 3. Prevalence of any DR and STR among patients with DM aged 12 and above was 33.8% and 12.3% respectively. When stratified by diabetes type, a higher proportion of patients with T1DM had a more severe form of retinopathy than patients with T2DM (prevalence of STR was 29.7% vs 11%), while prevalence of pre-STR (R0/R1 & M0) was higher among patients with T2DM (31.8% in T1DM vs 37.8% in T2DM). Each subcategory among STR population (R2 / R3 / M1 and their combinations), was present in higher proportion of patients with T1DM as compared to T2DM (R2: 3.7% vs 1.2%; R3: 12.1% vs 1.9%; and M1: 19.6% vs 7.0% respectively)]. A higher proportion of patients with T1DM compared to T2DM also received treatment procedures (Laser: 7.1% vs 1.3%; Vitreous injection and procedures: 5.1% vs 1.1%). There was also a higher proportion of documented cases of visual impairment or vision loss among T1DM [3.1% vs 2.8%].

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Table 3: Diabetic Retinopathy in patients with DM in IMRD data on 1st of January 2017

	DM		T1DM		T2DM	
Diabetes (N)	180,824	**%**	12,434	**%**	168,390	**%**
No Retinopathy coding available	82,119	45.41%	3,846	30.93%	78,273	46.48%
Retinopathy Coding available	98,705	54.59%	8,588	69.07%	90,117	53.52%
Pre-STR	**67750**	37.47%	**3951**	31.78%	**63699**	37.83%
No DR (R0M0)	37,618	20.80%	1,472	11.84%	36,146	21.47%
R1	30,132	16.66%	2,479	19.94%	27,553	16.36%
STR	**22,198**	12.28%	**3,693**	29.70%	**18,505**	10.99%
STR without Rx or vision loss	13,165	7.28%	2,271	18.26%	10,894	6.47%
R2	2,487	1.38%	454	3.65%	2,033	1.21%
R3	4,729	2.62%	1,505	12.10%	3,224	1.91%
M1	14,206	7.86%	2,440	19.62%	11,766	6.99%
STR with Rx and vision loss	9,033	5.00%	1,422	11.44%	7,611	4.52%
Laser	3,092	1.71%	885	7.12%	2,207	1.31%
Vitreous injections / procedures	2,536	1.40%	637	5.12%	1,899	1.13%
Vision loss / blindness	5,050	2.79%	384	3.09%	4,666	2.77%
None specific for STR or Pre-STR	**8,757**	4.84%	**844**	6.79%	**7913**	4.70%
Any retinopathy	61087	33.78%	7016	56.43%	53971	32.05%

DR – Diabetic retinopathy, R0 – no retinopathy, M0 – no maculopathy, R1, Background retinopathy, Pre-STR is combination of no diabetic retinopathy and background retinopathy, R2 is pre-proliferative diabetic retinopathy, R3 is proliferative diabetic retinopathy, M1 is diabetic maculopathy, STR is sight-threatening retinopathy which is a combination of R2, R3 and M1, Non-specific retinopathy is where it cannot be categorised into R1 or STR. Where colour codes are assigned, the same colour indicates that they are mutually exclusive. Where colour codes are not assigned they overlap within that category. For example, patients with M1 can have either R2 or R3, likewise patients who received laser treatment could have received vitreous injection. The WHO standards (31) were used for vision loss. Here all categories were combined into a single category.

Discussion

Principal findings

We explored the disease burden associated with DR in the UK from the past, present and future perspectives. Our study followed a tripartite structure, comprising of 1) a series of epidemiological studies throughout a 20-year span to document disease-specific trends, 2) training a forecasting model to predict the future disease burden to guide clinical practice and service development and 3) a detailed descriptive cross-sectional analysis in 2017 using a study population of 180,824 people with diabetes to explore contemporary prevalence estimates of different forms of DR.

Between 1998 and 2018, the prevalence of DR and STR increased. The prevalence of all DR in T2DM nearly tripled and STR almost quadrupled among patients with T1DM aged 12 and above. There was a parallel increase in the overall prevalence of DM. While the growth in the numbers of T1DM patients was less than that for patients with T2DM, stratifying the calculations by two decades showed a marked rise in the rate of increase in T1DM prevalence in the latter half of the whole period between 1998 and 2018. This was in sharp contrast to the trends in T2DM, STR and DR prevalence, which showed a higher rise in the decade between 1998 and 2007 but slowed down in the later decade between 2009 and 2018.

Our forecasting model showed that, in less than ten years, over 1.5 million people with diabetes will have some DR, almost two thirds of a million of whom will have STR. With T1DM expected to rise faster and higher, it is also likely to correspond to a comparatively higher rise in STR, forcing a further increase in demand on services.

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A key parameter when calculating the current and future prevalence of DR is the accuracy of estimates of the trend of the underlying condition, i.e. the presence of DM. T1DM showed a smaller increase in the period starting from 1998, but this has accelerated since 2009. This is the most concerning recent trend considering that these are younger patients (mean age of diagnosis of 21.4 vs 57), having to live with the condition and its complications for more life years, and also suffering from the more severe form of DR, with the consequent disability, treatment burden and treatment costs. There is a recent report of a 3.4% annual increase in the incidence rate of T1DM in children (13). Although there is an association between T1DM and obesity (32), it is believed that the cause may be multifactorial, including hygiene, viral factors and vitamin D deficiency amongst others (33).

The diagnosed DM prevalence based on the 2017 IMRD cross-sectional survey is 5.2%. The detailed descriptive analysis in 2017 showed that, out of 180,824 people with diabetes, 33.8% had any DR as a complication, 12.3% had STR and importantly, 2.8% had blindness or vision loss. STR was 52% of total DR in T1DM and 34% of total DR in T2DM. In 2017, nearly one third of all patients with T1DM were affected by a sight threatening form of DR. This analysis also confirmed the notion that, from the health care perspective, neither DM type is “benign” with regards to DR risk, since DR severity is graver in T1DM, and absolute numbers of affected individuals are higher in T2DM.

Diabetic complications are mainly macrovascular damage (coronary artery disease, peripheral arterial disease, and stroke) or microvascular damage to blood vessels in organs like kidney, foot and nerves (34). Tackling the first reduces mortality rate and might mean these patients living longer and consequently a higher prevalence of DR among higher risk patients. With greater efficacy and a rapid reduction of HBA1C,

the new agents might induce progression of DR (early worsening) (35). So, with increased prevalence there may be a disproportionate rise in more high-risk DR cases. There are conflicting reports on direct effect of newer medical treatments like Incretin based therapies on DR (35, 36) but the follow-up is limited at the moment.

Strengths and weaknesses of this study

This study reports up to date prevalence figures of DM, DR and STR, as well as trends from 1998 to 2018, in a clinically relevant form, which clinicians and managers leading hospital eye services can use in the management of services for diabetes and diabetic retinopathy. Our work is based on a cross-sectional analysis of primary care data and is therefore closer to routine practice. Our findings have also been verified against PHE, DESP, and other previously published figures (5-7, 14, 30, 37, 38). This is also the first observational IMRD based study to forecast the DM, DR and STR disease burden in the UK all together. While incorporating current evidence on the trend of underlying condition (DM), this study portrays a comprehensive analysis of the recent DR disease burden.

This study has not however been adjusted for the risk factors for the incidence/prevalence of DM or DR. Other limitations are possible coding errors, difficulties of missing data, and the potential risk of an overestimation of vision failure. The findings of this study should be interpreted within that context. Firstly, the possible impact of coding errors, as well as subjectivity in documentation across a retrospective nationwide database involving several practices in different areas, cannot be precluded. This potential risk was minimised through a strict Read code selection process. The prevalence of severe DR was higher for those of South Asian and mixed ethnicity (9), therefore could have implications for local variations in its

prevalence, and estimates could differ depending on the local ethnic mix. The potential impact of several concomitant medications on the course of DR was not captured in this study design. For the sake of future projections, estimates from individuals over 12 years old were applied to the whole population to calculate the final values, assuming that the number of DM patients under 12 is very low. Finally, we acknowledge that these projections are subject to the assumption that factors affecting the incidence, course and progression of the disease will remain stable over the next few years.

We wanted to verify our figures against data from DESP which screens everyone from age 12 (39) and Mathur et al. work (9). Both these research studies used a cut off of over 12 years for their estimates. We wanted our findings to be generalizable to the whole UK populations with diabetes including those under care of DRSP and Hospital Eye Services. We also wanted it to be generalisable internationally where majority of world population with diabetes is within one pool, without access to screening services. Limitations of this age cut off are that 2017 figures are not easily verifiable against PHE figures 2017 being over 17 years of age. So, verification against that estimate is a bit problematic and thus adds uncertainty to our UK forecast estimates

Strengths and weaknesses in relation to other studies, discussing particularly any differences in results

Gonzalez et al (14) reported an increasing prevalence of diabetes between the years 1996 and 2005 (10 years) based on THIN data analysis of patients aged 10 to 79 years old. They reported an overall increase of 54%. Our estimate between 1998 and 2005 (our data did not match the years) was 60%. In a Clinical Practice

Research Datalink (CPRD) based study, Zghebi et al (38) found an overall increase of 64% in the patient population between 2004 to 2014, but this was limited to patients over 16 years old with T2DM. Our corresponding figures are 63%. Thus, our estimates fall midway between these two studies. Bagust is a future forecast for UK, but is limited to T2DM and is an underestimation (11). It projected T2DM figures for 2036 to be 1.1 million.

The PHE estimate for prevalence of diabetes in UK in 2017 arrived at by Quality and Outcome Framework figures was 3.7 million (5.6%) in those aged 17 years and over (37) and included diagnosed patients with diabetes. Our estimate of diagnosed patients with diabetes in 2017 of 3.4 million (crude prevalence of 5.2%) in over 12 years old population contrasts with the 2017 PHE figures. Similarly, PHE predicted the diabetes burden for 2025 to be 4.9 million for people aged over 16 years (40). It is not possible to make a direct comparison with our forecast of just under 4.3 million for 2025 because of our estimate being for people over 12 years of age but could mean the present study to be an underestimation. Alternatively, PHE figures could be an overestimation for 2017, because of the inbuilt assumptions in that model. Our estimate for 2019 matches the quality and outcome estimate of 3.8 million. IDF (41) estimated total diabetes prevalent cases (20 to 79 years old) to be 2.7 million in 2017, which is an underestimation when compared to PHE and our study.

A recent DR prevalence study focussed on lower risk patients with diabetes under screening services (9). The DR period prevalence in the Mathur's study (2004 to 2014) was found to be 48.4% for patients with T1DM and 28.3% for patients with T2DM, contrasting with point prevalence (2017) of 56.4% and 32.0% for patients with T1DM and T2DM respectively in our study. They also did not split the pathology into maculopathy and pre-proliferative categories, and did not include treatment and

vision failure. Li et al 2019 (10) is the only study so far, that has projected DR till 2050. They estimated that 8.6 million people with diabetes (DR in 25% of the European population with T2DM and 50% with T1DM) will have diabetic eye disease inn 2050. The British studies included within this systematic review were based on diabetic screening services from pre-2009 (42) and pre-2003 data (7). Case definitions and patient pathways have since changed. Consequently, their figures are a significant underestimation as compared to ours (710,510 vs 1,612,395 in 2030)

Other prevalence studies from the UK (5-7, 30) are compared with estimates from our study in detail for completeness in Appendix 6 and Appendix 7. The majority of these UK studies are quite old, come from the screening programme setting, and do not deal with all of the categories of DR due to changed case definitions. Keenen et al (43) is a study based on work between 2007 and 2009 on hospital patients. They based their estimates of prevalence in eyes rather than patients, therefore, due to this heterogeneity, cannot be directly compared with our figures.

Meaning of the study: possible mechanisms and implications for clinicians or policymakers

Consecutive analyses over the course of over two decades provides information regarding the trend and severity of diabetic disease, and by a detailed analysis of different forms and severity groups, it captures the implications for the public health system. With the use of relevant outcomes, coupled with a prerequisite validation, the study provides a forecasting model which will be of use for clinicians and managers leading the professional services in planning the capacity to meet the increasing demand, and will guide public health strategy. Local demand can be

calculated with the help of national figures provided by taking local factors into account.

Out of the 33.8% of total DR in all patients with diabetes, 12.3% was made up of the STR. Those STR patients that actually needed treatment or experienced vision failure constituted a total of 5%. These figures reflect a high false-positive rate of referrals (50 - 70% as reported earlier (2, 44) and needs to be considered in the future relationship between DESP and overburdened hospital eye services. Our estimated prevalence figures, in a clinically relevant form will help the clinicians and managers leading hospital eye services to optimise capacity planning for the increased demand.

Unanswered questions and future research

PHE used a prevalence model to predict the disease burden of diabetes in 2016 (45). The predictive factors they used were age, ethnicity, gender and deprivation index. To accommodate local variation in populations and practices, final calculations can be made using these predictive factors. The above-mentioned limitations of the study can be overcome by a future collaborative study linking DR screening and hospital eye services data, with figures based on patient numbers and not eyes, to prevent heterogeneity among studies. Forecasting capacity needs is an area that should be repeated periodically with the help of the forecasting model presented.

Conclusion

In our study, the estimates suggested a trend of differential rise in prevalence rates in T1DM and T2DM. Overall, there is a continuing rise in the numbers of patients with DM and DR needing care. Preventive strategies and service planning can be

based on these projected prevalence estimates to meet demand over the next ten years. Future forecasting will need repeating periodically to capture any external factors causing a change in the present trend.

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Titles and legends to figures

Figure 1: Patients flow and case selection algorithm

Figure 2: Prevalence trends of DM from year 1998 to year 2018

T1DM - Type 1 Diabetes Mellitus, T2DM - Type 2 Diabetes Mellitus

Figure 3: Annual prevalence (95% CI) of DR and STR from year 1998 to year 2018

DR - Diabetic Retinopathy, STR - Sight threatening Retinopathy

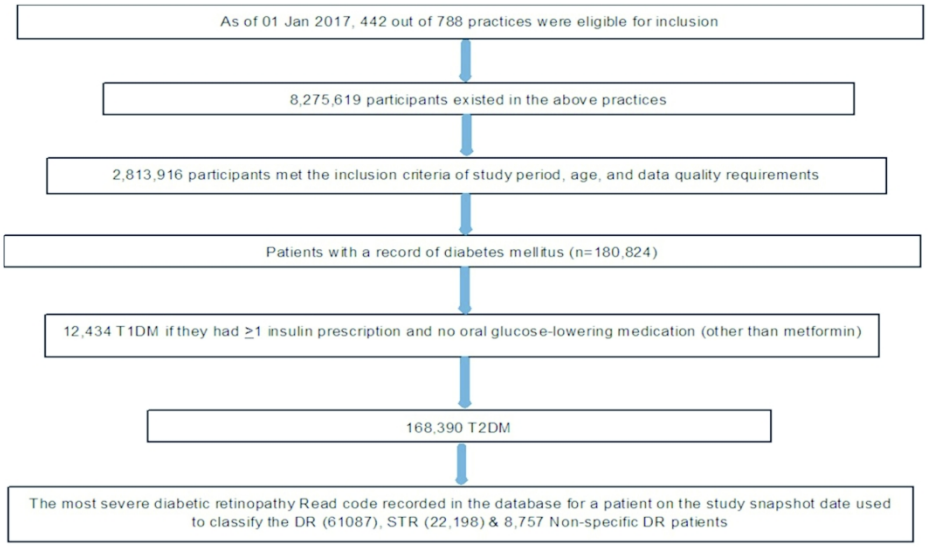

Figure 1: Patients flow and case selection algorithm

207x116mm (300 x 300 DPI)

