Author’s response to reviews

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

Authors:

Ana Filipa Macedo (filipa_macedopt@hotmail.com)
Ian Douglas (Ian.Douglas@lshtm.ac.uk)
Liam Smeeth (Liam.Smeeth@lshtm.ac.uk)
Harriet Forbes (Harriet.Forbes@lshtm.ac.uk)
Shah Ebrahim (Shah.Ebrahim@lshtm.ac.uk)

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Author’s response to reviews: see over
Statins and the risk of type 2 diabetes mellitus - Manuscript ID 5672117681141328
The questions/comments of the reviewers are answered point-by-point:

Reviewer's report
Title: Statins and the risk of type 2 diabetes mellitus: cohort study using the UK Clinical Practice Research Datalink
Version: 2 Date: 5 March 2014
Reviewer: Carol Coupland
Reviewer's report:
The authors have made many changes to the paper which have improved it considerably. They have addressed most of my previous comments very well although there are still a few points remaining.

Major Compulsory Revisions
1. “Missing data were quantified for each variable and 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 authors have still not adequately explained how they accounted for missing data in the analyses. They need to clarify whether their main analyses were complete case analyses (i.e. excluding all patients with missing data for any of the confounding variables), and also specify in the Methods precisely what sensitivity analyses they carried out. This is important in particular for BMI which is likely to be a major confounder. Also by treating it as a categorical variable they may not have adequately controlled for its confounding effect.

Missing data were quantified for each variable and classified as “unknown”. There were some missing data on smoking status (4.0%), alcohol consumption (11.7%), and BMI (12.5%). For these variables data was considered to be missing at random, so the main analyses didn’t exclude patients with missing data for any of the variables. BMI was treated as a categorical variable and since it is likely to be a major effect modifier, the analysis was stratified by categories of BMI (table 4 – in this table the rates for the category of unknown BMI were not presented since they are not informative because we had no information on the reasons for missing BMI). In a sensitivity analysis our findings didn’t change when our analysis was restricted to patients with low or normal BMI levels.

The Method and Discussion sections have now been revised for purposes of clarity.

2. Now that rates have been added to Table 4 we can see that the incidence rate of diabetes in statin users is fairly constant across all age bands, whereas there is a steep increase with age in non-statin users. This seems odd and rather implausible, and needs comment and some explanation.

In non-users the increase in T2DM with age is expected probably due to age-dependent loss of β-cells and increased obesity and reduced physical activity. In statin users the T2DM rates are higher and do not show an age gradient. There is a growing consensus that one mechanism by which statins increase incident diabetes is by pushing people over the diagnostic threshold of blood glucose earlier than people with similar risk factor profiles but not taking statins. A further mechanism is that younger people at high risk of developing diabetes are accurately targeted for statin treatment, which in conjunction with the former effect would attenuate the expected age gradient. Although we’ve tried to account for baseline differences in our propensity score analysis, as we have acknowledged, we can’t rule out residual confounding.

3. The duration categories given in the Methods now match with the categories in the Results and Tables 4 and 5. It would have been better though to combine the 15-20 and 20-25 year categories since there are so few events in the 20-25 year category. The authors also have not clarified whether the duration of exposure variable (also called follow-up time) was treated as
a time varying exposure in the analyses – this is important since otherwise results are susceptible to immortal time bias.

To avoid immortal time bias, we took into account the time during which the outcome couldn’t occur for statin users. So, we included the period of time between cohort entry (study start dates explained in the method) and the day before starting a statin in the pool of non-users that were matched with the users.

Then, hazard ratios were estimated for statins initiated at index date, analogous to an intention to treat analysis. The time varying exposure in the analysis was assessed by 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 Method section was revised for purposes of clarity.

Minor Essential Revisions

4. “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.”

It is strange that the authors have made this comment about NNH when they have already included NNH values in the manuscript although it is not an RCT. If they are keeping NNH in the paper then I think they should add them for age group, since they have given them for people with no diagnosed hypertension or cardiovascular disease. They should also add the caveat that these figures might imply causal findings. It would also be helpful to give some more explanation on how they were calculated, since various approaches can be used with survival type data and adjusted hazard ratios.

