Author’s response to reviews

Title: Risk of chronic kidney disease in young adults with impaired glucose tolerance/impaired fasting glucose: a retrospective cohort study using electronic primary care records

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Study Title: Risk of chronic kidney disease in young adults with impaired glucose regulation: a retrospective cohort study using electronic primary care records

Thank you for considering our manuscript for publication in your journal.

We have reviewed the above manuscript according to the reviewer’s comments. Please see below response to the concerns raised:

Reviewer 1: Giuseppina Russo

Reviewer comment:

Abstract section:

Subjects with “IGR”: better define them as IGT/IFG.

Response:

Changed throughout manuscript as requested

1. Methods:
Include number of subjects (male/female) and duration of observation.

THIN register; please specify the place of origin of this dataset.

Response: Page 3

Details added in method part of the abstract

2. Conclusions: conclusions are too “technical”, sounding as the summary of the results. It would be better to insert Authors’ interpretation and change the sentence, as in the following example:

Response: Page 4

Conclusion replaced by “Authors’ interpretation”

Sentence changed as requested

Authors’ interpretation

“Our results show that young IFG/IGT subjects are also at higher risk of developing CKD. This risk is modulated by the degree of baseline renal function and glucose tolerance, being higher in those developing T2DM”.

Introduction section:

To have a better frame of IGR, add a sentence on the rate of progression of IGT/IFG to overt diabetes

Response: Page 5

Sentence added

“In a ten year prospective study of 241 individuals with IGT, 15% developed T2DM, 53% reverted to normal glucose tolerance and 22% remained glucose intolerant [5]. Similarly, a 4 year prospective study conducted in 128 South African Indians with IGT at baseline, found that after 4 years, 50.4% progressed to diabetes, 24.8% persisted with IGT and 24.8 reverted to normoglycaemia”

Discussion section:

Table 2: better explain the reasons for the discrepancy between read code and biomedical data in CKD prevalence (26 vs 156).

Response: Page 16
Furthermore, the incidence and prevalence of recorded CKD depends on general practitioners (GPs) doing blood tests. This may underestimate the frequency of CKD and may also be biased because GPs are more likely to do blood tests for CKD in patients in whom they suspect CKD. This includes those with diabetes, hypertension, certain ethnic groups and those with IGT/IFG. This is reflected in the number of CKD recorded via Read code and laboratory measurements.

Table 3: Results should be better discussed in the discussion section.

Response: Page 14

“The objective of this study was to investigate the incidence of CKD in a retrospective matched cohort analysis using the THIN database and found that young adults with IGT/IFG were four times more at risk of developing CKD than individuals with normoglycaemia. After adjusting for age, sex, ethnic group, deprivation quintile, BMI categories, cardiovascular disease, heart failure, atrial fibrillation, hypertension and NSAID, the effect of CKD risk was attenuated but was still 2.6 times higher in individuals with IGT/IFG than those with normoglycaemia. Among the modifiable risk factors, hypertension was consistently linked to higher incidence of CKD. Individuals progressing from IGT/IFG to T2DM were approximately nine times more likely to be diagnosed with CKD following diabetes diagnosis than individuals with IGT/IFG. After adjustment for potential confounders, incidence of CKD was attenuated but still showed a significant association. The incidence was reduced to approximately 7 times higher in T2DM than the IGT/IFG cohort”.

Comparison with other studies

In the comparison with other study section, it would be interesting to compare risk factors associated with CKD in subjects with overt T2DM with those available in this dataset of young IGR subjects with CKD.

Response: Page 17

Additionally, A prospective study, using data from the Italian Association of Clinical Diabetologists (Associazione Medici Diabetologi, AMD) initiative, examined risk factors associated with the development of CKD in patients aged (≥18 years) with type 2 diabetes and without CKD or albuminuria at baseline. Patients were followed up between January 1, 2004 and June 30, 2008. During follow-up, patients who showed reduced kidney function and albuminuria were older males with poor glycaemic control, higher systolic blood pressure, hyperlipidaemia and on hypertensive and lipid lowering drugs [22]. The risk factors identified in this study are similar to those identified in the current study”.

Reviewer 2: Aya Kadota
With a large electronic patient’s record dataset, the authors examined the incidence rate ratio of CKD incidence between impaired glucose regulation and normoglycaemia although the median follow up was only 1.7 years.

1. The authors stated that IGR increases the risk of CKD 3-5 by approximately 4 times than the risk of CKD1-2. Regarding analysis and discussion about the results of table 5, this reviewer think it necessary to show the actual case numbers by CKD stages because the 95% CI of CKD 3-5 was broad. If the actual case number of CKD3-5 is small, we can't discuss by CKD stages. And also they have to show adjusted incidence rate of CKD1-2 and 3-5 for both IGR and normoglycaemia to get the conclusion. Because CKD 3-5; eGFR<60 is strongly related with age and blood pressure level, at least, age and hypertension should be adjusted. Based on the added analysis, further discussion will be required.

2. Reconfirm the sentences in P17, L20-28, there might be some mistakes.

Response:

Further to Reviewer 2 comments we have decided to remove this part of the analysis, instead providing the reader with the idea of the burden of the disease in IGT/IFG patients compared to those with normoglycaemia and those who go on to develop diabetes in the IGT/IFG cohort. Furthermore as Reviewer 2 pointed out the number of cases of CKD (3-5) was small to allow for a meaningful comparison.