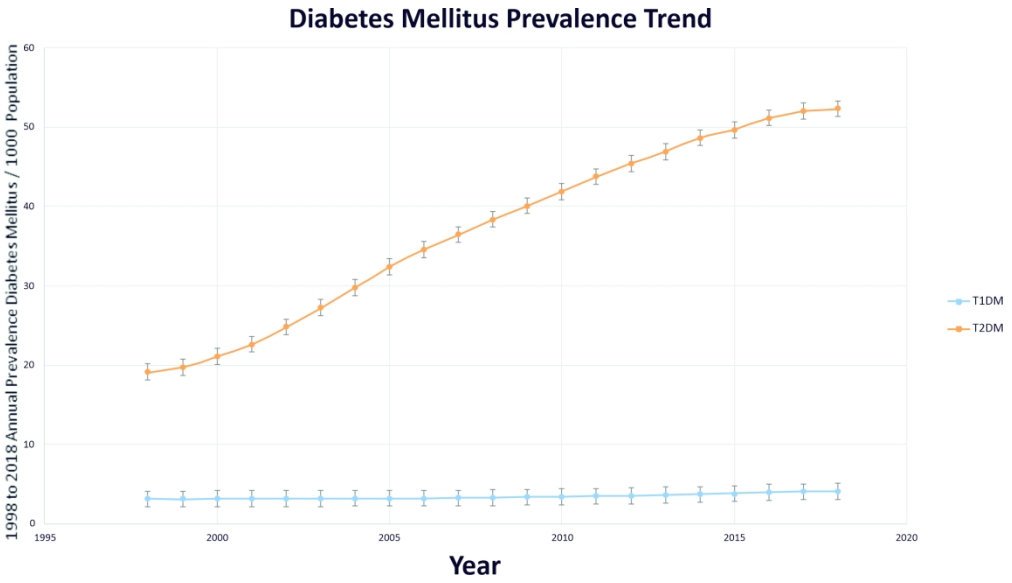

Figure 2: Prevalence trends of DM from year 1998 to year 2018

209x119mm (300 x 300 DPI)

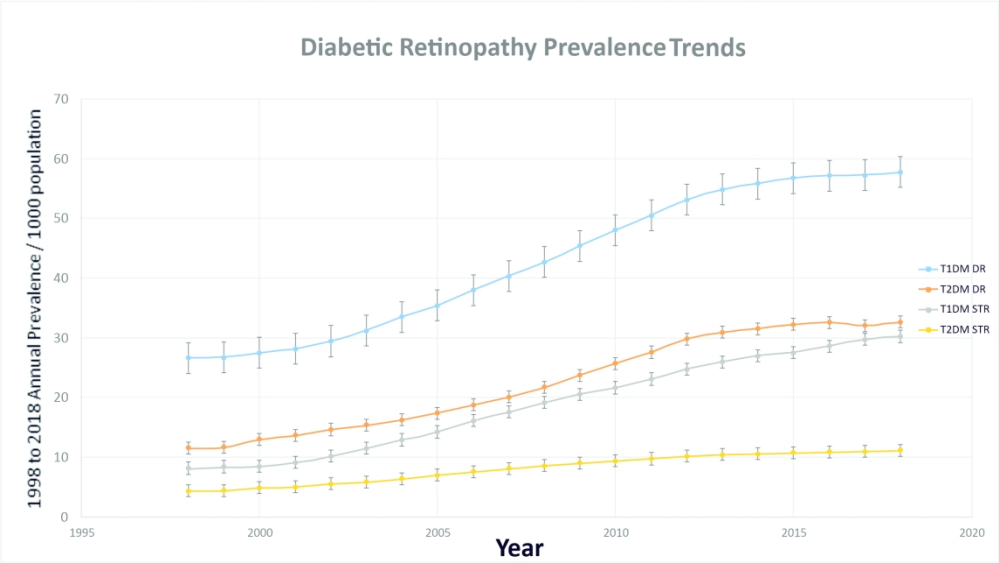

Figure 3: Annual prevalence (95% CI) of DR and STR from year 1998 to year 2018

206x115mm (300 x 300 DPI)

Appendix 1: 7 Step Process of Read codes selection methods

Read codes cover clinical features, diagnosis, procedures, some drugs and investigations (1). Ones used in IMRD consist of 7 characters. They have a hierarchy with more specific ones down the order. This was done in collaboration with Jhot Chandan, a fellow doctoral researcher and my supervisor Krishnarajah Nirantharakumar (Institute of Applied Health Research)

1. The Read code database (MsAcess, MsExcel) is divided into two main columns: A Medcode column with unique 8 character codes for each condition and a description column. Both were used.
2. We developed a list of key search terms for the read codes of interest. These were searched for in the description column. Appendix below provides a list of key search words.
3. Results from the key word search were used to identify the main stem codes where the Read codes of interest belong to.
4. The Next step involved searching the MedCode column for the main stem codes to pick out codes that were otherwise missed on searching the description column.
5. We then also conducted an online search of published articles that have published similar Read Codes (2, 3).
6. Once collected, they were split into possible, probable and definite. There was deliberation between clinicians in the THINking group to achieve these three lists.
7. They were then hand over to a group of data scientists within the THINking group who split them into various files following epidemiological principles and saved them in CSV files database.

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Appendix 2: Search Terms for diabetic Retinopathy

Keywords for identifying diabetic retinopathy in the Read Codes Dictionary
O/E or *PHOTOGRAPHY* or *RETINAL* or *SCR* **and** *HAEMORRHAGES* or *EXUDATE* or *MICROANEURYSMS* or *INTRARETINAL MICROVASCULAR ANAOMALY* or *ABNORMALITY*
RETINA or *FUNDUS* or *MACULAR* or *VITREOUS* **and** *LASER" or *PHOTOCOAGULATION* or *INTRA-VITREAL INJECTIONS* or *INJECTIONS* or *RANIBIZUMAB* or *BIVACIZUMAB* or *AFLIBERCEPT* or *TRIAMCINOLON* or *ILEUVIEN* or *DEXAMETHOSON*
RETINOPATHY or *FUNDOSCOPY* or *SEEN or *RETINAL SCR* or *RETINOSCOPY* or *SLIT LAMP* or *DIABETIC EYE* or *EXAMINATION OF RETINA* or *RETINA and OTHER PARTS OF EYE OPERATIONS* or *VITRECTOMY* or *MACULOPATHY* or *BACKGROUND* or *PRE PROLIFERATIVE* or *PROLIFERATIVE*
*BLIND" or *PARTIAL SIGHTED" or **SIGHT IMPAIRMENT" or *VISUAL IMPAIRMENT" or *VISUAL FAILURE"

Appendix 3: Read Codes

Code	Description	Status
	No Retinoipathy (ROMO)	
2BBD.00	O/E - Right retina normal	Probable
2BBJ.00	O/E - no right diabetic retinopathy	Definite
2BB1.00	O/E - retina normal	Probable
2BBI.00	O/E - no retinopathy	Definite
3128000	Fundoscopy normal	Probable
3128200	Dilated fundoscopy normal	Probable
2BBM.00	O/E - diabetic maculopathy absent both eyes	Possible
	Background Retinopathy (R1)	
2BBP.00	O/E - right eye background diabetic retinopathy	Definite
2BBQ.00	O/E - left eye background diabetic retinopathy	Definite
F420000	Background diabetic retinopathy	Definite
F421.00	Other background retinopathy	Definite
F421000	Unspecified background retinopathy	Definite
F421z00	Other background retinopathy NOS	Definite
2BB4.00	O/E - retinal microaneurysms	Definite
2BBa.00	O/E- non-referable retinopathy	Probable
	Pre proliferative Diabetic Retinopathy (R2)	
F420200	Pre proliferative diabetic retinopathy	Definite
2BBR.00	O/E - right eye pre proliferative diabetic retinopathy	Definite
2BBS.00	O/E - left eye pre proliferative diabetic retinopathy	Definite
F420800	High risk non proliferative diabetic retinopathy	Definite
	Proliefartive Diabetic Retinoipathy (R3)	
2BBk.00	O/E - right eye stable treated prolif diabetic retinopathy	Definite
2BBl.00	O/E - left eye stable treated prolif diabetic retinopathy	Definite
F420100	Proliferative diabetic retinopathy	Definite
F420700	High risk proliferative diabetic retinopathy	Definite
F422z00	Proliferative retinopathy NOS	Definite
F422.00	Other proliferative retinopathy	Definite
FyuF700	[X]Other proliferative retinopathy	Definite
2BBT.00	O/E - right eye proliferative diabetic retinopathy	Definite
2BBV.00	O/E - left eye proliferative diabetic retinopathy	Definite
7272500	Panretinal laser photocoagulation to lesion of retina NEC	Definite
7272800	Panretinal laser photocoagulation to lesion of retina	Definite
2BB7.00	O/E - retinal vascular prolif.	Probable
2BB8.00	O/E - vitreous haemorrhages	Probable
7276	Pan retinal photocoagulation for diabetes	Definite
F420500	Advanced diabetic retinal disease	Possible
F422y00	Other specified other proliferative retinopathy	Definite

F4K2800	Vitreous haemorrhage	Probable
FyuH400	[X]Vitreous haemorrhage in diseases classified elsewhere	Probable
2BB8.00	O/E - vitreous haemorrhages	Probable
	Diabetic Maculopathy (M1)	
2BBL.00	O/E - Diabetic maculopathy present both eyes	Definite
2BBm.00	O/E - right eye clinically significant macular oedema	Definite
2BBn.00	O/E - left eye clinically significant macular oedema	Definite
2BBW.00	O/E - right eye diabetic maculopathy	Definite
2BBX.00	O/E - left eye diabetic maculopathy	Definite
F425900	Maculopathy	Definite
F42y900	Macular oedema	Definite
C10EP00	Type 1 diabetes mellitus with exudative maculopathy	Definite
C10EP11	Type I diabetes mellitus with exudative maculopathy	Definite
C10FQ00	Type 2 diabetes mellitus with exudative maculopathy	Definite
C10FQ11	Type II diabetes mellitus with exudative maculopathy	Definite
F420300	Advanced diabetic maculopathy	Definite
7272900	Focal laser photocoagulation of retina	Probable
F420400	Diabetic maculopathy	Definite
	Referrable Retinopathy (R2, R3, M1)	
2BBY.00	O/E - referable retinopathy	Definite
2BBo.00	O/E - sight threatening diabetic retinopathy	Definite
	Advanced diabetic retinal disease	
F420500	Advanced diabetic retinal disease	Definite

Code	Description	Status
	Laser Procedures	
7276	Pan retinal photocoagulation for diabetes	Definite
7272012	Photocoagulation of the retina NEC	Definite
7272013	Laser therapy lesion of retina	Definite
7272300	Laser destruction of lesion of retina	Definite
7272500	Pan retinal laser photocoagulation to lesion of retina NEC	Definite
7272600	Laser photocoagulation to lesion of retina NEC	Definite
7272800	Pan retinal laser photocoagulation to lesion of retina	Definite
7272900	Focal laser photocoagulation of retina	Definite
2BBk.00	O/E - right eye stable treated proliferative diabetic retinopathy	Definite
2BBl.00	O/E - left eye stable treated proliferative diabetic retinopathy	Definite
2BBO.00	O/E - Laser photocoagulation scars	Definite
5B4..11	Retinal laser therapy	Definite
Z6F..11	Laser therapy	Definite

5B42.00	Laser therapy - retinal lesion	Definite
	Vitreous/ Peribulbar procedures / haemorrhage	
7270D00	Injection of Ranibizumab into vitreous body	Definite
7270z00	Operation on vitreous body NOS	Definite
7270300	Injection into vitreous body NEC	Definite
7274800	Injection of therapeutic substance around the eye	Possible
727C200	Injection therapeutic substance posterior segment of eye NEC	Definite
7270D00	Injection of Ranibizumab into vitreous body	Definite
7L19E00	Injection of triamcinolone	Probable
727C100	Injection of steroid into posterior segment of eye	Definite
7270200	Injection of vitreous substitute into vitreous body	Definite
7277600	Injection of therapeutic substance into macula	Definite
7270C00	Injection of vitreous substitute into vitreous body NEC	Definite
727C100	Injection of steroid into posterior segment of eye	Definite
7270400	Pars plana vitrectomy	Definite
727Cy00	Other specified operations on posterior segment of eye	Probable
727Cz00	Operations on posterior segment of eye NOS	Probable
7273000	Epiretinal dissection	Possible
727C000	Insertion sustained release device posterior segment of eye	Definite
7270y00	Other specified operation on vitreous body	Definite
7270800	Internal tamponade of retina using liquid	Possible
7270900	Internal tamponade of retina using oil	Possible
7270A00	Removal of internal tamponade agent from vitreous body	Possible
7270411	Vitrectomy using pars plana approach	Probable
7270500	Air/gas exchange of vitreous	Possible
7270600	Internal tamponade of retina using gas	Probable
7270200	Injection of vitreous substitute into vitreous body	Probable
7270300	Injection into vitreous body NEC	Definite
7270400	Pars plana vitrectomy	Definite
7270	Operations on vitreous body	Probable
7270100	Extirpation of vitreous body NEC	Probable
F4K2800	Vitreous haemorrhage	Definite
FyuH400	[X]Vitreous haemorrhage in diseases classified elsewhere	Definite
2BB8.00	O/E - vitreous haemorrhages	Definite
	Vision loss / blindness	
ZV52200	[V]Fitting or adjustment of artificial eye	Probable
ZV43000	[V]Has artificial eye globe	Probable
ZV43100	[V]Has artificial eye lens	Possible
FyuL.00	[X]Visual disturbances and blindness	Definite
F49z.11	Acquired blindness	Definite
F490900	Acquired blindness, both eyes	Definite
F495A00	Acquired blindness, one eye	Definite

F491.00	Better eye: low vision, Lesser eye: profound VI	Definite
F491500	Better eye: moderate VI, Lesser eye: blind, unspecified	Definite
F492300	Better eye: moderate VI, Lesser eye: low vision unspecified	Definite
F492500	Better eye: moderate VI, Lesser eye: moderate VI	Definite
F491700	Better eye: moderate VI, Lesser eye: near total VI	Definite
F491800	Better eye: moderate VI, Lesser eye: profound VI	Definite
F492400	Better eye: moderate VI, Lesser eye: severe VI	Definite
F491600	Better eye: moderate VI, Lesser eye: total VI	Definite
F490400	Better eye: near total VI, Lesser eye: near total VI	Definite
F490300	Better eye: near total VI, Lesser eye: total VI	Definite
F490200	Better eye: near total VI, Lesser eye: unspecified	Definite
F490700	Better eye: profound VI, Lesser eye: near total VI	Definite
F490800	Better eye: profound VI, Lesser eye: profound VI	Definite
F490600	Better eye: profound VI, Lesser eye: total VI	Definite
F490500	Better eye: profound VI, Lesser eye: unspecified	Definite
F491100	Better eye: severe VI, Lesser eye: blind, unspecified	Definite
F492100	Better eye: severe VI, Lesser eye: low vision unspecified	Definite
F491300	Better eye: severe VI, Lesser eye: near total VI	Definite
F491400	Better eye: severe VI, Lesser eye: profound VI	Definite
F492200	Better eye: severe VI, Lesser eye: severe VI	Definite
F491200	Better eye: severe VI, Lesser eye: total VI	Definite
8F62.00	Blind lead dog rehabilitation	Definite
8F6..11	Blind rehabilitation	Definite
8F61.00	Blind rehabilitation	Definite
ZN56800	Blind telephone user	Definite
F49..00	Blindness and low vision	Definite
F490z00	Blindness both eyes NOS	Definite
F490.00	Blindness, both eyes	Definite
F49A.00	Blindness, monocular	Definite
F495000	Blindness, one eye, unspecified	Definite
F490100	Both eyes total visual impairment	Definite
668C.00	Certificate of vision impairment	Definite
Fy1..00	Combined visual and hearing impairment	Definite
Fy1..12	Deafblind	Definite
ZN56A00	Deaf-blind telephone user	Definite
Fy1..11	Dual sensory impairment - deafblind	Definite
9m08.00	Exclu diab ret screen as blind	Definite
2BBr.00	Impair vision due diab retinop	Definite
F49..11	Impaired vision	Definite
ZK74.00	Issue of local authority blind registration	Definite
F494.00	Legal blindness USA	Definite
F496500	Lesser eye: moderate VI, Better eye: near normal vision	Definite
F496600	Lesser eye: moderate VI, Better eye: normal vision	Definite

