PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Disease burden of diabetes, diabetic retinopathy and their future projections in the United Kingdom: Cross sectional analyses of a primary care database.
AUTHORS	haider, sajjad; Thayakaran, Rasiah; Subramanian, Anuradhaa; Toulis, Konstantinos A; Moore, David; Price, Malcolm; Nirantharakumar, Krishnarajah

VERSION 1 – REVIEW

REVIEWER	Romero-Aroca, Pedro Hospital Universitario Sant Joan, Opthalmology
REVIEW RETURNED	31-Mar-2021

GENERAL COMMENTS	Revision of the manuscript entitled: “Disease burden of diabetes, diabetic retinopathy and their future projections” ID bmjopen-2021-050058 Declaration of interest: I am no conflicts of interest in the review of the present manuscript A. Summary Very interesting study that can be useful for journal readers. The authors make a forecast of the prevalence of diabetes mellitus, diabetic retinopathy and sight threatening diabetic retinopathy until the year 2030, based on the prevalence changes between the years 1998 and 2018. B. Strengths: The greatest strength of the study is the sample size of 15 millions of patient records that represents 6.2% of the UK population, with data from 1998 to 2018. C. Weaknesses The greatest weakness is the lack of data regarding the control of diabetes mellitus. There are no data on blood glucose, HbA1c or treatment in these patients, which may alter the results of the prevalence of diabetic retinopathy or especially of STDR. D. Commentaries. 1. The authors began the study in 1998, but in 2000 the diagnostic criteria for diabetes mellitus were changed. Have the authors taken these changes into account? Revised diagnostic criteria for diabetes was performed in 2000, the World health Organization (WHO) recognizes the 2-h glucose level are a good standard for diagnosis of diabetes but indicate that a fasting plasma glucose of N7.0 mmol/l (126 mg/dl) can be

	accepted as a satisfactory alternative in epidemiological studies (The expert committee on the diagnosis and classification of diabetes mellitus, 2000). 2. The study is based on the data extracted from the IQVIA medical Research Data (IMRD), the authors have taken into account if in the database they have extracted there may be data losses or if all the patients have periodically gone to the control of their general practitioners bedside between 1998 and 2018?? 3. Who made the diagnosis of diabetic retinopathy or STDR? Was it performed by ophthalmologists or general practitioners based on retinographies? 4. In the weaknesses section I have indicated the lack of data on glycemic control, HbA1c, or the treatment of diabetes. Can the authors indicate in the text how changes in metabolic control may influence the future projection of the prevalence of diabetic retinopathy? 5. Has any study been done to extrapolate the results of the population studied to the rest of the UK population? What differential characteristics in terms of demographic and socioeconomic data does the population studied have compared to the UK population? E. Resume. In summary interesting study but that needs to improve the discussion.

REVIEWER	Costagliola, Ciro Universitð degli Studi del Molise, Dipartimento di Scienze per la Salute
REVIEW RETURNED	09-Apr-2021

GENERAL COMMENTS	The paper is interesting, concise and well written. In Its present form it is suitable for publication

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Pedro Romero-Aroca, Hospital Universitario Sant Joan

Comments to the Author:
A. Summary
Very interesting study that can be useful for journal readers.
The authors make a forecast of the prevalence of diabetes mellitus, diabetic retinopathy and sight threatening diabetic retinopathy until the year 2030, based on the prevalence changes between the years 1998 and 2018.

We thank the expert Reviewer for this comment.
B. Strengths:
The greatest strength of the study is the sample size of 15 millions of patient records that represents 6.2% of the UK population, with data from 1998 to 2018.

We thank the expert Reviewer for this comment.

C. Weaknesses

The greatest weakness is the lack of data regarding the control of diabetes mellitus. There are no data on blood glucose, HbA1c or treatment in these patients, which may alter the results of the prevalence of diabetic retinopathy or especially of STDR.

We thank the expert Reviewer for this comment. The phrase "The findings of this study should be interpreted within the context of its limitations. In specific, the inability to incorporate evidence regarding the potential impact of glycaemia control and concomitant medications on the impact of diabetic retinopathy should be promptly acknowledged" was added to revised version of the manuscript (Lines 64-67, Page 18).

