Author's response to reviews

Title: Statins and the risk of type 2 diabetes mellitus: cohort study using the UK Clinical Practice Research Datalink

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Author's response to reviews: see over
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The authors would like to thank all the comments and suggestions kindly sent by the reviewers. All of them were considered valuable and have been incorporated into a revised manuscript (changes highlighted in blue). The quality of the manuscript improved and we hope that it is now acceptable for publication.

The questions/comments of the reviewers are answered point-by-point:

**Reviewer:** Carol Coupland  
**Reviewer's report:**
This paper reports on the analysis of a large cohort study to assess the association between statin use and risk of type 2 diabetes. There have been several studies addressing this issue in the last few years, but this study adds to the overall evidence since it is large, representative of the general population of statin users, and has long follow-up. The analysis is extensive with detailed analyses of subgroups, and time periods of follow-up.

**Major Compulsory Revisions**
1. Information is needed in the Statistical analysis section in the Methods on how missing data were treated in the analysis. The Discussion should also cover this aspect and how it might influence the results.

   **Missing data** were quantified for each variable. For the majority of variables data was considered to be missing at random, unlikely to bias the estimated measures. However, when the nature or the extent of missingness was considered important (e.g. BMI) we conducted sensitivity analyses to explore its impact on the results.

   The methods and discussion sections were revised to include this information.

2. The analysis section should also clarify whether the exposure variables were treated as time-varying exposures in the analysis (e.g. duration of use).

   In the primary analysis hazard ratios and 95% confidence intervals were estimated for statins initiated at index date, analogous to an intention to treat analysis. In addition, we assessed the effect of censoring observation periods for each individual at the time they stopped taking statins and at the time their exposure status changed (Table S1). This re-analysis didn’t change our findings.

   The analysis section was revised for purposes of clarity.

3. The Results show a striking decrease in risk with age. This should be highlighted more in the Discussion, including discussion of possible reasons for this decrease and comparisons with other studies. It would also be helpful to have NNH by ageband.

   We agree with this comment and improved the Discussion section to emphasize the role of age in the progression of T2DM, including comparisons with other studies (new references were added: 46-48). We are reluctant to present NNH because these might be taken to imply that we believe the findings were causal. Typically NNH are derived from RCTs which is not the case here.

**Minor Essential Revisions**
4. It would be useful to have details on how many of the non-users were prescribed statins after the index date. It is not clear how these are treated in the primary analysis, and whether for example they are included in both columns in Table 1.

   The primary analysis was analogous to an intention to treat analysis. The columns in Table 1 represent baseline characteristics of mutually exclusive groups. The impact of the changes in exposure status (non-users being prescribed statins or users stop taking statins) was assessed trough a sensitivity analysis (table S1) and didn’t change our findings.
The changes made in the method section to elucidate the analysis (see comment nº 2) will clear this doubt.

5. The duration categories given in the Methods don’t match with the categories in the Results /Tables 4 and 5. This has now been corrected.

6. The NNH and/or excess risk values should be added to the Abstract. The abstract was revised as suggested.

7. The Abstract should also mention the large decrease in hazard ratios with age. The abstract was revised as suggested.

8. A few things to check:
Table 1. Although cardiovascular disease is much higher in new users cardiovascular drug use is lower which seems strange.
Table 1. Annual consultation rates and prescription rates look high in both groups. Also there’s a big difference between the two groups for annual prescription rate – what drugs explain this difference as there is not much difference for the individual drugs listed? Table 3. I wouldn’t have thought the number of subjects in the first 6 months and after 6 months analysis would be the same. Haven’t some subjects been censored (e.g. died, diagnosed with diabetes) in the first 6 months, so they wouldn’t contribute to the analysis after 6 months? Table 3. Nearly 30% of subjects are excluded in the PS[5-95%] analysis. I would have expected it to be around 10%, based on the percentile values.

9. Table 4. Add numbers of subjects at baseline and number of events (diabetes in follow-up) in each subgroup.

10. Table 5. This is a very complex table and would be easier to read if it was simplified, perhaps by reducing the number of time periods to match the ones in the Methods section, particularly since numbers were too small to estimate values in the 20-25 year band. Otherwise the incidence rate columns could be left out, or put in a supplementary table.

11. List S1. Several of the codes don’t seem to indicate type 2 diabetes, for example:
44T1000RANDOM BLOOD SUGAR NORMAL
44U8.00BLOOD GLUCOSE NORMAL
4661.00URINE GLUCOSE TEST NOT DONE
L180811GESTATIONAL DIABETES MELLITUS
This needs clarification.