F496400	Lesser eye: moderate VI, Better eye: unspecified	Definite
F495500	Lesser eye: near total VI, Better eye: near normal vision	Definite
F495600	Lesser eye: near total VI, Better eye: normal vision	Definite
F495400	Lesser eye: near total VI, Better eye: unspecified	Definite
F495800	Lesser eye: profound VI, Better eye: near normal vision	Definite
F495900	Lesser eye: profound VI, Better eye: normal vision	Definite
F495700	Lesser eye: profound VI, Better eye: unspecified	Definite
F496200	Lesser eye: severe VI, Better eye: near normal vision	Definite
F496300	Lesser eye: severe VI, Better eye: normal vision	Definite
F496100	Lesser eye: severe VI, Better eye: unspecified	Definite
F495200	Lesser eye: total VI, Better eye: near normal vision	Definite
F495300	Lesser eye: total VI, Better eye: normal vision	Definite
F495100	Lesser eye: total visual impairment, Better eye: unspecified	Definite
F49..12	Low vision	Definite
F492.00	Low vision, both eyes	Definite
F492z00	Low vision, both eyes NOS	Definite
F492000	Low vision, both eyes unspecified	Definite
F496.00	Low vision, one eye	Definite
F496z00	Low vision, one eye NOS	Definite
F496000	Low vision, one eye, unspecified	Definite
F498.00	Moderate visual impairment, binocular	Definite
F49C.00	Moderate visual impairment, monocular	Definite
2B7A.11	O/E - blind L-eye	Definite
2B6A.11	O/E - blind R-eye	Definite
22E6.11	O/E - false eye	Definite
22E6.00	O/E - glass (prosthetic) eye	Definite
22E6.12	O/E - glass eye	Definite
22EF.00	O/E - has one eye	Definite
2B7B.00	O/E - L-eye completely blind	Definite
2B7C.00	O/E - L-eye sees hand movements	Definite
2B7T.00	O/E - L-eye visual acuity (corrected) 1/60	Definite
2B7V.00	O/E - L-eye visual acuity (corrected) 2/60	Definite
2B7W.00	O/E - L-eye visual acuity (corrected) 4/60	Definite
2B7X.00	O/E - L-eye visual acuity (corrected) 5/60	Definite
2B7S.00	O/E - pinhole L-eye completely blind	Definite
2B7Q.00	O/E - pinhole L-eye counts fingers only	Definite
2B7R.00	O/E - pinhole L-eye perceives light only	Definite
2B7P.00	O/E - pinhole L-eye sees hand movements	Definite
2B6S.00	O/E - pinhole R-eye completely blind	Definite
2B6Q.00	O/E - pinhole R-eye counts fingers only	Definite
2B6R.00	O/E - pinhole R-eye perceives light only	Definite
2B6P.00	O/E - pinhole R-eye sees hand movements	Definite
2B7L.00	O/E - pinhole visual acuity L-eye=6/60	Definite

2B6L.00	O/E - pinhole visual acuity R-eye=6/60	Definite
22E6.13	O/E - prosthetic eye	Definite
2B6B.00	O/E - R-eye completely blind	Definite
2B6C.00	O/E - R-eye sees hand movements	Definite
2B6T.00	O/E - R-eye visual acuity (corrected) 1/60	Definite
2B6V.00	O/E - R-eye visual acuity (corrected) 2/60	Definite
2B6W.00	O/E - R-eye visual acuity (corrected) 4/60	Definite
2B6X.00	O/E - R-eye visual acuity (corrected) 5/60	Definite
2B7E.00	O/E - visual acuity L-eye=3/60	Definite
2B78.00	O/E - visual acuity L-eye=6/60	Definite
2B6E.00	O/E - visual acuity R-eye=3/60	Definite
2B68.00	O/E - visual acuity R-eye=6/60	Definite
2B79.00	O/E -L-eye counts fingers only	Definite
2B69.00	O/E -R-eye counts fingers only	Definite
2B7A.00	O/E-L-eye perceives light only	Definite
2B6A.00	O/E-R-eye perceives light only	Definite
F491000	One eye blind, one eye low vision	Definite
F491z00	One eye blind, one eye low vision NOS	Definite
Z9E2.00	Optical low vision aid provision	Definite
F49..13	Partial sight	Definite
F495z00	Profound impairment one eye NOS	Definite
F495.00	Profound impairment, one eye	Definite
Z96..00	Provision for visual and hearing impairment	Definite
Z9E5400	Provision of ancillary low vision aid	Definite
Z9E1100	Provision of artificial eye	Definite
Z962.00	Provision of communicator for visual and hearing impairment	Definite
Z9E5100	Provision of electronic low vision aid	Definite
Z961.00	Provision of guide help for visual and hearing impairment	Definite
Z9E3200	Provision of low vision hand magnifier	Definite
Z9E3400	Provision of low vision headband magnifier	Definite
Z9E3300	Provision of low vision stand magnifier	Definite
Z9E3100	Provision of magnifier low vision aid - near	Definite
Z9E5.00	Provision of non-optical low vision aid	Definite
Z9E4.00	Provision of optical low vision aid - distance	Definite
Z9E3.00	Provision of optical low vision aid - near	Definite
Z9E1200	Provision of removable artificial eye	Definite
Z9E3500	Provision of spectacle low vision aid - near	Definite
8HIE.00	Referral to visual impairment multidisciplinary team	Definite
6689	Registered blind	Definite
6688.11	Registered partially blind	Definite
6688	Registered partially sighted	Definite
6689.11	Registered severely sight impaired	Definite
668D.00	Registered sight impaired	Definite

8D36.00	Removable artificial eye	Definite
9Nfb.00	Requires deafblind block alphabet interpreter	Definite
9NfB.00	Requires deafblind communicator guide	Definite
9Nfc.00	Requires deafblind haptic communication interpreter	Definite
9Nfa.00	Requires deafblind manual alphabet interpreter	Definite
F497.00	Severe visual impairment, binocular	Definite
F49B.00	Severe visual impairment, monocular	Definite
F49..14	Sight impaired	Definite
F490000	Unspecified blindness both eyes	Definite
1a00000	Uses guide dog for the blind	Definite
F49D.00	Visual impairment	Definite
F493.00	Visual loss, both eyes unqualified	Definite
F49y.00	Visual loss, one eye, unqualified	Definite
F404200	Blind hypertensive eye	Definite
F404100	Blind hypotensive eye	Definite
Z9E3900	Near low vision aid - clip-on spectacle magnifier	Definite
Z9E3C00	Near low vision aid - clip-on spectacle telescope	Definite
Z9E3D00	Near low vision aid - extra cap for telescope	Definite
Z9E3800	Near low vision aid - integral spectacle magnifier	Definite
Z9E3B00	Near low vision aid - integral spectacle telescope	Definite
9NlD.00	Seen by visual impairment teacher	Definite
1B75.00	Loss of vision, Severe visual loss	Definite
1B77.00	Deteriorating vision, Severe visual loss	Definite

Unclassifiable

Code	Description
2BB5.00	O/E - retinal haemorrhages
2BB6.00	O/E - retinal exudates
2BBF.00	Retinal abnormality-diabetes related
2BBr.00	Impaired vision due diab retinop
C105.00	Diabetes mellitus with ophthalmic manifestation
C105000	Diabetes mellitus, juvenile type, + ophthalmic manifestation
C105100	Diabetes mellitus, adult onset, + ophthalmic manifestation
C105y00	Other specified diabetes mellitus with ophthalmic complicatn
C105z00	Diabetes mellitus NOS with ophthalmic manifestation
C108100	Insulin-dependent diabetes mellitus with ophthalmic comps
C108111	Type I diabetes mellitus with ophthalmic complications
C108112	Type 1 diabetes mellitus with ophthalmic complications
C108700	Insulin dependent diabetes mellitus with retinopathy
C108711	Type I diabetes mellitus with retinopathy
C108712	Type 1 diabetes mellitus with retinopathy
C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps

C109111	Type II diabetes mellitus with ophthalmic complications
C109112	Type 2 diabetes mellitus with ophthalmic complications
C109600	Non-insulin-dependent diabetes mellitus with retinopathy
C109611	Type II diabetes mellitus with retinopathy
C109612	Type 2 diabetes mellitus with retinopathy
C10A300	Malnutrit-related diabetes mellitus wth ophthalmic complicat
C10E100	Type 1 diabetes mellitus with ophthalmic complications
C10E111	Type I diabetes mellitus with ophthalmic complications
C10E112	Insulin-dependent diabetes mellitus with ophthalmic comps
C10E700	Type 1 diabetes mellitus with retinopathy
C10E711	Type I diabetes mellitus with retinopathy
C10E712	Insulin dependent diabetes mellitus with retinopathy
C10F600	Type 2 diabetes mellitus with retinopathy
C10F611	Type II diabetes mellitus with retinopathy
F420.00	Diabetic retinopathy
F420600	Non proliferative diabetic retinopathy
F420z00	Diabetic retinopathy NOS
F421.11	Microvascular retinal changes
2BB5.00	O/E - retinal haemorrhages
2BBM.00	O/E - diabetic maculopathy absent both eyes

Appendix 4: Summary of Prevalence Trends 1998 to 2018

Decade	Prevalence estimate at the start of the decade	Prevalence estimate at the end of the decade	Percentage increase in prevalence within the decade	Percentage increase in prevalence between the decades
STR in T1DM in two decades				
1998 to 2007	8.15	17.57	216%	
2009 to 2018	20.54	30.22	147%	371%
STR in T2DM in two decades				
1998 to 2007	4.36	8.1	186%	
2009 to 2018	9.01	11.15	124%	256%
DR in T1DM in two decades				
1998 to 2007	26.62	40.32	151%	
2009 to 2018	45.39	57.75	127%	217%
DR in T2DM in two decades				
1998 to 2007	11.53	20.06	174%	
2009 to 2018	23.7	32.64	138%	283%
STR in DM in two decades				
1998 to 2007	4.87	8.84	182%	
2009 to 2018	9.86	12.48	127%	256%
DR in DM in two decades				
1998 to 2007	13.57	21.64	159%	
2009 to 2018	25.3	34.39	136%	253%
T1DM in two decades				
1998 to 2007	0.31%	0.32%	104%	
2009 to 2018	0.33%	0.41%	123%	132%
T2DM in two decades				
1998 to 2007	1.91%	3.65%	191%	
2009 to 2018	4.01%	5.24%	131%	273%

Appendix 5: Future projections

In the four figures below, the grey area is the prediction band (95% confidence interval) and signifies the uncertainty of the estimates.

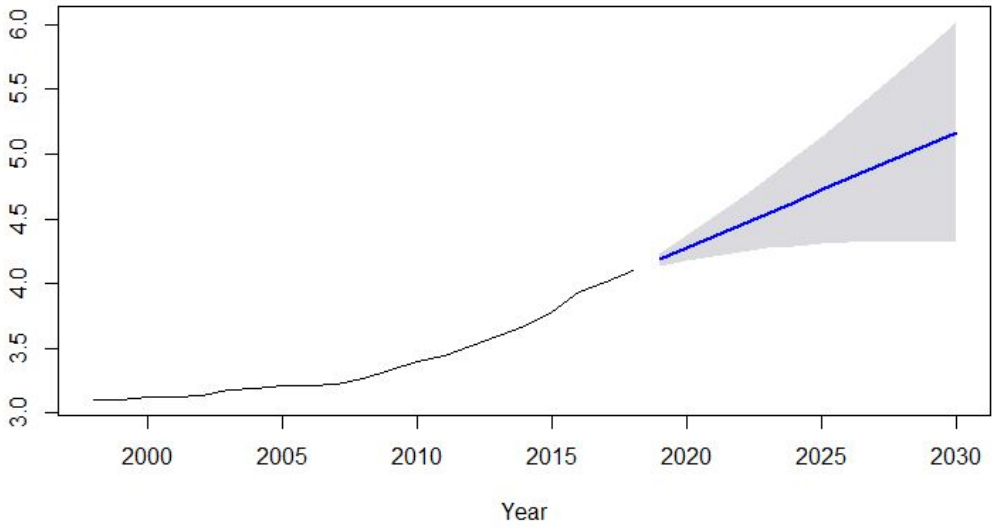

Figure 1: T1DM Projections / 1000 individuals

X axis is calendar years and Y axis is prevalence (cases per 1000 individuals general population), starts at 3.0

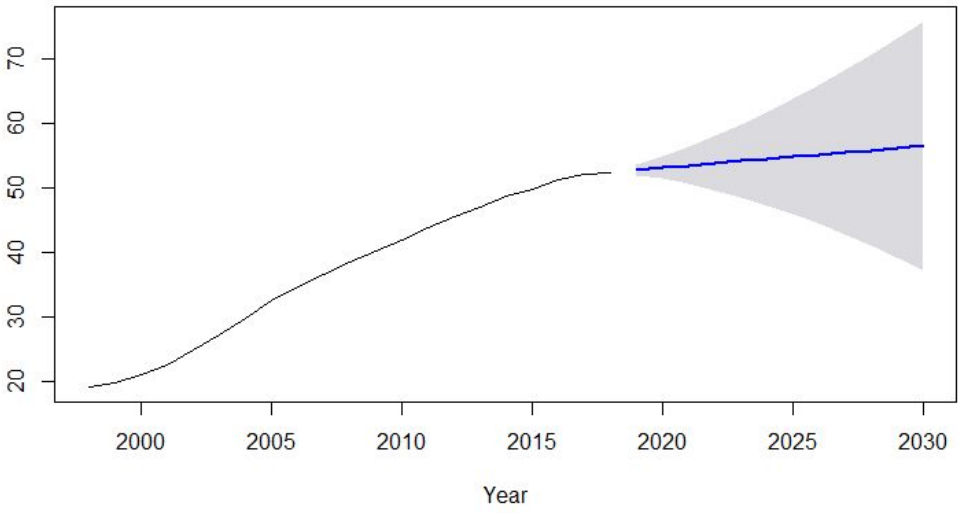

Figure 2: T2DM Projections / 1000 individuals

X axis is calendar years and Y axis is prevalence (cases per 1000 individuals general population) starts at 17

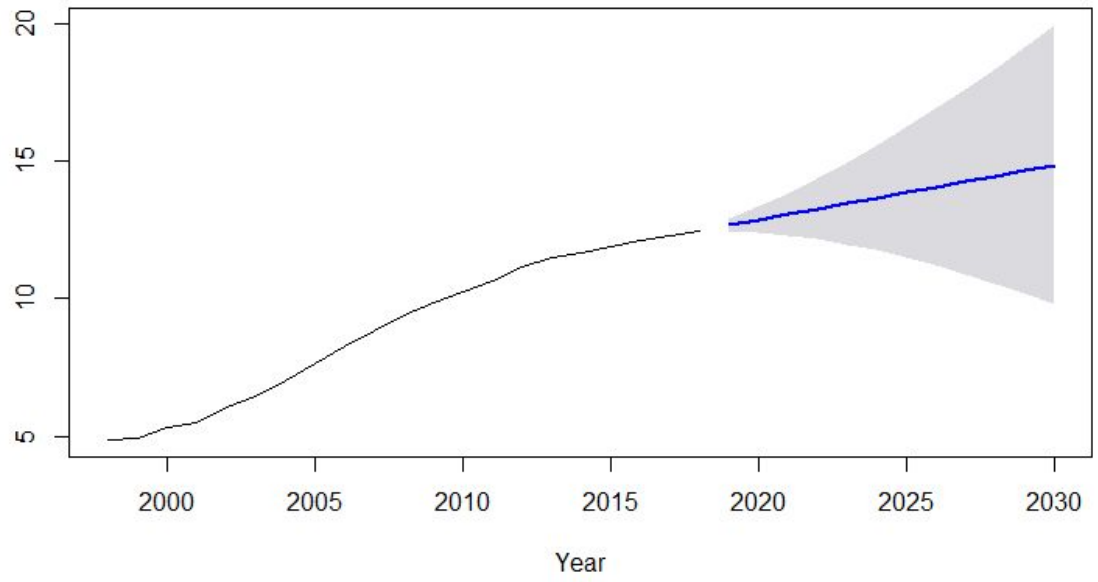

Figure 3: STR Projections (%)

X axis is calendar years and Y axis is prevalence (cases per 100 individuals with diabetes) starts at 4

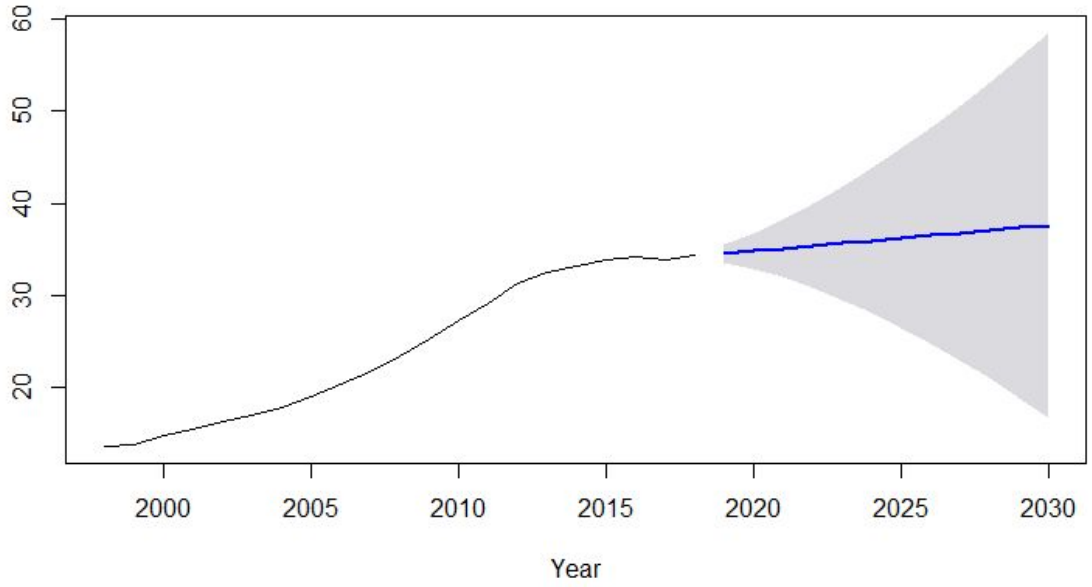

Figure 4: DR Projections (%)