D. Commentaries.

1 The authors began the study in 1998, but in 2000 the diagnostic criteria for diabetes mellitus were changed. Have the authors taken these changes into account? Revised diagnostic criteria for diabetes was performed in 2000, the World health Organization (WHO) recognizes the 2-h glucose level are a good standard for diagnosis of diabetes but indicate that a fasting plasma glucose of N7.0 mmol/l (126 mg/dl) can be accepted as a satisfactory alternative in epidemiological studies (The expert committee on the diagnosis and classification of diabetes mellitus, 2000).

We thank the expert Reviewer for this comment. We agree with the Reviewer stating that changes in the diagnostic criteria throughout the course of the study may pose additional challenges in the interpretation of the results. In the present study, we have followed the Read codes for diagnosis and the treatment of diabetes mellitus and diabetic retinopathy. Fortunately, pre-2000 data constitute a minor percentage of the study observation period (2 years in 21 years) and in this respect, it is highly unlikely that the evolution of diagnostic criteria might have had a significant impact in the present analysis. However, the phrase "changes in the diagnostic criteria of DM" was added to the limitations paragraph of the revised version of the manuscript, according to the Reviewer's comment (Line 72 on page 18).

2 The study is based on the data extracted from the IQVIA medical Research Data (IMRD), the authors have taken into account if in the database they have extracted there may be data losses or if all the patients have periodically gone to the control of their general practitioners bedside between 1998 and 2018??

We thank the expert Reviewer for this comment. We agree with the Reviewer stating that missing data in epidemiological studies could potentially cause bias in the analysis and this was added as a limitation to the revised version of the manuscript, according to the Reviewer's comment (Line 71 on page 18).

3. Who made the diagnosis of diabetic retinopathy or STDR?
Was it performed by ophthalmologists or general practitioners based on retinographies?

We thank the expert Reviewer for this comment. The Read codes for diabetic retinopathy used for this purpose were a constellation of codes from diabetic eye screening programme and hospital eye service, mostly performed by consultant ophthalmologists following routine clinical practice and adhering to national guidelines. This is detailed in the case definition paragraph (Lines 126 - 128 Page 7). However, in case further information is requested by the review process, we could promptly provide it.

4. In the weaknesses section I have indicated the lack of data on glycemic control, HbA1c, or the treatment of diabetes. Can the authors indicate in the text how changes in metabolic control may influence the future projection of the prevalence of diabetic retinopathy?

   We thank the expert Reviewer for this comment. The phrase “suboptimal glycaemic control is a well-established risk factor for microvascular complications (such as DR), whereas fenofibrate, an used in agent in some patients with diabetes may have a positive effect on the course of DR” was added to the revised version of the manuscript, according to the Reviewer’s comment (Line 64-70, Page 18).

5. Has any study been done to extrapolate the results of the population studied to the rest of the UK population?

   We thank the expert Reviewer for this comment. The phrase “Several studies have already been performed on IMRD (previously The Health Improvement Network) and their findings have been extrapolated to UK and European population” has been added to the revised version of the manuscript, according to the Reviewer’s comment (Lines 86-89, Page 5)

   6. What differential characteristics in terms of demographic and socioeconomic data does the population studied have compared to the UK population?

   We thank the expert Reviewer for this comment. An overview of study sample characteristics is detailed in Table 1 (page 11). The gender distribution and classification of diabetes is generally similar to the UK official statistics (Diabetes in the United Kingdom (UK) - Statistics & Facts | Statista). However, we agree with the Reviewer underscoring the fact that local variations should be taken into account in designing health policy. To address this, we suggest that age, ethnicity, gender and deprivation index, all clinically significant determinant of DR incidence should be co-factored when implementing health directives on a regional level. This is discussed in lines 162-165 on page 22 revised version of the manuscript, according to the Reviewer’s comment.

   E. Resume.
   In summary interesting study but that needs to improve the discussion.

   We thank the expert Reviewer for this comment. We have made changes in discussion pages accordingly.

   Reviewer: 2
   Dr. Ciro Costagliola, Universite degli Studi del Molise

   Comments to the Author:
   The paper is interesting, concise and well written. In Its present form it is suitable for publication

We thank the expert Reviewer for this comment.