12. Table S2. Add numbers in the groups. Also relabel the CVD or hypertension row (or split into 2 to avoid confusion).
Table 1. Although cardiovascular disease is much higher in new users cardiovascular drug use is lower. We assume this difference is due to the fact that in cardiovascular drugs we included anti-hypertensive drugs, while hypertension was assessed separated from cardiovascular disease.
Annual consultation rate (defined as the number of times a patient initiated contact with a general practice in the 12 months prior to the index date) and annual prescription rate (defined as the number of prescriptions in the 12 months prior to the index date) are different between groups. This difference was expected since people are likely to start a statin during a period of time when their health is of concern; so they will tend to see their general practitioner more often and may be more likely to receive other prescriptions. To avoid this ascertainment bias, both these variables were included in our final regression model. We can’t say what drugs explain the differences in prescription rates because these measures were calculated just by adding the total number of codes of prescriptions recorded in one year, without checking for specific drugs.
Indeed, some subjects were censored (e.g. died, diagnosed with diabetes) in the first 6 months, so they didn’t contribute to the analysis after 6 months. This is a very important remark. Table 3 was corrected. Table 4 was revised as suggested. The number of time periods in table 5 is important when rates vary with time (as it seems to be the case). Time bands should be short enough to assume that during each band of follow-up the rate is constant.

We are very grateful for the remarks on the code list presented. In error we included a preliminary code list initially developed for proposes of protocol submission. Our final code list was developed as part of the study and was validated by two researchers (SE, AFM). The correct code list is now included in the appendix. The final code list did not include the codes highlighted by the reviewer: we agree these do not indicate diabetes. Table S2 was revised as suggested.

Minor issues not for publication
13. The 3rd sentence of the 4th paragraph of the Results doesn’t make sense (“an association of OAD an insulin”). This has now been corrected.

Discretionary Revisions
14. The authors speculate in the Results and Discussion sections that statin initiation is likely to be associated with having blood tests including glucose. It would be helpful if they could use their data to see whether this is the case, comparing rates of glucose tests over time after the index date in statin users and non-users.

We agreed with this suggestion, but unfortunately this analysis would be very difficult to perform in CPRD due to missing information on glucose tests performed in hospital and outpatient clinics; in addition to the ascertainment bias already mentioned because people prescribed statins may consult their general practitioner more often and have more blood tests.

Reviewer: Gregory A Nichols
Reviewer’s report:
This manuscript uses data from the CPRD to assess the association between statin use and incident diabetes. In general it is well-designed containing only minor flaws. However, the findings are not novel, except to the extent that they are much stronger than previously reported. Yet this was not addressed. I don’t think this adds much to the current literature.

Major Compulsory:
1. As noted in the background section, the risk of developing diabetes is strongly associated with baseline fasting glucose. This is true regardless of statin use. The major shortcoming of previous studies is the inability to account for FPG level. Apparently lab data aren’t available. If there are read codes for pre-diabetes, impaired glucose regulation, impaired glucose tolerance or impaired fasting glucose, you should us these to try to account those at greatest risk of developing diabetes. Many researchers suspect that the statin effect is minimal and that it merely pushes people over the diagnostic threshold of diabetes and that it is likely these people would have eventually crossed that threshold anyway. The current manuscript does nothing to close this critical knowledge gap so the findings as presented are of limited value.

In our study we assessed the severity of T2DM, measured by the type of treatment used (no drug therapy, oral anti-diabetic drugs and/or insulin). The majority (77.34%) of statin users that developed T2DM were not being prescribed any hypoglycemic medicine 6 months after diagnosis. This suggests that impaired insulin secretion induced by statins worsens over time, increasing the risk of developing T2DM with longer statin use, consistent with our findings.
We agree that given the complex interactions between different predictors of disease progression, the contribution of each single factor is difficult to assess. The “Discussion” section was revised to reinforce this point of view and new references were added (46-48).

2. Consistent with the above, the first conclusion is that statins increase risk with longer duration of use and higher BMI. BMI is of course a very strong risk factor for incident diabetes, and high BMI is associated with dysglycemia, so this suggests to me that the statin effect is probably marginal at best. And longer duration of use is probably impossible to separate from worsening beta cell function/decreased insulin sensitivity over time that is the real cause of diabetes. Indeed, this is one of the possible explanations we present for our findings, as explained above.

3. The hazard ratios reported are substantially higher than the ~9% increased risk in previous meta-analyses. In the discussion, the authors merely state that their findings confirm clinical trials and are consistent with higher hazard in WHI, but the findings are considerably higher than WHI. An increased risk of about 2-fold deserves much more discussion and explanation. Our findings are consistent with those of WHI and are certainly higher than those reported from RCTs. Clearly with these observational data uncontrolled residual confounding cannot be ruled out.

4. I may be confused about the methods, but it appears that censoring those in the unexposed group once they initiated a statin was only done as a sensitivity analysis. This should have been included in the primary design, otherwise it confounds the results (although it biases toward the null).

The impact of the changes in exposure status (non-users being prescribed statins or users stop taking statins) was assessed through a sensitivity analysis (table S1) and didn’t change our findings. Since in CPRD we don’t have information on the reasons for stopping or changing a drug treatment, we decided to use an intention to treat analysis in primary design. This avoids the bias of excluding non-adherent patients when we don’t know if the reasons for that are associated with poor health, and eventually correlated with the outcome studied.