X axis is calendar years and Y axis is prevalence (cases per 100 individuals with diabetes), starts at 10

Annual Prevalence Diabetes Mellitus per 1000 Population and Diabetic Retinopathy per 100 diabetic population (95% PI)

	T1DM Forecast			T2DM Forecast			DR Forecast			STR Forecast		
Year	Forecast	Low 95	High 95	Forecast	Low 95	High 95	Forecast	Low 95	High 95	Forecast	Low 95	High 95
2019	4.2	4.1	4.2	52.7	51.9	53.6	34.5	33.5	35.5	12.7	12.4	12.9
2020	4.3	4.2	4.4	53.1	51.4	54.8	34.8	32.9	36.7	12.9	12.4	13.3
2021	4.4	4.2	4.5	53.4	50.6	56.3	35.1	31.9	38.2	13.1	12.3	13.8
2022	4.5	4.2	4.7	53.8	49.6	57.9	35.4	30.8	39.9	13.3	12.2	14.4
2023	4.5	4.3	4.8	54.1	48.5	59.7	35.6	29.5	41.8	13.5	12.0	15.0
2024	4.6	4.3	5.0	54.4	47.2	61.6	35.9	28.1	43.8	13.7	11.8	15.6
2025	4.7	4.3	5.1	54.8	45.8	63.7	36.2	26.5	45.9	13.9	11.5	16.2
2026	4.8	4.3	5.3	55.1	44.3	65.9	36.5	24.7	48.2	14.1	11.2	16.9
2027	4.9	4.3	5.5	55.4	42.7	68.2	36.8	22.9	50.6	14.3	10.9	17.6
2028	5.0	4.3	5.7	55.8	41.0	70.6	37.0	20.9	53.2	14.5	10.5	18.4
2029	5.1	4.3	5.8	56.1	39.1	73.1	37.3	18.8	55.8	14.7	10.2	19.1
2030	5.2	4.3	6.0	56.4	37.2	75.7	37.6	16.7	58.5	14.9	9.8	19.9

Appendix 6: Previous prevalence studies compared with IMRD based analysis

Publication	Population	T1DM	T2DM	Any DM
Younis et al (1)	Liverpool diabetic retinopathy screening programme 1991 to 1999 – baseline prevalence at entry into the programme	Any DR 45.7% STED 16.4% PDR 3.7%	Any DR 25.3% STED 6.0% PDR 0.5%	
Misra et al (2)	Norwich Diabetic retinopathy screening programme 2006 with dynamic cohort design with repeated measures			Any DR 25.6% STDR 0.6% PPDR 4.6% PDR 0.08% Maculopathy 0.44% Referable (R2, R3, M1) retinopathy 4.7%
Thomas (3) and Minassian et al (4)	Welsh Diabetic retinopathy screening programme 2005 to 2009 and application to England	Any DR 56.3% STDR 11.2%	Any DR 30.9% STDR 2.9%	Any DR 32.4% STDR 3.4% Diabetic Macular Oedema 7.12%
Looker et al (5)	Newly diagnosed type 2 diabetes attending Scottish National screening programme 2005 to 2008. prevalence at first screening		Any DR 19.3% Referable DR 1.9% PPDR ± any maculopathy 0.4% PDR ± any maculopathy 0.3%	

Mathur et al (6)	CPRD based UK wide study 2014 - crude prevalence rate	Any DR 54.8% Severe DR 8.1%	Any DR 30.6% Severe DR 1.2%	Any DR 32.6% Severe DR 1.8%
The present study	IMRD based cross sectional study - 2017	Any DR 57.8% STR 30.2% Any maculopathy 19.62%	Any DR 32.6% STR 11.2% Any maculopathy 6.99%	Any DR 34.4% STR 12.3% Any maculopathy 7.86%

References:

1. Younis N, Broadbent DM, Harding SP, Vora JR. Prevalence of diabetic eye disease in patients entering a systematic primary care-based eye screening programme. Diabetic medicine : a journal of the British Diabetic Association. 2002;19(12):1014-21.
2. Misra A, Bachmann MO, Greenwood RH, Jenkins C, Shaw A, Barakat O, et al. Trends in yield and effects of screening intervals during 17 years of a large UK community-based diabetic retinopathy screening programme. Diabetic medicine : a journal of the British Diabetic Association. 2009;26(10):1040-7.

3. Thomas RL, Dunstan FD, Luzio SD, Chowdhury SR, North RV, Hale SL, et al. Prevalence of diabetic retinopathy within a national diabetic retinopathy screening service. The British journal of ophthalmology. 2015;99(1):64-8.

4. Minassian DC, Owens DR, Reidy A. Prevalence of diabetic macular oedema and related health and social care resource use in England. The British journal of ophthalmology. 2012;96(3):345-9.

5. Looker H, Nyangoma S, Cromie D, Olson J, Leese G, Black M, et al. Diabetic retinopathy at diagnosis of type 2 diabetes in Scotland. Diabetologia. 2012;55(9):2335-42.
6. Mathur R, Bhaskaran K, Edwards E, Lee H, Chaturvedi N, Smeeth L, et al. Population trends in the 10-year incidence and prevalence of diabetic retinopathy in the UK: a cohort study in the Clinical Practice Research Datalink 2004-2014. BMJ open. 2017;7(2):e014444.

Appendix 7: Previous publications reporting trends in prevalence rates of DR in the UK compared with IMRD based analysis

Publication	Population	T1DM	T2DM	Any DM
Misra et al (1)	Norwich Diabetic retinopathy screening programme 1990 to 2006 (Mostly Type 2) with dynamic cohort design with repeated measures			All DR prevalence increased from 23.2% to 25.3% Referable DR increased from 2 to 4.7%
Mathur et al (2)	CPRD based UK wide study population from 2004 to 2014	All DR remained stable at 55% Severe DR increased from 3.5% in 2004 to 8.0% in 2014	All DR reduced from 24.6% in 2004 to 23.1% in 2014 Severe DR increased from 0.3% in 2004 to 0.9% in 2014	All DR prevalence decreased from 2.6% to 2.2% Severe DR remained stable at 0.1%
This study	IMRD based serial cross-sectional studies 1998 to 2018			

References:

1. Misra A, Bachmann MO, Greenwood RH, Jenkins C, Shaw A, Barakat O, et al. Trends in yield and effects of screening intervals during 17 years of a large UK community-based diabetic retinopathy screening programme. Diabetic medicine : a journal of the British Diabetic Association. 2009;26(10):1040-7.

2. Mathur R, Bhaskaran K, Edwards E, Lee H, Chaturvedi N, Smeeth L, et al. Population trends in the 10-year incidence and prevalence of diabetic retinopathy in the UK: a cohort study in the Clinical Practice Research Datalink 2004-2014. BMJ open. 2017;7(2):e014444.

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cross sectionalreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	2
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2

Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4,5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	#4	Present key elements of study design early in the paper	2
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-9
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	6-7
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	NA
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	NA
Bias	#9	Describe any efforts to address potential sources of bias	5, 6

Study size	#10	Explain how the study size was arrived at	All eligible patients included
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	NA
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	NA
Statistical methods	#12c	Explain how missing data were addressed	NA
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	NA
Statistical methods	#12e	Describe any sensitivity analyses	NA
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	Figure 1

Participants	#13b	Give reasons for non-participation at each stage	Figure 1
Participants	#13c	Consider use of a flow diagram	Figure 1
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	Table 1
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	Table 1
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	Table 3
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
Main results	#16b	Report category boundaries when continuous variables were categorized	NA
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	NA

Discussion			
Key results	#18	Summarise key results with reference to study objectives	16 - 18
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	18 - 20
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	19 – 20, appendices 6, 7
Generalisability	#21	Discuss the generalisability (external validity) of the study results	21 - 22
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA

BMJ Open

Disease burden of diabetes, diabetic retinopathy and their future projections in the United Kingdom: Cross sectional analyses of a primary care database.

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Secondary Subject Heading:	Diabetes and endocrinology
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1

Disease burden of diabetes, diabetic retinopathy and their future Projections in the United Kingdom: Cross sectional analyses of a primary care database. .

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Key words

Diabetes Mellitus, Diabetic Retinopathy, Current Disease Burden, Future Projections

Abstract

Objectives

To estimate the current disease burden, trends, and future projections for Diabetes Mellitus (DM) and Diabetic Retinopathy in the IQVIA Medical Research Data (IMRD).

Participants / Design / Setting

We performed a cross-sectional study of patients aged 12 and above to determine the prevalence of Diabetes Mellitus (DM) and Diabetic Retinopathy from the IMRD database (primary care database) in January 2017, involving a total population of 180,824 patients with DM. We also carried out a series of cross-sectional studies to investigate prevalence trends, and then applied a double exponential smoothing model to forecast the future burden of Diabetes Mellitus and Diabetic Retinopathy in the United Kingdom.

Results

The crude Diabetes Mellitus prevalence in 2017 was 5.2%. The Diabetic Retinopathy, Sight Threatening Retinopathy (STR) and Diabetic Maculopathy prevalence figures in 2017 were 33.78%, 12.28% and 7.86% respectively in our IMRD cross-sectional study. There were upward trends in the prevalence of Diabetes Mellitus, Diabetic Retinopathy, and Sight-threatening retinopathy, most marked and accelerating in Sight-threatening retinopathy in type 1 Diabetes Mellitus (T1DM) but slowing in type 2 Diabetes Mellitus (T2DM), and in the overall prevalence of Diabetic Retinopathy.

Conclusion

Our results suggest differential rising trends in the prevalence of Diabetes Mellitus and diabetic retinopathy. Preventive strategies, as well as treatment services planning can be based on these projected prevalence estimates. Improvements that are necessary for the optimisation of care pathways, and preparations to meet demand and capacity challenges, can also be based on this information. The limitations of the study can be overcome by a future collaborative study linking Diabetic Retinopathy (DR) screening and hospital eye services data.

Article Summary: Strengths and limitations of this study

- This is an up-to-date study to give DM and Diabetic Retinopathy prevalence trends from 1998 to 2018.
- This study forecasts the future Diabetic Retinopathy disease burden up to 2030 to enable preparation for impending challenges.
- Current prevalence of age 12 and over, diagnosed DM, DR, STR, Diabetic Macular Oedema disease and treatment burden in United Kingdom.
- This study has not however been adjusted for the risk factors for the incidence/prevalence of Diabetes Mellitus or Diabetic Retinopathy.
- A possible impact of coding errors and subjectivity in documentation cannot be precluded.

Introduction

DR is the fourth most common cause of blindness and visual impairment in high-income countries (1). Services are overburdened and optimisation requires accurate estimates of disease and the expected treatment burden (2). A recent systematic review of studies estimating the incidence of DR (3) highlighted the paucity of contemporary evidence from developed countries on the disease burden and recommended that estimates should be based on populations with Diabetes Mellitus (DM) rather than the general population so as not to dilute the estimates. A recent attempt to forecast the UK-wide disease burden of DR was hindered by the need for reliable data (4).

Previous studies have been conducted on the prevalence of DR (5-9), with the most recent UK-wide study being performed in 2014 based on Clinical Practice Research Datalink (CPRD). Two of these studies also explored trends in DR incidence and prevalence (6, 9). A significant amount of heterogeneity in the populations studied, the classification of DR, the definition of its presence and severity was present in these studies. Studies of the forecasts of the future disease burden of DR would be useful both for preparing health care delivery systems for the future, and in preventing blindness in patients with DM. There is a Europe wide forecast study with UK component based on pre 2009 data dealing with DR only (10). The disease burden estimate of DR will not be complete without a similar estimate for the diabetes burden. A UK wide upto date study dealing with DM, DR and STR is needed.

A previous study on future projections of DM in the United Kingdom was found to underestimate prevalence (11). Moreover, evidence suggests that the rate of

increase is not constant or uniform across DM subtypes (namely T2DM and T1DM, especially in children (12). The incidence rate of T1DM (pooled estimate of European centres, UK included) in children is expected to continue to rise at a rate of 3.4% per annum (13). Gonzalez et al (14) reported an increasing prevalence of DM for the 10 years up to 2005. Public Health England (PHE) figures are available for 2019, based on the Quality Outcome Framework, except in Scotland where they are based on Scottish Diabetes Survey (15). However, these figures are limited to those over 17 years old. We aimed to estimate recent trends in the disease burden of DM, and to use this as a base on which to estimate the current disease burden for DR and STR in the UK. We then wanted to design, train, and validate a forecasting model to support future projections of these disease burdens. Since DR screening is offered after age 12 only, the population of interest to us was age 12 or over only.

Methods

Study design and data source

Several studies have already been performed on IMRD (previously The Health Improvement Network) and their findings have been extrapolated to UK and European population (16-21). This database has documented generalisability to the UK population (22).

To study the trend, and to forecast the future burden of diagnosed DM, DR and STR, we used the IMRD database to conduct a series of yearly cross-sectional analyses on the 1st of each year from 1998 to 2018. In addition, a detailed cross-sectional

study was carried out on the 1st of January 2017 to estimate the prevalence of T1DM and T2DM in the whole UK population, and of DR in patients with T1DM and T2DM.

IMRD is a large UK general practice electronic database containing anonymised patient records from 787 general practices, with over 15 million patient records, of which around 3.7 million are active at a given time point (6.2% of the UK population). IMRD provides information on demographics, lifestyle, diagnoses, and prescriptions, and is quality checked (23). Based on the demographic distribution observed in IMRD, it is considered generalizable to the UK population (22). IMRD has previously been used and validated to estimate prevalence trends of DM and DR, and to identify risk factors for DR (14, 24-27).

Study population

To ensure that only high quality data was included, and that all important covariates were documented, general practices were eligible only if they showed acceptable mortality rates one year before the cross-sectional study date (23), and had been using the electronic medical record system for at least a year. Patients from eligible general practices must have been registered with their practice for at least one year and must be aged 12 years or above to be included in the study to match the Diabetic Eye Screening Programme criteria (DESP). For estimation of the prevalence of T1DM and T2DM, the whole registered population was included as the denominator population (per 1000). For estimation of STR and DR prevalence, patients with DM served as the denominator (per 100). Estimates are stratified by type of diabetes.

Patient and public involvement:

There was no patient and public involvement in this research project.

Case definition of diagnoses of DM and DR

Clinical diagnosis and symptoms in the IMRD database are recorded using the Read code classification system (28). Read codes were selected using a rigorous seven step process and selected search terms (Appendix 1, 2). Read codes are given in Appendix 3. Patients with a Read code record of DM before the study entry date were identified. Patients with a record of DM were categorised as type 1 if they had at least one prescription record for insulin and no record for any oral glucose-lowering medication other than metformin in the database. The remaining patients with diabetes were categorized as type 2. Prevalence estimates calculated were verified against PHE estimates of DM (29).

The most severe DR Read code recorded before patient's study entry was used to classify their DR or STR status. Stages of DR among those patients identified with DM were classified using the Royal College of Ophthalmology modified classification (30). However, patients with a retinopathy record were stratified into mutually exclusive categories of 1) Pre-STR including no retinopathy and background retinopathy, 2) STR and 3) Retinopathy unspecified as either pre-STR (background retinopathy) or STR. Pre-STR was further categorized into mutually exclusive categories: 1) R0 or 2) R1. STR was further categorized into mutually exclusive categories of 1) STR based on diagnostic codes and 2) STR that needed treatment or resulted in vision loss. Within STR we categorised pre-proliferative DR (R2) and proliferative DR (R3) as mutually exclusive groups. STR was further stratified into overlapping categories based on the presence of STR (R2/3) and maculopathy (M1). Treatment and vision loss codes included: (i) laser therapy, (ii) vitreous injection and other vitreous procedures, (iii) low vision or blindness.