After receiving the reviewers’ comments we agreed that the best option would be not to present NNH at all for the reasons already pointed out.

5. The authors say in the Methods that “Secondly, we restricted the analysis to the first 6 months of exposure, since a positive association over a short exposure duration could indicate a possible bias.” There is very little mention of the results of this analysis in the Results section (“The hazard ratios were higher in the first 6 months of exposure”), and very little in the Discussion, yet this seems to contradict their finding reported in the Abstract and elsewhere that “Statin use was associated with an increased risk of T2DM ... which increases with longer duration of use”. Finding a larger hazard ratio in the first 6 months of use does suggest detection/ascertainment bias which might be most marked soon after starting statins but continue throughout use. Because of this I think the authors overstate their conclusions in several places (e.g. “The increased risk of T2DM should be taken into account when considering the risk-benefit balance and cost-effectiveness of statin therapy”), although they do have a more general cautious statement (“These findings should be interpreted with caution as observational studies are subject to residual confounding by indication and other biases that cannot be ruled out.”).

We agree that the higher hazard ratios in the first 6 months of exposure might indicate a possible detection bias. According to our analysis (Table 5 – showing median time for T2DM diagnosis at different follow-up times) we think this bias doesn’t continue throughout statin use.

We have modified the text to ensure that our conclusions are consistent and not over-stated.

6. The 3rd sentence of the 4th paragraph of the Results still is unclear – “were being prescribed an association of OAD and insulin”. It would be better to change “association” to “combination”.

This has now been corrected.

7. There is a hazard ratio of 170 in Table 3, which I presume should be 1.70.

Thank you for the correction. Indeed this should be 1.70.
Reviewer's report
Title: Statins and the risk of type 2 diabetes mellitus: cohort study using the UK Clinical Practice Research Datalink
Version: 2
Date: 13 February 2014
Reviewer: Gregory A Nichols

This manuscript is a revision of a previously submitted work that uses data from the CPRD to assess the association between statin use and incident diabetes.

As before, the study is generally well-designed and executed. I maintain that the findings are not novel, except to the extent that they are much stronger than previously reported. The authors point out that the stronger findings could be explained by the difference between observational and clinical trial data, which is a fair and important point.

My previous major concern was that the statin effect is minimal and that it merely pushes people over the diagnostic threshold of diabetes. It is likely these people would have eventually crossed that threshold anyway. The inability to control for glucose level at baseline, which is the most significant predictor of progression to diabetes, leaves me with the same impression as before; the findings as presented are of limited value, but there isn’t really anything to be done about this.

I was a little surprised that the authors were unwilling to make a number of changes suggested by the reviewers. For example, I previously noted that censoring those in the unexposed group once they initiated a statin was only done as a sensitivity analysis. I think this should have been the design of the primary analysis. The authors argued that because the sensitivity analysis showed that it didn’t affect the results, they didn’t need to make the change. I understand but disagree. There were several other comments from me and reviewer #3 (Swapnil Rajpathak) that were ignored or argued against, leaving me feeling unenthusiastic about this manuscript.

The novelty of our paper is limited because several previous studies have focused on the risk of developing diabetes in people taking statins, this analysis is highly relevant to primary care practice as it draws on routine data sources collected from British general practices and gives an indication of the ‘real world’ effects of statins on diabetes incidence in typical patients prescribed statins rather than those entered into clinical trials.

We appreciate that this reviewer would like us to make a change in our primary analysis at this late stage in the review process. However, our primary analysis was pre-specified in a protocol approved by the Independent Scientific Advisory Committee for MHRA Database Research, and we think it would not be good practice to change the analysis strategy retrospectively. We explored the impact of the changes in exposure status (non-users being prescribed statins or users stop taking statins) through a sensitivity analysis (table S1) and our findings didn’t change so the reviewer’s point is, we believe, adequately covered.

We also believe that we have considered carefully to the points raised by the reviewers and have made full responses. We do not accept that we have been unwilling to make changes to the manuscript as evidenced by comment by Coupland: “The authors have made many changes to the paper which have improved it considerably. They have addressed most of my previous comments very well…”

Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare that I have no competing interests.