5. It is curious that <7% of those exposed to statins have hyperlipidemia and <23% have CVD. Obviously this means that indications for statins are not being fully recorded. Thus it is unclear what you stratification by CVD really means. Only the most severe cases?

The characteristic of the population studied were assessed at baseline. We didn’t assess potential changes during follow up and we recognize that as a limitation of our study. However, we have not assumed that all statin use is driven by hyperlipidemia and CVD, and precise indications for medication are not recorded in our data. A substantial proportion of patients could be given statins for a perceived increased risk of vascular outcomes for reasons other than hyperlipidemia and CVD. Although, some under recording of CVD and Hyperlipidemia cannot be ruled out, diagnostic validity in CPRD data has been shown to be high (Herret et al, 2010 Br J Clin Pharmacol. 2010 Jan;69(1):4-14. doi: 10.1111/j.1365-2125.2009.03537.x.).

6. Why aren’t anti-hypertensives (many of which effect glycemic levels) included?

Anti-hypertensive drugs (including β-blockers, diuretics, calcium antagonists, angiotensin converting enzyme inhibitors and angiotensin receptor blockers) were included in our propensity score model, to adjust for systematic differences between statin users and non-users that could bias the estimated exposure effect.

Minor Essential:
7. There are several places in the results text where the authors attempt to explain their findings (e.g., “the hazard ratios were higher in the first 6 months of exposure which might indicate a possible detection bias...”). Such statements should be saved for the discussion. We agree with this remark. The Results section was revised accordingly.

8. Tables 1 & 2, with this sample size I imagine nearly everything is significant but you should include p values anyway or if everything is indeed statistically significant, add a footnote to that effect.
All the analyses gave a p value of 0.000. We already have a footnote in table 1 saying: “All the differences between groups were significant at the 0.05 level (two-sided)”.

Reviewer: Swapnil Rajpathak
Reviewer’s report:
**Major Compulsory Revisions**
1. The final sample included, users and non-users, is mentioned in the results section. However, it will be useful to show a flow chart that resulted in this final sample size (especially to understand the drop in sample size related to inclusion and exclusion criteria and due to the choice of 1:5 matching).

   After applying the inclusion and exclusion criteria, the sample size comprised 430,890 statin new users, which were randomly match up to 5 non-users from a pool of more than 4 million individuals. The mean number of matches per user was 3.7. Attempting to present these data in a flow chart is not straight forward and has the potential to confuse the reader. We believe our current description of the sample is adequate.

2. The time period from 1989-2009 is very long and guidelines for use of statins changed during this time. One could argue that given that the average risk of a statin patient for diabetes may be different during different time periods -- did the investigators conduct analysis separately for last 10 years vs. earlier years to see if results are different in the different time periods. This analysis was not conducted. A wide range of potential confounding factors expected to change the average risk of a statin patient for diabetes during different time periods were included in our propensity score model. Propensity score analysis can successfully adjust for much confounding by indication, although we recognize in our limitations that residual confounding is possible due to risk factors that have not been considered in the analysis. Of note, calendar year was included in this model, and will to some extent account for changing trends in statin prescribing.

3. In the matching process, can a user at a later time, matched as a non-user for an earlier user? If not, if it is required that non-users should be non-users throughout this time period -- how does impact of validity of the measures of association observed?

   The primary analysis was analogous to an intention to treat analysis. However, non-users could start a statin at a later time and users could stop taking statins or change statin type/dose. The impact of these changes in exposure status was assessed through a sensitivity analysis (table S1) and didn’t change our findings.

4. Would it be possible to conduct an analysis within the users for a dose response (e.g. high vs. low dose)? We think this suggestion is valuable. However, it requires a classification of statins according to their relative efficacy (according to expected amounts of LDL-cholesterol reduction from baseline), which means we would need to stratify our analysis according to both type of statin and individual dose. Unfortunately information on dose is frequently not available in our data and this analysis will not be possible.
5. the mean follow-up time differed significantly between users (5.43 y) vs. non-users (3.89 y). what is the explanation for this? Did the authors conduct an analysis with mortality as the outcome? Does survival bias impact the study results?

In our discussion section we recognized the potential for survival bias in our study, as the mean follow up time was different between groups (5.43 years for statin users and 3.89 years for nonusers) and statin users were slightly less likely to die (10.79%) compared to the nonusers group (11.66%). This means that statin nonusers might die earlier and, consequently, don’t have the same probability of developing T2DM as the statin users who remain under follow up. This could bias the estimate of effect for statin use away from the null.

6. Table 4. Add reference groups. almost follow-up time categories don’t seem mutually exclusive.

Reference groups were added to table 4. Time categories are not mutually exclusive. For each individual the time at risk has been split into different time bands, e.g. one patient at risk during 2.5 years has been split into 1 year in the band 0-1year and 1.5 years in the band 1-3 years.

Minor Essential Revisions
Use Type 2 Diabetes and not Type two Diabetes as in the abstract
Thanks for this remark. The correction was done.