Time trend analysis and forecasting models

A double exponential smoothing model was chosen to cover the level and trend, as this was yearly cross-sectional data with no seasonal / cyclical variation expected or observed (31) not unlike Adams et al published model (32). The IMRD serial cross-sectional data for the prevalence of DM and DR (STR and any retinopathy) were split into two portions - 1998 to 2013 (training data) and 2014 to 2018 (test data). The model was fitted to the training data and then prediction was carried out from 2014 to 2018. This was then compared with the test data for validation. Thereafter, the yearly prevalence of DR and STR were projected up to 2030 using the same model with 95% prediction intervals. This was done using the statistical software R (2019) (33). Prevalence rates were then converted into patient numbers, using projected population figures from the Office of National Statistics (34).

IMRD data analysis for annual prevalence of DM and DR.

Prevalence trends between the two decades before and after 2008 were compared for trend analysis. Patients identified as T1DM or T2DM on or before 1st of January in each year analysed were identified as the numerators for calculating the prevalence of T1DM and T2DM. The prevalence was estimated by dividing the numerator population by the eligible registered population aged above 12 years (denominator) on 1st of January for the corresponding year. Among these patients, those diagnosed with any retinopathy and those with STR were numerators for calculating the prevalence of DR and STR respectively. Prevalence estimates are provided for patients with T1DM and T2DM separately with 95% confidence intervals. A description of patients aged 12 or above with a diagnosis of DM is also given for the year 2017. Baseline characteristics such as age, and age at diagnosis of diabetes

were summarized as the mean (SD), and as frequency (percentage) for sex, Townsend deprivation quintile and ethnicity. These characteristics were also reported as stratified by type of DM. A detailed description of the proportion of DM patients (T1DM and T2DM aged 12 or above) with DR in the year 2017 categorized by DR severity is also presented. Estimates from IMRD were compared to estimates obtained from data from UK studies (5-7, 9, 35) for verification and comparison.

Results

Figure 1 gives the Patients flow and case selection algorithm. As of 1st January 2017, 2,813,916 people were eligible to be included in the primary cross-sectional analysis. The demography characteristics of the sample are given in Table 1. The mean age of patients with T1DM and T2DM as of 1st January 2017 was 42.5 (17.2) and 66.3 (13.0) respectively. The mean age at diagnosis of T1DM and T2DM were 21.4 (14.3) and 57.0 (13.1) respectively. Nearly 80% and 55% of patients respectively had their Townsend deprivation and ethnicity recorded in the IMRD database.

Prevalence trends

The results in figures 2 and 3 show an almost a global upward trend in the prevalence of both types of diabetes (T1DM and T2DM) and in DR (all types of DR / STR). The highest rise was seen in STR in those with T1DM (3.7 times increase in two decades). The second highest rise was in all types of DR in the T2DM population (2.8 times). Splitting this data by the decades (1998 to 2007 versus 2009 to 2018), the end of the first decade showed a higher increase in every category (diabetes as well as diabetic retinopathy) as compared to the second decade, except in T1DM where it was higher in second decade (Appendix 4). T2DM increased more than

T1DM between 1998 and 2018, but while the increase in T2DM prevalence slowed recently, the increase in T1DM prevalence accelerated significantly in the recent decade.

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Table 1: Demography of patients with DM in IMRD data on 1st of January 2017

	DM (N)	% / (SD)	T1DM (N)	% / (SD)	T2DM (N)	% / (SD)
Total	180,824	100.00%	12,434	6.88%	168,390	93.12%
Gender						
Male	101,628	56.20%	7,192	57.84%	94,436	56.08%
Female	79,196	43.80%	5,242	42.16%	73,954	43.92%
Age	180,824	64.7 (SD 14.7)	12,434	42.5 (SD 17.2)	168,390	66.3 (SD 13.0)
Age at diagnosis	180,788	54.6 (SD 16.0)	12,422	21.4 (SD 14.3)	168,366	57.0 (SD 13.1)
Townsend						
1	27,616	15.27%	2,037	16.38%	25,579	15.19%
2	30,011	16.60%	2,206	17.74%	27,805	16.51%
3	32,434	17.94%	2,222	17.87%	30,212	17.94%
4	31,332	17.33%	1,978	15.91%	29,354	17.43%
5	24,606	13.61%	1,568	12.61%	23,038	13.68%
Missing	34,825	19.26%	2,423	19.49%	32,402	19.24%
Ethnicity						
Caucasian	88,420	48.90%	6,584	52.95%	81,836	48.60%
Black afro Caribbean	2,738	1.51%	98	0.79%	2640	1.57%
Chinese/Middle eastern/ others	567	0.31%	45	0.36%	522	0.31%
South Asians	6,361	3.52%	124	1.00%	6237	3.70%
Mixed race	1243	0.69%	32	0.26%	1211	0.72%
Missing	81,495	45.07%	5551	44.64%	75944	45.10%

DM-Diabetes Mellitus; T2DM – Type 2 Diabetes Mellitus; T1DM – Type 1 Diabetes Mellitus Number; N, Standard deviation; (SD)

Forecasting model

The forecasted annual UK prevalence values of T1DM, T2DM, DR and STR, with their 95% prediction intervals (PI), are given in the Appendix 5. These suggest that the prevalence will increase by 24% (5 to 43%), 7% (-28 to 41%), 9% (-50 to 65%) and 17% (-21 to 54%) respectively by 2030. Corresponding estimates of the absolute numbers of people in the UK forecast to have these conditions are shown in Table 2. These correspond to 0.36 (.3 -.4), 4 (2.6 - 5.3), 1.6 (.7-2.5), and 0.64 (.42-.86) million people respectively having each condition, respectively. We verified our UK forecast for 2019 and found the total figure (3,800,920) to be close to the Quality Outcome Framework provided estimate of diagnosed DM of 3,809,119.

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Table 2: Future Projections of Diabetes and DR disease Burden

Year	Projected Population	*T1DM	*T2DM	*Total DM	#DR	#STR
2019	66800000	280560	3520360	3800920	1311317	482717
2020	67200000	288960	3568320	3857280	1342333	497589
2021	67500000	297000	3604500	3901500	1369427	511097
2022	67800000	305100	3647640	3952740	1399270	525714
2023	68100000	306450	3684210	3990660	1420675	538739
2024	68400000	314640	3720960	4035600	1448780	552877
2025	68700000	322890	3764760	4087650	1479729	568183
2026	68900000	330720	3796390	4127110	1506395	581923
2027	69200000	339080	3833680	4172760	1535576	596705
2028	69400000	347000	3872520	4219520	1561222	611830
2029	69600000	354960	3904560	4259520	1588801	626149
2030	69800000	362960	3936720	4299680	1616680	640652

*The DR and STR forecast is actual IMRD based figures projected for the UK population (34). Formula used is Affected Population = Projected Prevalence X Projected Population. # In calculating projections for diabetic retinopathy, we have applied the retinopathy rates of those aged 12 and above for the whole diabetes population rather than for those above 12 years old (age at which retinopathy screening commences and was one of our inclusion criteria). This approximately gives the projected total population, as breakdown for over 12 years is not available but the number of patients with DM below 12 years is negligibly small.

2017 Cross-sectional analysis

In the 2017 data analysis, 180,824 patients had a code for diabetes prior to this date of which 12,434 (6.9%) were identified as T1DM and 168,390 (93.1%) were identified as T2DM. Patients with DM were more likely to be men (56.2% vs 43.8%). The prevalence of DR in different stages of progression is given in Table 3. Prevalence of any DR and STR among patients with DM aged 12 and above was 33.8% and 12.3% respectively. When stratified by diabetes type, a higher proportion of patients with T1DM had a more severe form of retinopathy than patients with T2DM (prevalence of STR was 29.7% vs 11%), while prevalence of pre-STR (R0/R1 & M0) was higher among patients with T2DM (31.8% in T1DM vs 37.8% in T2DM). Each subcategory among STR population (R2 / R3 / M1 and their combinations), was present in higher proportion of patients with T1DM as compared to T2DM (R2: 3.7% vs 1.2%; R3: 12.1% vs 1.9%; and M1: 19.6% vs 7.0% respectively)]. A higher proportion of patients with T1DM compared to T2DM also received treatment procedures (Laser: 7.1% vs 1.3%; Vitreous injection and procedures: 5.1% vs 1.1%). There was also a higher proportion of documented cases of visual impairment or vision loss among T1DM [3.1% vs 2.8%].

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Table 3: Diabetic Retinopathy in patients with DM in IMRD data on 1st of January 2017

	DM		T1DM		T2DM	
Diabetes (N)	180,824	**%**	12,434	**%**	168,390	**%**
No Retinopathy coding available	82,119	45.41%	3,846	30.93%	78,273	46.48%
Retinopathy Coding available	98,705	54.59%	8,588	69.07%	90,117	53.52%
Pre-STR	**67750**	37.47%	**3951**	31.78%	**63699**	37.83%
No DR (R0M0)	37,618	20.80%	1,472	11.84%	36,146	21.47%
R1	30,132	16.66%	2,479	19.94%	27,553	16.36%
STR	**22,198**	12.28%	**3,693**	29.70%	**18,505**	10.99%
STR without Rx or vision loss	13,165	7.28%	2,271	18.26%	10,894	6.47%
R2	2,487	1.38%	454	3.65%	2,033	1.21%
R3	4,729	2.62%	1,505	12.10%	3,224	1.91%
M1	14,206	7.86%	2,440	19.62%	11,766	6.99%
STR with Rx and vision loss	9,033	5.00%	1,422	11.44%	7,611	4.52%
Laser	3,092	1.71%	885	7.12%	2,207	1.31%
Vitreous injections / procedures	2,536	1.40%	637	5.12%	1,899	1.13%
Vision loss / blindness	5,050	2.79%	384	3.09%	4,666	2.77%
None specific for STR or Pre-STR	**8,757**	4.84%	**844**	6.79%	**7913**	4.70%
Any retinopathy	61087	33.78%	7016	56.43%	53971	32.05%

DR – Diabetic retinopathy, R0 – no retinopathy, M0 – no maculopathy, R1, Background retinopathy, Pre-STR is combination of no diabetic retinopathy and background retinopathy, R2 is pre-proliferative diabetic retinopathy, R3 is proliferative diabetic retinopathy, M1 is diabetic maculopathy, STR is sight-threatening retinopathy which is a combination of R2, R3 and M1, Non-specific retinopathy is where it cannot be categorised into R1 or STR. Where colour codes are assigned, the same colour indicates that they are mutually exclusive. Where colour codes are not assigned, they overlap within that category. For example, patients with M1 can have either R2 or R3, likewise patients who received laser treatment could have received vitreous injection. The WHO standards (36) were used for vision loss. Here all categories were combined into a single category.

Discussion

Principal findings

We explored the disease burden associated with DM and DR in the UK from the past, present and future perspectives. Our study followed a tripartite structure, comprising of 1) a series of epidemiological studies throughout a 20-year span to document disease-specific trends, 2) training a forecasting model to predict the future disease burden to guide clinical practice and service development and 3) a detailed descriptive cross-sectional analysis in 2017 using a study population of 180,824 people with diabetes to explore contemporary prevalence estimates of different forms of DR.

Between 1998 and 2018, the prevalence of DR and STR increased. The prevalence of all DR in T2DM nearly tripled and STR almost quadrupled among patients with T1DM aged 12 and above. There was a parallel increase in the overall prevalence of DM. While the growth in the numbers of T1DM patients was less than that for patients with T2DM, stratifying the calculations by two decades showed a marked rise in the rate of increase in T1DM prevalence in the latter half of the whole period between 1998 and 2018. This was in sharp contrast to the trends in T2DM, STR and DR prevalence, which showed a higher rise in the decade between 1998 and 2007 but slowed down in the later decade between 2009 and 2018.

Our forecasting model showed that, in less than ten years, over 1.5 million people with diabetes will have some DR, almost two thirds of a million of whom will have STR. With T1DM expected to rise faster and higher, it is also likely to correspond to a comparatively higher rise in STR, forcing a further increase in demand on services.

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A key parameter when calculating the current and future prevalence of DR is the accuracy of estimates of the trend of the underlying condition, i.e., the presence of DM. T1DM showed a smaller increase in the period starting from 1998, but this has accelerated since 2009. This is the most concerning recent trend considering that these are younger patients (mean age of diagnosis of 21.4 vs 57), having to live with the condition and its complications for more life years, and suffering from the more severe form of DR, with the consequent disability, treatment burden and treatment costs. There is a recent report of a 3.4% annual increase in the incidence rate of T1DM in children (13). Although there is an association between T1DM and obesity (37), it is believed that the cause may be multifactorial, including hygiene, viral factors and vitamin D deficiency amongst others (38).

The diagnosed DM prevalence based on the 2017 IMRD cross-sectional survey is 5.2%. The detailed descriptive analysis in 2017 showed that, out of 180,824 people with diabetes, 33.8% had any DR as a complication, 12.3% had STR and importantly, 2.8% had blindness or vision loss. STR was 52% of total DR in T1DM and 34% of total DR in T2DM. In 2017, nearly one third of all patients with T1DM were affected by a sight threatening form of DR. This analysis also confirmed the notion that, from the health care perspective, neither DM type is “benign” with regards to DR risk, since DR severity is graver in T1DM, and absolute numbers of affected individuals are higher in T2DM.

Diabetic complications are mainly macrovascular damage (coronary artery disease, peripheral arterial disease, and stroke) or microvascular damage to blood vessels in organs like kidney, foot and nerves (39). Tackling the first reduces mortality rate and might mean these patients living longer and consequently a higher prevalence of DR among higher risk patients. With greater efficacy and a rapid reduction of HBA1C,

the new agents might induce progression of DR (early worsening) (40). So, with increased prevalence there may be a disproportionate rise in more high-risk DR cases. There are conflicting reports on direct effect of newer medical treatments like Incretin based therapies on DR (40, 41) but the follow-up is limited at the moment.

Strengths and weaknesses of this study

This study reports up to date prevalence figures of DM, DR and STR, as well as trends from 1998 to 2018, in a clinically relevant form, which clinicians and managers leading hospital eye services can use in the management of services for diabetes and diabetic retinopathy. Our work is based on a cross-sectional analysis of primary care data and is therefore closer to routine practice. Our findings have also been verified against PHE, DESP, and other previously published figures (5-7, 14, 35, 42, 43). This is also the first observational IMRD based study to forecast the DM, DR and STR disease burden in the UK all together. While incorporating current evidence on the trend of underlying condition (DM), this study portrays a comprehensive analysis of the recent DR disease burden.

The findings of this study should be interpreted within the context of its limitations. In particular, the inability to incorporate evidence regarding the potential impact of glycaemia control and concomitant medications on the incidence of diabetic retinopathy should be promptly acknowledged. Suboptimal glycaemic control is a well-established risk factor for microvascular complications (such as DR), whereas fenofibrate, an agent used in in some patients with diabetes may have a positive effect on the course of DR.

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Additional limitations are possible coding errors, challenges of addressing missing data, changes in the diagnostic criteria of DM and the potential risk of an overestimation of vision failure. The findings of this study should be interpreted within that context. Firstly, the possible impact of coding errors, as well as subjectivity in documentation across a retrospective nationwide database involving several practices in different areas, cannot be precluded. This potential risk was minimised through a strict Read code selection process. The prevalence of severe DR was higher for those of South Asian and mixed ethnicity (9), therefore could have implications for local variations in its prevalence, and estimates could differ depending on the local ethnic mix. The potential impact of several concomitant medications on the course of DR was not captured in this study design. For the sake of future projections, estimates from individuals over 12 years old were applied to the whole population to calculate the final values, assuming that the number of DM patients under 12 is extremely low. Finally, we acknowledge that these projections are subject to the assumption that factors affecting the incidence, course and progression of the disease will remain stable over the next few years.

We wanted to verify our figures against data from DESP which screens everyone from age 12 (44) and Mathur et al. work (9). Both these research studies used a cut off of over 12 years for their estimates. We wanted our findings to be generalizable to the whole UK populations with diabetes including those under care of DRSP and Hospital Eye Services. We also wanted it to be generalisable internationally where majority of world population with diabetes is within one pool, without access to screening services. Limitations of this age cut off are that 2017 figures are not easily verifiable against PHE figures 2017 being over 17 years of age. So, verification

against that estimate is a bit problematic and thus adds uncertainty to our UK forecast estimates.

Strengths and weaknesses in relation to other studies, discussing particularly any differences in results

Gonzalez et al (14) reported an increasing prevalence of diabetes between the years 1996 and 2005 (10 years) based on THIN data analysis of patients aged 10 to 79 years old. They reported an overall increase of 54%. Our estimate between 1998 and 2005 (our data did not match the years) was 60%. In a Clinical Practice Research Datalink (CPRD) based study, Zghebi et al (43) found an overall increase of 64% in the patient population between 2004 to 2014, but this was limited to patients over 16 years old with T2DM. Our corresponding figures are 63%. Thus, our estimates fall midway between these two studies. Bagust et al presented a future forecast for UK, but is limited to T2DM and is an underestimation (11). It projected T2DM figures for 2036 to be 1.1 million.

The PHE estimate for prevalence of diabetes in UK in 2017 arrived at by Quality and Outcome Framework figures was 3.7 million (5.6%) in those aged 17 years and over (42) and included diagnosed patients with diabetes. Our estimate of diagnosed patients with diabetes in 2017 of 3.4 million (crude prevalence of 5.2%) in over 12 years old population contrasts with the 2017 PHE figures. Similarly, PHE predicted the diabetes burden for 2025 to be 4.9 million for people aged over 16 years (45). It is not possible to make a direct comparison with our forecast of just under 4.3 million for 2025 because of our estimate being for people over 12 years of age but could mean the present study to be an underestimation. Alternatively, PHE figures could be an overestimation for 2017, because of the inbuilt assumptions in that model. Our

estimate for 2019 matches the quality and outcome estimate of 3.8 million. International Diabetes Federation (IDF) (46) estimated total diabetes prevalent cases (20 to 79 years old) to be 2.7 million in 2017, which is an underestimation when compared to PHE and our study.

A recent DR prevalence study focussed on lower risk patients with diabetes under screening services (9). The DR period prevalence in the Mathur's study (2004 to 2014) was found to be 48.4% for patients with T1DM and 28.3% for patients with T2DM, contrasting with point prevalence (2017) of 56.4% and 32.0% for patients with T1DM and T2DM respectively in our study. They also did not split the pathology into maculopathy and pre-proliferative categories and did not include treatment and vision failure. Li et al 2019 (10) is the only study so far, that has projected DR till 2050. They estimated that 8.6 million people with diabetes (DR in 25% of the European population with T2DM and 50% with T1DM) will have diabetic eye disease inn 2050. The British studies included within this systematic review were based on diabetic screening services from pre-2009 (47) and pre-2003 data (7). Case definitions and patient pathways have since changed. Consequently, their figures are a significant underestimation as compared to ours (710,510 vs 1,612,395 in 2030)

Other prevalence studies from the UK (5-7, 35) are compared with estimates from our study in detail for completeness in Appendix 6 and Appendix 7. Majority of these UK studies are quite old, come from the screening programme setting, and do not deal with all of the categories of DR due to changed case definitions. Keenen et al (48) is a study based on work between 2007 and 2009 on hospital patients. They based their estimates of prevalence in eyes rather than patients, therefore, due to this heterogeneity, cannot be directly compared with our figures.

Meaning of the study: possible mechanisms and implications for clinicians or policymakers

Consecutive analyses over the course of over two decades provides information regarding the trend and severity of diabetic disease, and by a detailed analysis of different forms and severity groups, it captures the implications for the public health system. With the use of relevant outcomes, coupled with a prerequisite validation, the study provides a forecasting model which will be of use for clinicians and managers leading the professional services in planning the capacity to meet the increasing demand, and will guide public health strategy. Local demand can be calculated with the help of national figures provided by taking local factors into account (49).

Out of the 33.8% of total DR in all patients with diabetes, 12.3% was made up of the STR. Those STR patients that actually needed treatment or experienced vision failure constituted a total of 5%. These figures reflect a high false-positive rate of referrals (50 - 70% as reported earlier (2, 50) and needs to be considered in the future relationship between DESP and overburdened hospital eye services. Our estimated prevalence figures, in a clinically relevant form will help the clinicians and managers leading hospital eye services to optimise capacity planning for the increased demand.

Unanswered questions and future research

PHE used a prevalence model to predict the disease burden of diabetes in 2016 (49). The predictive factors they used were age, ethnicity, gender, and deprivation index. To accommodate local variation in populations and practices, final calculations can be made using these predictive factors. The above-mentioned

limitations of the study can be overcome by a future collaborative study linking DR screening and hospital eye services data, with figures based on patient numbers and not eyes, to prevent heterogeneity among studies. Forecasting capacity needs is an area that should be repeated periodically with the help of the forecasting model presented.

Conclusion

In our study, the estimates suggested a trend of differential rise in prevalence rates in T1DM and T2DM. Overall, there is a continuing rise in the numbers of patients with DM and DR needing care. Preventive strategies and service planning can be based on these projected prevalence estimates to meet demand over the next ten years. Future forecasting will need repeating periodically to capture any external factors causing a change in the present trend.

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Data Sharing Statement:

Data was part of a digital database and is not available to be shared. Analysis details are in the publication / appendices.

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Competing interest

The authors have no competing interest to disclose.

Ethical approvals:

The IMRD database has blanket approval by the NHS South East Multi-centre Research Ethics Committee (MREC) in 2003 (51). The study protocols were submitted to both the Scientific Review Committee and the Science, Technology, Engineering and Mathematics Ethical Review Committee at the University of Birmingham for review and approval, which were granted. Consent was not required.

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Titles and legends to figures

Figure 1: Patients flow and case selection algorithm

Figure 2: Prevalence trends of DM from year 1998 to year 2018

T1DM - Type 1 Diabetes Mellitus, T2DM - Type 2 Diabetes Mellitus

Figure 3: Annual prevalence (95% CI) of DR and STR from year 1998 to year 2018

DR - Diabetic Retinopathy, STR - Sight threatening Retinopathy

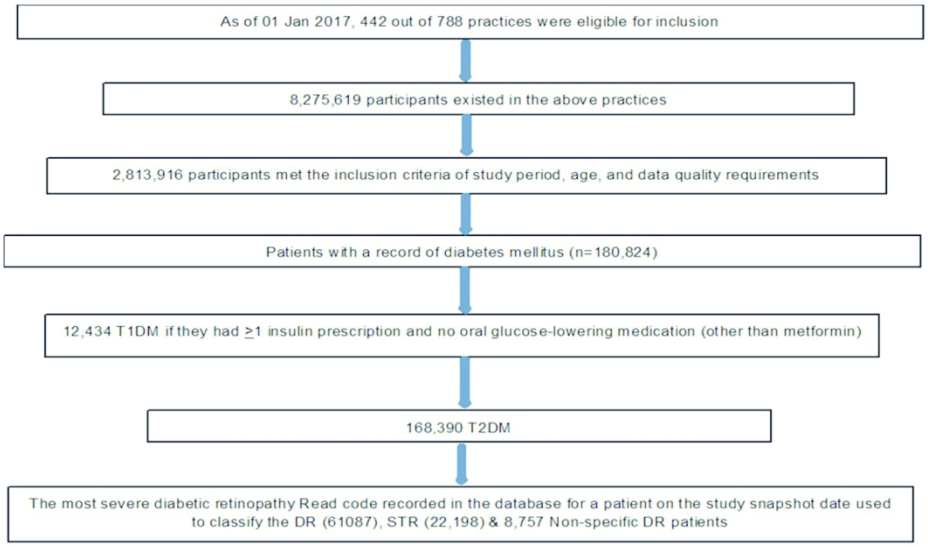

Figure 1: Patients flow and case selection algorithm

207x116mm (300 x 300 DPI)

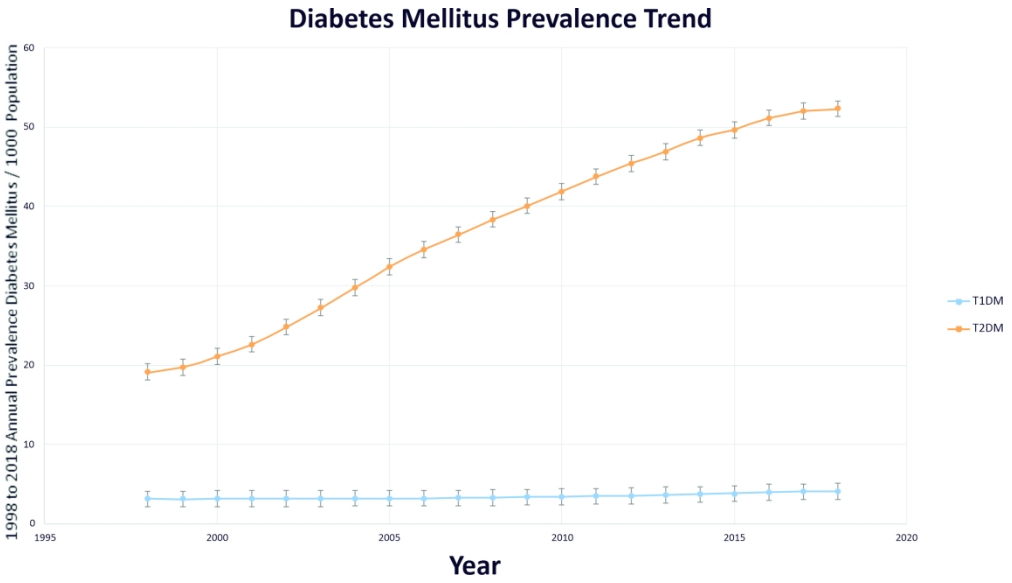

Figure 2: Prevalence trends of DM from year 1998 to year 2018

209x119mm (300 x 300 DPI)

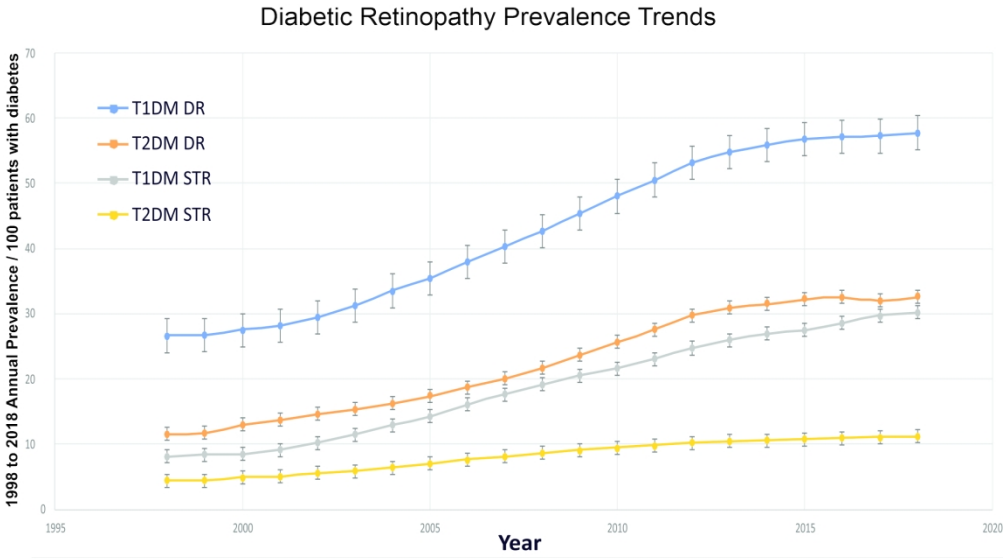

Figure 3: Annual prevalence (95% CI) of DR and STR from year 1998 to year 2018
DR - Diabetic Retinopathy, STR - Sight threatening Retinopathy

201x120mm (300 x 300 DPI)

Appendix 1: 7 Step Process of Read codes selection methods

Read codes cover clinical features, diagnosis, procedures, some drugs and investigations (1). Ones used in IMRD consist of 7 characters. They have a hierarchy with more specific ones down the order. This was done in collaboration with Jhot Chandan, a fellow doctoral researcher and my supervisor Krishnarajah Nirantharakumar (Institute of Applied Health Research)

1. The Read code database (MsAcess, MsExcel) is divided into two main columns: A Medcode column with unique 8 character codes for each condition and a description column. Both were used.
2. We developed a list of key search terms for the read codes of interest. These were searched for in the description column. Appendix below provides a list of key search words.
3. Results from the key word search were used to identify the main stem codes where the Read codes of interest belong to.
4. The Next step involved searching the MedCode column for the main stem codes to pick out codes that were otherwise missed on searching the description column.
5. We then also conducted an online search of published articles that have published similar Read Codes (2, 3).
6. Once collected, they were split into possible, probable and definite. There was deliberation between clinicians in the THINking group to achieve these three lists.
7. They were then hand over to a group of data scientists within the THINking group who split them into various files following epidemiological principles and saved them in CSV files database.

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Appendix 2: Search Terms for diabetic Retinopathy

Keywords for identifying diabetic retinopathy in the Read Codes Dictionary
O/E or *PHOTOGRAPHY* or *RETINAL* or *SCR* **and** *HAEMORRHAGES* or *EXUDATE* or *MICROANEURYSMS* or *INTRARETINAL MICROVASCULAR ANAOMALY* or *ABNORMALITY*
RETINA or *FUNDUS* or *MACULAR* or *VITREOUS* **and** *LASER" or *PHOTOCOAGULATION* or *INTRA-VITREAL INJECTIONS* or *INJECTIONS* or *RANIBIZUMAB* or *BIVACIZUMAB* or *AFLIBERCEPT* or *TRIAMCINOLON* or *ILEUVIEN* or *DEXAMETHOSON*
RETINOPATHY or *FUNDOSCOPY* or *SEEN or *RETINAL SCR* or *RETINOSCOPY* or *SLIT LAMP* or *DIABETIC EYE* or *EXAMINATION OF RETINA* or *RETINA and OTHER PARTS OF EYE OPERATIONS* or *VITRECTOMY* or *MACULOPATHY* or *BACKGROUND* or *PRE PROLIFERATIVE* or *PROLIFERATIVE*
*BLIND" or *PARTIAL SIGHTED" or **SIGHT IMPAIRMENT" or *VISUAL IMPAIRMENT" or *VISUAL FAILURE"

Appendix 3: Read Codes

Code	Description	Status
	No Retinoipathy (ROMO)	
2BBD.00	O/E - Right retina normal	Probable
2BBJ.00	O/E - no right diabetic retinopathy	Definite
2BB1.00	O/E - retina normal	Probable
2BBI.00	O/E - no retinopathy	Definite
3128000	Fundoscopy normal	Probable
3128200	Dilated fundoscopy normal	Probable
2BBM.00	O/E - diabetic maculopathy absent both eyes	Possible
	Background Retinopathy (R1)	
2BBP.00	O/E - right eye background diabetic retinopathy	Definite
2BBQ.00	O/E - left eye background diabetic retinopathy	Definite
F420000	Background diabetic retinopathy	Definite
F421.00	Other background retinopathy	Definite
F421000	Unspecified background retinopathy	Definite
F421z00	Other background retinopathy NOS	Definite
2BB4.00	O/E - retinal microaneurysms	Definite
2BBa.00	O/E- non-referable retinopathy	Probable
	Pre proliferative Diabetic Retinopathy (R2)	
F420200	Pre proliferative diabetic retinopathy	Definite
2BBR.00	O/E - right eye pre proliferative diabetic retinopathy	Definite
2BBS.00	O/E - left eye pre proliferative diabetic retinopathy	Definite
F420800	High risk non proliferative diabetic retinopathy	Definite
	Proliefartive Diabetic Retinoipathy (R3)	
2BBk.00	O/E - right eye stable treated prolif diabetic retinopathy	Definite
2BBl.00	O/E - left eye stable treated prolif diabetic retinopathy	Definite
F420100	Proliferative diabetic retinopathy	Definite
F420700	High risk proliferative diabetic retinopathy	Definite
F422z00	Proliferative retinopathy NOS	Definite
F422.00	Other proliferative retinopathy	Definite
FyuF700	[X]Other proliferative retinopathy	Definite
2BBT.00	O/E - right eye proliferative diabetic retinopathy	Definite
2BBV.00	O/E - left eye proliferative diabetic retinopathy	Definite
7272500	Panretinal laser photocoagulation to lesion of retina NEC	Definite
7272800	Panretinal laser photocoagulation to lesion of retina	Definite
2BB7.00	O/E - retinal vascular prolif.	Probable
2BB8.00	O/E - vitreous haemorrhages	Probable
7276	Pan retinal photocoagulation for diabetes	Definite
F420500	Advanced diabetic retinal disease	Possible
F422y00	Other specified other proliferative retinopathy	Definite

F4K2800	Vitreous haemorrhage	Probable
FyuH400	[X]Vitreous haemorrhage in diseases classified elsewhere	Probable
2BB8.00	O/E - vitreous haemorrhages	Probable
	Diabetic Maculopathy (M1)	
2BBL.00	O/E - Diabetic maculopathy present both eyes	Definite
2BBm.00	O/E - right eye clinically significant macular oedema	Definite
2BBn.00	O/E - left eye clinically significant macular oedema	Definite
2BBW.00	O/E - right eye diabetic maculopathy	Definite
2BBX.00	O/E - left eye diabetic maculopathy	Definite
F425900	Maculopathy	Definite
F42y900	Macular oedema	Definite
C10EP00	Type 1 diabetes mellitus with exudative maculopathy	Definite
C10EP11	Type I diabetes mellitus with exudative maculopathy	Definite
C10FQ00	Type 2 diabetes mellitus with exudative maculopathy	Definite
C10FQ11	Type II diabetes mellitus with exudative maculopathy	Definite
F420300	Advanced diabetic maculopathy	Definite
7272900	Focal laser photocoagulation of retina	Probable
F420400	Diabetic maculopathy	Definite
	Referrable Retinopathy (R2, R3, M1)	
2BBY.00	O/E - referable retinopathy	Definite
2BBo.00	O/E - sight threatening diabetic retinopathy	Definite
	Advanced diabetic retinal disease	
F420500	Advanced diabetic retinal disease	Definite

Code	Description	Status
	Laser Procedures	
7276	Pan retinal photocoagulation for diabetes	Definite
7272012	Photocoagulation of the retina NEC	Definite
7272013	Laser therapy lesion of retina	Definite
7272300	Laser destruction of lesion of retina	Definite
7272500	Pan retinal laser photocoagulation to lesion of retina NEC	Definite
7272600	Laser photocoagulation to lesion of retina NEC	Definite
7272800	Pan retinal laser photocoagulation to lesion of retina	Definite
7272900	Focal laser photocoagulation of retina	Definite
2BBk.00	O/E - right eye stable treated proliferative diabetic retinopathy	Definite
2BBl.00	O/E - left eye stable treated proliferative diabetic retinopathy	Definite
2BBO.00	O/E - Laser photocoagulation scars	Definite
5B4..11	Retinal laser therapy	Definite
Z6F..11	Laser therapy	Definite

5B42.00	Laser therapy - retinal lesion	Definite
	Vitreous/ Peribulbar procedures / haemorrhage	
7270D00	Injection of Ranibizumab into vitreous body	Definite
7270z00	Operation on vitreous body NOS	Definite
7270300	Injection into vitreous body NEC	Definite
7274800	Injection of therapeutic substance around the eye	Possible
727C200	Injection therapeutic substance posterior segment of eye NEC	Definite
7270D00	Injection of Ranibizumab into vitreous body	Definite
7L19E00	Injection of triamcinolone	Probable
727C100	Injection of steroid into posterior segment of eye	Definite
7270200	Injection of vitreous substitute into vitreous body	Definite
7277600	Injection of therapeutic substance into macula	Definite
7270C00	Injection of vitreous substitute into vitreous body NEC	Definite
727C100	Injection of steroid into posterior segment of eye	Definite
7270400	Pars plana vitrectomy	Definite
727Cy00	Other specified operations on posterior segment of eye	Probable
727Cz00	Operations on posterior segment of eye NOS	Probable
7273000	Epiretinal dissection	Possible
727C000	Insertion sustained release device posterior segment of eye	Definite
7270y00	Other specified operation on vitreous body	Definite
7270800	Internal tamponade of retina using liquid	Possible
7270900	Internal tamponade of retina using oil	Possible
7270A00	Removal of internal tamponade agent from vitreous body	Possible
7270411	Vitrectomy using pars plana approach	Probable
7270500	Air/gas exchange of vitreous	Possible
7270600	Internal tamponade of retina using gas	Probable
7270200	Injection of vitreous substitute into vitreous body	Probable
7270300	Injection into vitreous body NEC	Definite
7270400	Pars plana vitrectomy	Definite
7270	Operations on vitreous body	Probable
7270100	Extirpation of vitreous body NEC	Probable
F4K2800	Vitreous haemorrhage	Definite
FyuH400	[X]Vitreous haemorrhage in diseases classified elsewhere	Definite
2BB8.00	O/E - vitreous haemorrhages	Definite
	Vision loss / blindness	
ZV52200	[V]Fitting or adjustment of artificial eye	Probable
ZV43000	[V]Has artificial eye globe	Probable
ZV43100	[V]Has artificial eye lens	Possible
FyuL.00	[X]Visual disturbances and blindness	Definite
F49z.11	Acquired blindness	Definite
F490900	Acquired blindness, both eyes	Definite
F495A00	Acquired blindness, one eye	Definite

F491.00	Better eye: low vision, Lesser eye: profound VI	Definite
F491500	Better eye: moderate VI, Lesser eye: blind, unspecified	Definite
F492300	Better eye: moderate VI, Lesser eye: low vision unspecified	Definite
F492500	Better eye: moderate VI, Lesser eye: moderate VI	Definite
F491700	Better eye: moderate VI, Lesser eye: near total VI	Definite
F491800	Better eye: moderate VI, Lesser eye: profound VI	Definite
F492400	Better eye: moderate VI, Lesser eye: severe VI	Definite
F491600	Better eye: moderate VI, Lesser eye: total VI	Definite
F490400	Better eye: near total VI, Lesser eye: near total VI	Definite
F490300	Better eye: near total VI, Lesser eye: total VI	Definite
F490200	Better eye: near total VI, Lesser eye: unspecified	Definite
F490700	Better eye: profound VI, Lesser eye: near total VI	Definite
F490800	Better eye: profound VI, Lesser eye: profound VI	Definite
F490600	Better eye: profound VI, Lesser eye: total VI	Definite
F490500	Better eye: profound VI, Lesser eye: unspecified	Definite
F491100	Better eye: severe VI, Lesser eye: blind, unspecified	Definite
F492100	Better eye: severe VI, Lesser eye: low vision unspecified	Definite
F491300	Better eye: severe VI, Lesser eye: near total VI	Definite
F491400	Better eye: severe VI, Lesser eye: profound VI	Definite
F492200	Better eye: severe VI, Lesser eye: severe VI	Definite
F491200	Better eye: severe VI, Lesser eye: total VI	Definite
8F62.00	Blind lead dog rehabilitation	Definite
8F6..11	Blind rehabilitation	Definite
8F61.00	Blind rehabilitation	Definite
ZN56800	Blind telephone user	Definite
F49..00	Blindness and low vision	Definite
F490z00	Blindness both eyes NOS	Definite
F490.00	Blindness, both eyes	Definite
F49A.00	Blindness, monocular	Definite
F495000	Blindness, one eye, unspecified	Definite
F490100	Both eyes total visual impairment	Definite
668C.00	Certificate of vision impairment	Definite
Fy1..00	Combined visual and hearing impairment	Definite
Fy1..12	Deafblind	Definite
ZN56A00	Deaf-blind telephone user	Definite
Fy1..11	Dual sensory impairment - deafblind	Definite
9m08.00	Exclu diab ret screen as blind	Definite
2BBr.00	Impair vision due diab retinop	Definite
F49..11	Impaired vision	Definite
ZK74.00	Issue of local authority blind registration	Definite
F494.00	Legal blindness USA	Definite
F496500	Lesser eye: moderate VI, Better eye: near normal vision	Definite
F496600	Lesser eye: moderate VI, Better eye: normal vision	Definite

F496400	Lesser eye: moderate VI, Better eye: unspecified	Definite
F495500	Lesser eye: near total VI, Better eye: near normal vision	Definite
F495600	Lesser eye: near total VI, Better eye: normal vision	Definite
F495400	Lesser eye: near total VI, Better eye: unspecified	Definite
F495800	Lesser eye: profound VI, Better eye: near normal vision	Definite
F495900	Lesser eye: profound VI, Better eye: normal vision	Definite
F495700	Lesser eye: profound VI, Better eye: unspecified	Definite
F496200	Lesser eye: severe VI, Better eye: near normal vision	Definite
F496300	Lesser eye: severe VI, Better eye: normal vision	Definite
F496100	Lesser eye: severe VI, Better eye: unspecified	Definite
F495200	Lesser eye: total VI, Better eye: near normal vision	Definite
F495300	Lesser eye: total VI, Better eye: normal vision	Definite
F495100	Lesser eye: total visual impairment, Better eye: unspecified	Definite
F49..12	Low vision	Definite
F492.00	Low vision, both eyes	Definite
F492z00	Low vision, both eyes NOS	Definite
F492000	Low vision, both eyes unspecified	Definite
F496.00	Low vision, one eye	Definite
F496z00	Low vision, one eye NOS	Definite
F496000	Low vision, one eye, unspecified	Definite
F498.00	Moderate visual impairment, binocular	Definite
F49C.00	Moderate visual impairment, monocular	Definite
2B7A.11	O/E - blind L-eye	Definite
2B6A.11	O/E - blind R-eye	Definite
22E6.11	O/E - false eye	Definite
22E6.00	O/E - glass (prosthetic) eye	Definite
22E6.12	O/E - glass eye	Definite
22EF.00	O/E - has one eye	Definite
2B7B.00	O/E - L-eye completely blind	Definite
2B7C.00	O/E - L-eye sees hand movements	Definite
2B7T.00	O/E - L-eye visual acuity (corrected) 1/60	Definite
2B7V.00	O/E - L-eye visual acuity (corrected) 2/60	Definite
2B7W.00	O/E - L-eye visual acuity (corrected) 4/60	Definite
2B7X.00	O/E - L-eye visual acuity (corrected) 5/60	Definite
2B7S.00	O/E - pinhole L-eye completely blind	Definite
2B7Q.00	O/E - pinhole L-eye counts fingers only	Definite
2B7R.00	O/E - pinhole L-eye perceives light only	Definite
2B7P.00	O/E - pinhole L-eye sees hand movements	Definite
2B6S.00	O/E - pinhole R-eye completely blind	Definite
2B6Q.00	O/E - pinhole R-eye counts fingers only	Definite
2B6R.00	O/E - pinhole R-eye perceives light only	Definite
2B6P.00	O/E - pinhole R-eye sees hand movements	Definite
2B7L.00	O/E - pinhole visual acuity L-eye=6/60	Definite

2B6L.00	O/E - pinhole visual acuity R-eye=6/60	Definite
22E6.13	O/E - prosthetic eye	Definite
2B6B.00	O/E - R-eye completely blind	Definite
2B6C.00	O/E - R-eye sees hand movements	Definite
2B6T.00	O/E - R-eye visual acuity (corrected) 1/60	Definite
2B6V.00	O/E - R-eye visual acuity (corrected) 2/60	Definite
2B6W.00	O/E - R-eye visual acuity (corrected) 4/60	Definite
2B6X.00	O/E - R-eye visual acuity (corrected) 5/60	Definite
2B7E.00	O/E - visual acuity L-eye=3/60	Definite
2B78.00	O/E - visual acuity L-eye=6/60	Definite
2B6E.00	O/E - visual acuity R-eye=3/60	Definite
2B68.00	O/E - visual acuity R-eye=6/60	Definite
2B79.00	O/E -L-eye counts fingers only	Definite
2B69.00	O/E -R-eye counts fingers only	Definite
2B7A.00	O/E-L-eye perceives light only	Definite
2B6A.00	O/E-R-eye perceives light only	Definite
F491000	One eye blind, one eye low vision	Definite
F491z00	One eye blind, one eye low vision NOS	Definite
Z9E2.00	Optical low vision aid provision	Definite
F49..13	Partial sight	Definite
F495z00	Profound impairment one eye NOS	Definite
F495.00	Profound impairment, one eye	Definite
Z96..00	Provision for visual and hearing impairment	Definite
Z9E5400	Provision of ancillary low vision aid	Definite
Z9E1100	Provision of artificial eye	Definite
Z962.00	Provision of communicator for visual and hearing impairment	Definite
Z9E5100	Provision of electronic low vision aid	Definite
Z961.00	Provision of guide help for visual and hearing impairment	Definite
Z9E3200	Provision of low vision hand magnifier	Definite
Z9E3400	Provision of low vision headband magnifier	Definite
Z9E3300	Provision of low vision stand magnifier	Definite
Z9E3100	Provision of magnifier low vision aid - near	Definite
Z9E5.00	Provision of non-optical low vision aid	Definite
Z9E4.00	Provision of optical low vision aid - distance	Definite
Z9E3.00	Provision of optical low vision aid - near	Definite
Z9E1200	Provision of removable artificial eye	Definite
Z9E3500	Provision of spectacle low vision aid - near	Definite
8HlE.00	Referral to visual impairment multidisciplinary team	Definite
6689	Registered blind	Definite
6688.11	Registered partially blind	Definite
6688	Registered partially sighted	Definite
6689.11	Registered severely sight impaired	Definite
668D.00	Registered sight impaired	Definite

8D36.00	Removable artificial eye	Definite
9Nfb.00	Requires deafblind block alphabet interpreter	Definite
9NfB.00	Requires deafblind communicator guide	Definite
9Nfc.00	Requires deafblind haptic communication interpreter	Definite
9Nfa.00	Requires deafblind manual alphabet interpreter	Definite
F497.00	Severe visual impairment, binocular	Definite
F49B.00	Severe visual impairment, monocular	Definite
F49..14	Sight impaired	Definite
F490000	Unspecified blindness both eyes	Definite
1a00000	Uses guide dog for the blind	Definite
F49D.00	Visual impairment	Definite
F493.00	Visual loss, both eyes unqualified	Definite
F49y.00	Visual loss, one eye, unqualified	Definite
F404200	Blind hypertensive eye	Definite
F404100	Blind hypotensive eye	Definite
Z9E3900	Near low vision aid - clip-on spectacle magnifier	Definite
Z9E3C00	Near low vision aid - clip-on spectacle telescope	Definite
Z9E3D00	Near low vision aid - extra cap for telescope	Definite
Z9E3800	Near low vision aid - integral spectacle magnifier	Definite
Z9E3B00	Near low vision aid - integral spectacle telescope	Definite
9NlD.00	Seen by visual impairment teacher	Definite
1B75.00	Loss of vision, Severe visual loss	Definite
1B77.00	Deteriorating vision, Severe visual loss	Definite

Unclassifiable

Code	Description
2BB5.00	O/E - retinal haemorrhages
2BB6.00	O/E - retinal exudates
2BBF.00	Retinal abnormality-diabetes related
2BBr.00	Impaired vision due diab retinop
C105.00	Diabetes mellitus with ophthalmic manifestation
C105000	Diabetes mellitus, juvenile type, + ophthalmic manifestation
C105100	Diabetes mellitus, adult onset, + ophthalmic manifestation
C105y00	Other specified diabetes mellitus with ophthalmic complicatn
C105z00	Diabetes mellitus NOS with ophthalmic manifestation
C108100	Insulin-dependent diabetes mellitus with ophthalmic comps
C108111	Type I diabetes mellitus with ophthalmic complications
C108112	Type 1 diabetes mellitus with ophthalmic complications
C108700	Insulin dependent diabetes mellitus with retinopathy
C108711	Type I diabetes mellitus with retinopathy
C108712	Type 1 diabetes mellitus with retinopathy
C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps

C109111	Type II diabetes mellitus with ophthalmic complications
C109112	Type 2 diabetes mellitus with ophthalmic complications
C109600	Non-insulin-dependent diabetes mellitus with retinopathy
C109611	Type II diabetes mellitus with retinopathy
C109612	Type 2 diabetes mellitus with retinopathy
C10A300	Malnutrit-related diabetes mellitus wth ophthalmic complicat
C10E100	Type 1 diabetes mellitus with ophthalmic complications
C10E111	Type I diabetes mellitus with ophthalmic complications
C10E112	Insulin-dependent diabetes mellitus with ophthalmic comps
C10E700	Type 1 diabetes mellitus with retinopathy
C10E711	Type I diabetes mellitus with retinopathy
C10E712	Insulin dependent diabetes mellitus with retinopathy
C10F600	Type 2 diabetes mellitus with retinopathy
C10F611	Type II diabetes mellitus with retinopathy
F420.00	Diabetic retinopathy
F420600	Non proliferative diabetic retinopathy
F420z00	Diabetic retinopathy NOS
F421.11	Microvascular retinal changes
2BB5.00	O/E - retinal haemorrhages
2BBM.00	O/E - diabetic maculopathy absent both eyes

Appendix 4: Summary of Prevalence Trends 1998 to 2018

Decade	Prevalence estimate at the start of the decade	Prevalence estimate at the end of the decade	Percentage increase in prevalence within the decade	Percentage increase in prevalence between the decades
STR in T1DM in two decades				
1998 to 2007	8.15	17.57	216%	
2009 to 2018	20.54	30.22	147%	371%
STR in T2DM in two decades				
1998 to 2007	4.36	8.1	186%	
2009 to 2018	9.01	11.15	124%	256%
DR in T1DM in two decades				
1998 to 2007	26.62	40.32	151%	
2009 to 2018	45.39	57.75	127%	217%
DR in T2DM in two decades				
1998 to 2007	11.53	20.06	174%	
2009 to 2018	23.7	32.64	138%	283%
STR in DM in two decades				
1998 to 2007	4.87	8.84	182%	
2009 to 2018	9.86	12.48	127%	256%
DR in DM in two decades				
1998 to 2007	13.57	21.64	159%	
2009 to 2018	25.3	34.39	136%	253%
T1DM in two decades				
1998 to 2007	0.31%	0.32%	104%	
2009 to 2018	0.33%	0.41%	123%	132%
T2DM in two decades				
1998 to 2007	1.91%	3.65%	191%	
2009 to 2018	4.01%	5.24%	131%	273%

Appendix 5: Future projections

In the four figures below, the grey area is the prediction band (95% confidence interval) and signifies the uncertainty of the estimates.

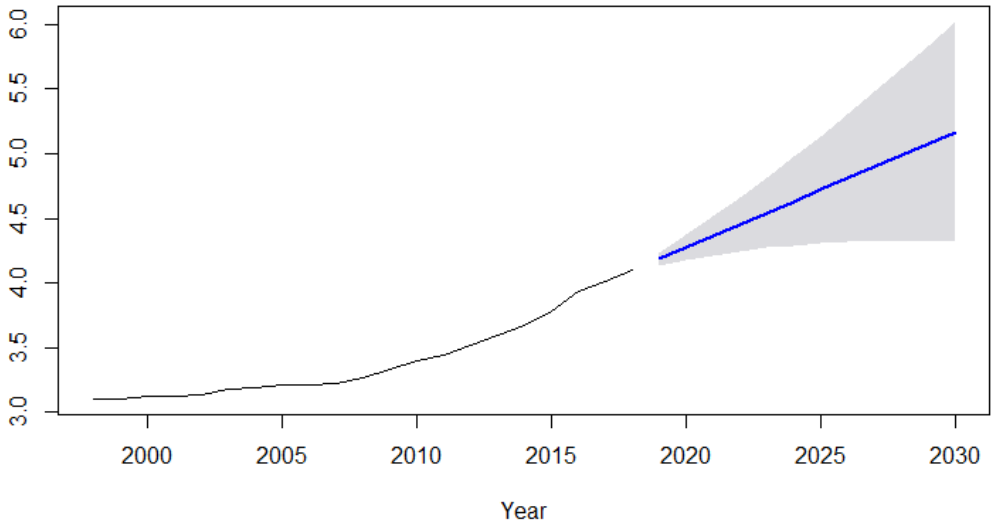

Figure 1: T1DM Projections / 1000 individuals

X axis is calendar years and Y axis is prevalence (cases per 1000 individuals general population), starts at 3.0

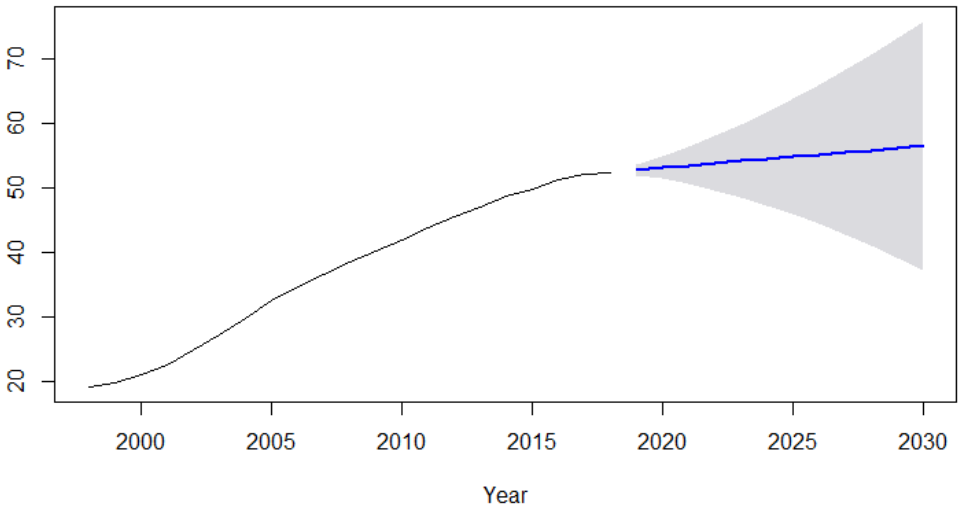

Figure 2: T2DM Projections / 1000 individuals

X axis is calendar years and Y axis is prevalence (cases per 1000 individuals general population)

starts at 17

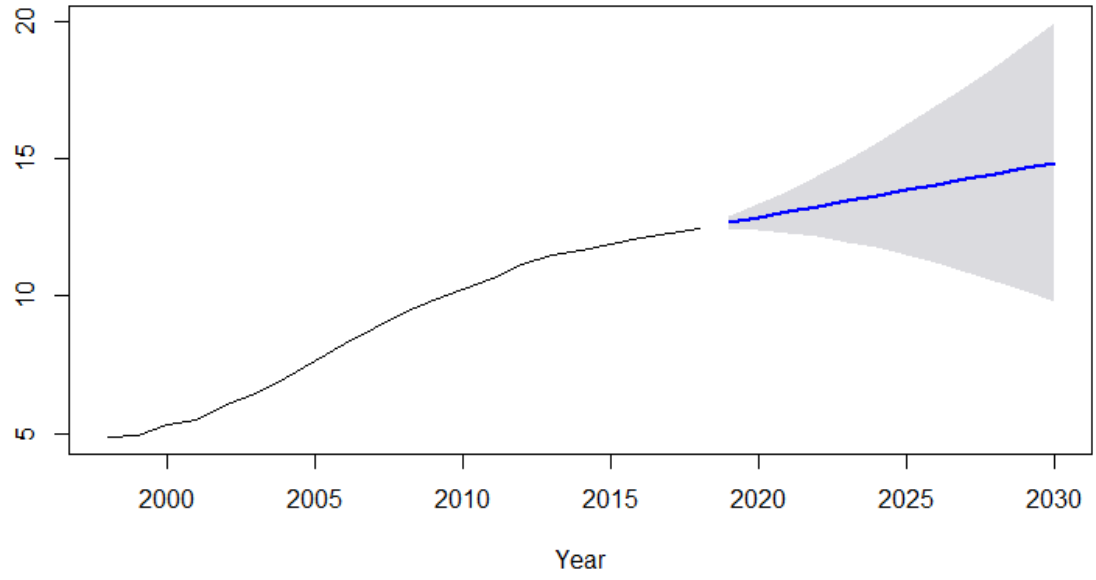

Figure 3: STR Projections (%)

X axis is calendar years and Y axis is prevalence (cases per 100 individuals with diabetes) starts at 4

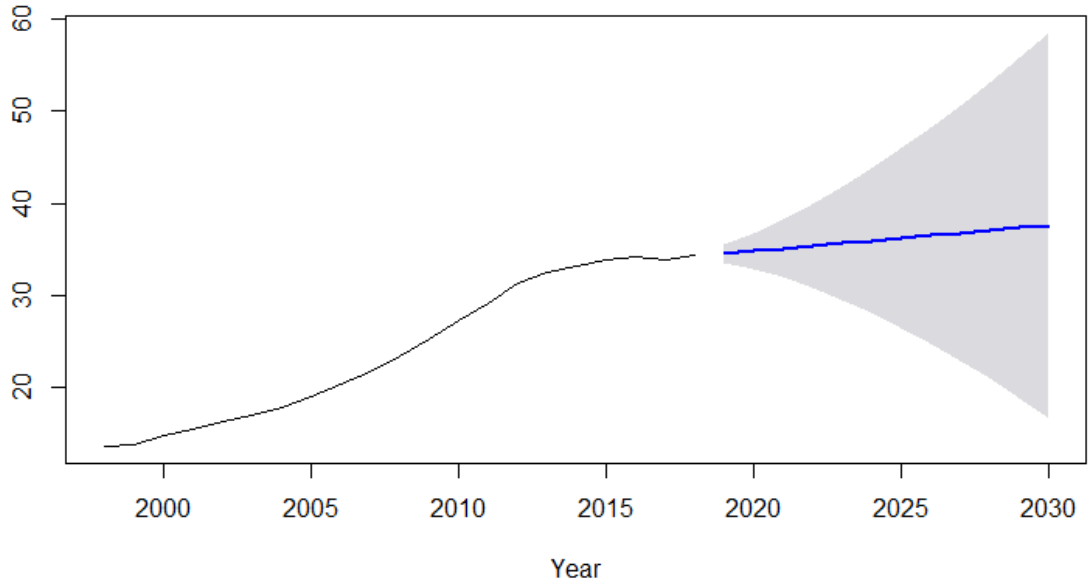

Figure 4: DR Projections (%)

X axis is calendar years and Y axis is prevalence (cases per 100 individuals with diabetes), starts at 10

Annual Prevalence Diabetes Mellitus per 1000 Population and Diabetic Retinopathy per 100 diabetic population (95% PI)

	T1DM Forecast			T2DM Forecast			DR Forecast			STR Forecast		
Year	Forecast	Low 95	High 95	Forecast	Low 95	High 95	Forecast	Low 95	High 95	Forecast	Low 95	High 95
2019	4.2	4.1	4.2	52.7	51.9	53.6	34.5	33.5	35.5	12.7	12.4	12.9
2020	4.3	4.2	4.4	53.1	51.4	54.8	34.8	32.9	36.7	12.9	12.4	13.3
2021	4.4	4.2	4.5	53.4	50.6	56.3	35.1	31.9	38.2	13.1	12.3	13.8
2022	4.5	4.2	4.7	53.8	49.6	57.9	35.4	30.8	39.9	13.3	12.2	14.4
2023	4.5	4.3	4.8	54.1	48.5	59.7	35.6	29.5	41.8	13.5	12.0	15.0
2024	4.6	4.3	5.0	54.4	47.2	61.6	35.9	28.1	43.8	13.7	11.8	15.6
2025	4.7	4.3	5.1	54.8	45.8	63.7	36.2	26.5	45.9	13.9	11.5	16.2
2026	4.8	4.3	5.3	55.1	44.3	65.9	36.5	24.7	48.2	14.1	11.2	16.9
2027	4.9	4.3	5.5	55.4	42.7	68.2	36.8	22.9	50.6	14.3	10.9	17.6
2028	5.0	4.3	5.7	55.8	41.0	70.6	37.0	20.9	53.2	14.5	10.5	18.4
2029	5.1	4.3	5.8	56.1	39.1	73.1	37.3	18.8	55.8	14.7	10.2	19.1
2030	5.2	4.3	6.0	56.4	37.2	75.7	37.6	16.7	58.5	14.9	9.8	19.9

Appendix 6: Previous prevalence studies compared with IMRD based analysis

Publication	Population	T1DM	T2DM	Any DM
Younis et al (1)	Liverpool diabetic retinopathy screening programme 1991 to 1999 – baseline prevalence at entry into the programme	Any DR 45.7% STED 16.4% PDR 3.7%	Any DR 25.3% STED 6.0% PDR 0.5%	
Misra et al (2)	Norwich Diabetic retinopathy screening programme 2006 with dynamic cohort design with repeated measures			Any DR 25.6% STDR 0.6% PPDR 4.6% PDR 0.08% Maculopathy 0.44% Referable (R2, R3, M1) retinopathy 4.7%
Thomas (3) and Minassian et al (4)	Welsh Diabetic retinopathy screening programme 2005 to 2009 and application to England	Any DR 56.3% STDR 11.2%	Any DR 30.9% STDR 2.9%	Any DR 32.4% STDR 3.4% Diabetic Macular Oedema 7.12%
Looker et al (5)	Newly diagnosed type 2 diabetes attending Scottish National screening programme 2005 to 2008. prevalence at first screening		Any DR 19.3% Referable DR 1.9% PPDR ± any maculopathy 0.4% PDR ± any maculopathy 0.3%	

Mathur et al (6)	CPRD based UK wide study 2014 - crude prevalence rate	Any DR 54.8% Severe DR 8.1%	Any DR 30.6% Severe DR 1.2%	Any DR 32.6% Severe DR 1.8%
The present study	IMRD based cross sectional study - 2017	Any DR 57.8% STR 30.2% Any maculopathy 19.62%	Any DR 32.6% STR 11.2% Any maculopathy 6.99%	Any DR 34.4% STR 12.3% Any maculopathy 7.86%

References:

1. Younis N, Broadbent DM, Harding SP, Vora JR. Prevalence of diabetic eye disease in patients entering a systematic primary care-based eye screening programme. Diabetic medicine : a journal of the British Diabetic Association. 2002;19(12):1014-21.
2. Misra A, Bachmann MO, Greenwood RH, Jenkins C, Shaw A, Barakat O, et al. Trends in yield and effects of screening intervals during 17 years of a large UK community-based diabetic retinopathy screening programme. Diabetic medicine : a journal of the British Diabetic Association. 2009;26(10):1040-7.
3. Thomas RL, Dunstan FD, Luzio SD, Chowdhury SR, North RV, Hale SL, et al. Prevalence of diabetic retinopathy within a national diabetic retinopathy screening service. The British journal of ophthalmology. 2015;99(1):64-8.
4. Minassian DC, Owens DR, Reidy A. Prevalence of diabetic macular oedema and related health and social care resource use in England. The British journal of ophthalmology. 2012;96(3):345-9.
5. Looker H, Nyangoma S, Cromie D, Olson J, Leese G, Black M, et al. Diabetic retinopathy at diagnosis of type 2 diabetes in Scotland. Diabetologia. 2012;55(9):2335-42.
6. Mathur R, Bhaskaran K, Edwards E, Lee H, Chaturvedi N, Smeeth L, et al. Population trends in the 10-year incidence and prevalence of diabetic retinopathy in the UK: a cohort study in the Clinical Practice Research Datalink 2004-2014. BMJ open. 2017;7(2):e014444.

Appendix 7: Previous publications reporting trends in prevalence rates of DR in the UK compared with IMRD based analysis

Publication	Population	T1DM	T2DM	Any DM
Misra et al (1)	Norwich Diabetic retinopathy screening programme 1990 to 2006 (Mostly Type 2) with dynamic cohort design with repeated measures			All DR prevalence increased from 23.2% to 25.3% Referable DR increased from 2 to 4.7%
Mathur et al (2)	CPRD based UK wide study population from 2004 to 2014	All DR remained stable at 55% Severe DR increased from 3.5% in 2004 to 8.0% in 2014	All DR reduced from 24.6% in 2004 to 23.1% in 2014 Severe DR increased from 0.3% in 2004 to 0.9% in 2014	All DR prevalence decreased from 2.6% to 2.2% Severe DR remained stable at 0.1%
This study	IMRD based serial cross-sectional studies 1998 to 2018			

References:

1. Misra A, Bachmann MO, Greenwood RH, Jenkins C, Shaw A, Barakat O, et al. Trends in yield and effects of screening intervals during 17 years of a large UK community-based diabetic retinopathy screening programme. Diabetic medicine : a journal of the British Diabetic Association. 2009;26(10):1040-7.

2. Mathur R, Bhaskaran K, Edwards E, Lee H, Chaturvedi N, Smeeth L, et al. Population trends in the 10-year incidence and prevalence of diabetic retinopathy in the UK: a cohort study in the Clinical Practice Research Datalink 2004-2014. BMJ open. 2017;7(2):e014444.

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cross sectionalreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	2
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2

Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4,5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	#4	Present key elements of study design early in the paper	2
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-9
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	6-7
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	NA
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	NA
Bias	#9	Describe any efforts to address potential sources of bias	5, 6

Study size	#10	Explain how the study size was arrived at	All eligible patients included
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	NA
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	NA
Statistical methods	#12c	Explain how missing data were addressed	NA
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	NA
Statistical methods	#12e	Describe any sensitivity analyses	NA
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	Figure 1

Participants	#13b	Give reasons for non-participation at each stage	Figure 1
Participants	#13c	Consider use of a flow diagram	Figure 1
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	Table 1
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	Table 1
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	Table 3
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
Main results	#16b	Report category boundaries when continuous variables were categorized	NA
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	NA

Discussion			
Key results	#18	Summarise key results with reference to study objectives	16 - 18
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	18 - 20
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	19 – 20, appendices 6, 7
Generalisability	#21	Discuss the generalisability (external validity) of the study results	21 - 22
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA