Author's response to reviews

Title: Variations in statin prescribing for primary cardiovascular disease prevention: cross-sectional analysis

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Author's response to reviews: see over
Dear Editor,

Thank you for inviting us to response to the reviewer’s comments. We found these comments most helpful, and have given point-by-point responses to their comments below. We have also extensively copyedited the manuscript, following BMC house style.

**Reviewer 1: James Sheppard**

**Major Compulsory Revisions**

The data used in these analyses are at a practice level, and thus all estimates of patient level statin prescribing are based on a number of assumptions. The sensitivity analyses are helpful in this respect and this limitation is acknowledged in the discussion. However, I am concerned about the validity of the main study conclusion that “statin prescription was low given the prevalence of diabetes and hypertension”. Whilst this may be true, it is difficult to draw this conclusion from the present data because there is no way of knowing what % of the eligible population were prescribed statins. Identifying patients eligible for primary prevention therapy is difficult even when individual patient data are available because the criteria for treatment is complex and, as the authors acknowledge, there is no routinely collected prescribing data for this indication.

*Response: we agree with this statement, and have removed this from the text.*

It is possible (although unlikely) that all eligible patients were prescribed therapy for primary prevention and none were prescribed therapy for secondary prevention.
Response: We agree, and we have included this sentence in the ‘strengths and limitations’ section.

Unfortunately is it impossible to know from the present data and thus difficult to know if statin prescribing really was ‘low’. I wonder whether the dichotomisation between primary and secondary prevention is appropriate given the data available. The findings of social, ethnic and age related inequalities in prescribing would still be of interest even if this analysis studied both primary and secondary prevention as a single group.

Response: we agree with the suggestion that there would be fewer assumptions and limitations if the study addressed statin prescribing as a single group. However this would change our research question, and also present a quite different paper. On balance we have reached the conclusion that despite the number of assumptions we have made, our approach is valuable as it has reported new data on estimates for the level or statin prescribing for primary prevention.

The data used are almost 8 years old. Given the changes to guidelines, QOF and evidence for statin prescription, some discussion about how relevant these data are today and how prescribing might have changed is needed.

Response: We have added the sentence “This study used data from 2006-7. Since then guidelines have changed which have increased the indications for prescribing statins form
primary prevention, including lowering the 10 year CVD risk threshold to 10% and also including patients with rheumatoid arthritis and chronic kidney disease.”

The statement in the discussion page 9, line 210 ‘There are no other indications for statin prescription which could confound these results’ seems slightly erroneous given the way in which estimates were derived – for example, statins are indicated for secondary prevention in patients with TIA and peripheral vascular disease which may not have been captured here.

**Response:** thank you for raising the point that we have not mentioned peripheral vascular disease. We have now included the following sentence in the strength and weaknesses section “We could not determine how many patients were receiving a statin for peripheral vascular disease.” We have already accounted for patients with TIA as these are included in the Quality and Outcomes Framework definition of stroke. We have clarified this in the manuscript in the methods section.

The discussion of the study results in the context of existing literature incomplete. Our recent study of prescription of therapy for primary and secondary prevention offers some useful comparisons. (1) Although this study was conducted in a smaller cohort of patients, data were analysed at an individual patient level and detailed analyses of which patients were eligible for treatment was conducted. We found that 80% of eligible patients are prescribed statins for primary prevention of CVD, and 74% are prescribed therapy for secondary prevention. The latter estimate is important given the assumption here that all patients with existing CVD will be prescribed treatment. The EUROASPIRE III (2) study is also relevant. Conducted across Europe, it suggested that 50% of patients were
prescribed lipid lowering therapy for primary prevention of CVD.

Response: We have included the finding of both of these studies in the manuscript, in the introduction and strengths and limitations.

Minor Essential revisions

Prevalence estimates are given with SDs, but 95% confidence intervals would be easier to interpret.

Response: We are sorry that we have not explained this clearly and have caused confusion. These data simply describe the characteristics of the sample and this is why we have used standard deviations. We did calculate the 95% CIs but these are so narrow that they do not add meaningful interpretation. We have therefore retained the standard deviations when presenting the descriptive statistics.

There is no mention (in the abstract or main text) the number of patients in the study (i.e. sum of the list size of all practices in the study), this would be helpful to help the reader appreciated the size of the study.

Response: we have included the total number of patients in the abstract and the main text.

Please do not use the phrase ‘further research is needed’ – be specific – what type of research? What type of interventions? – given the findings of your study, surely an intervention targeting socially deprived and ethnic minority groups would be appropriate?
Response: we have revised this section, which now reads “further research using individual patient level data targeting socially deprived groups, ethnic minority groups and elderly groups is indicated.”

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I declare that I have no competing interests

Reviewer 2: Jan Van der Meulen

Compulsory revisions

The paper contains a large number of deficiencies which are minor in itself but all together undermine what could be a good paper. They authors show a lack of attention to detail. I'll give a number of examples:

1) On page 2, they write in the Methods paragraph of the Abstract: "Linear regression modelling of data including estimates for prescribing rates of statins for primary CVD prevention, IMD quintile, proportion of population from an ethnic minority, and age of 65 years." Albeit not "wrong" this sentence could be a lot clearer and reflect better the structure of the actual analysis: "Linear regression was used to model prescribing rates of statins for primary CVD prevention as a function of IMD quintile, proportion of .... and age over 65 years."
Response: we have altered this sentence as suggested.

2) There is no mention in the Abstract of the methods they used to overcome the two main challenges that were mentioned above.

Response: we have added the following passage to the methods section in the abstract:

’ve defined daily doses’ (DDDs) were used to calculate the numbers of patients receiving a statin. Statin prescriptions were allocated to primary and secondary prevention, based on the prevalence of CVD and stroke.

3) On page 2, the Results paragraph of the Abstract does not contain any quantitative results.

Response: we have added β coefficients with p values to this section.

4) More subtle but indicative of a lack of attention to detail: in Results paragraph of Abstract, the authors write "Practice with higher estimated levels of statins prescribing ... had a smaller proportion of ethnic minorities, were less deprived and had fewer elderly patients", which doesn't reflect the structure of the analysis with has prescribing levels as dependent and the practice characteristics as independent variables. Confusingly, the results are also summarised in the Conclusion paragraph in a correct way (in terms of distinguishing dependent and independent variables but now referring to lower prescribing rates (in other words, changing the direction of the way the results are being presented). In all, no major mistakes were made but a lot of subtle little stumbling blocks for the
reader were created.

**Response:** We agree this is confusing, we have reworded this section in the following way

“Practices with higher prevalence of hypertension ($\beta$ co-efficient 0.299 $p < 0.001$) and diabetes ($\beta$ co-efficient 0.566 $p < 0.001$) prescribed more statins for primary prevention.

Practices with higher levels of ethnicity ($\beta$ co-efficient -0.026 $p < 0.001$), greater deprivation ($\beta$ co-efficient -0.152 $p < 0.001$), older patients ($\beta$ co-efficient -0.032 $p < 0.002$), larger lists ($\beta$ co-efficient -0.085, $p < 0.001$) and were more rural ($\beta$ co-efficient -0.121, $p < 0.026$) prescribed fewer statins.”

5) In Introduction, the "UK" is mentioned several times, and I thought that in several places should be replaced by "England".

**Response:** We have replaced ‘UK’ with England in several places in the text as suggested.

6) In the Introduction, the authors refer to the "QOF" without introducing the acronym or explaining what it is which is required for an international readership.

**Response:** we have defined the acronym, and written a sentence explaining its purpose. “The QOF is a pay-for-performance contract introduced in England in 2004, financially rewarding primary care practices for performance in clinical, organisational, patient experience and additional services”

7) The standardisation of statin use based on the "defined daily doses" should be better explained (page 5).
Response: we have altered the text and now use the precise definition as used by the WHO which we have referenced. This now reads

“The DDD is an international measure of prescribing developed by the World Health Organization and is the assumed average maintenance dose per day for a drug used for its main indication in adults”

8) It is also unclear to what extent the different data sources all relate to the same period (the data on statins prescribing is from 2006/7). See for example, the description of data sources at bottom of page 5.

Response. We have added information on the period of collection for each set of data to the methods section.

9) The adjustment for the fact that patients can have both CVD and stroke should be described in greater detail in this paper rather than referring to another source.

Response: We have added the following sentence: “This method uses prevalence data from QOF for each practice to estimate the proportion of the population who have a comorbidity, in order to avoid double counting of individuals who have a diagnosis for both CVD and stroke.”

10) I did not fully understand how some of the sensitivity analyses were carried out. The authors "assumed only patients with heart disease and stroke who had
a cholesterol $< 5$ mmol/l were taking a statin." What does that mean in practice?

They also assumed that only 70% of prescriptions were dispensed. How does this related to the adherence factor of 1.25 that they originally used (I thought a factor of 1.25 suggested that 80% ($=1 / 1.25$) of prescriptions were dispensed which does not differ a lot from 70%)

**Response:** We have given more detail regarding the background to the first sensitivity analysis which now reads “First we assumed only patients with heart disease and stroke who had a cholesterol $< 5$mmol/l were taking a statin, as most patients taking a statin will have a cholesterol lower than 5mmol/l;[31]”

We use the term “adherence” to mean that the prescription given to the patient was dispensed by the pharmacy. It is correct that the primary analysis makes the assumption that 80% of prescriptions were dispensed- this is in line with published data- however this data does come from the USA and might not be representative of England. To meet concerns that perhaps less than 70% of prescriptions might be collected at the chemist we have added an additional sensitivity analysis assuming a 60% rate.

11) "dependant" should be "dependent" (page 8).

**Response:** thank you for pointing that out, we have corrected the manuscript.

12) What criterion was used to decide whether a data point was an "influential outlier" (page 8).

**Response:** we used visual inspection of scatterplots to identify influential outliers.
13) I'm confused about what is meant by "1% increase in relative prevalence" (page 8)? What does this mean? How does this relate to the results presented in Table 2? A better link between text and tables would help the reader to digest the result.

Response: We agree that this is a confusing sentence. We have reworded the sentence and used a specific example linking to the data tables. This now reads

“For every 10% increase in the prevalence of diabetes (e.g. from 3.7% to 4.1%) there was approximately a 5% increase in the percentage of the population taking a statin for primary prevention (from 6.3% to 6.6%); and for every 10% increase in the prevalence of hypertension (e.g. from 12.5% to 13.7%) there was approximately a 3% increase in the percentage of the population taking a statin for primary prevention (from 6.3% to 6.5%).”

14) An example of poor writing: "There was evidence for inequity with lower estimates of statins .... with respect to ethnicity .... and social deprivation.” This statement can be a lot clearer and easier to read with a bit rewriting.

Response: we have reworded this as

“There was evidence for social inequities with higher ethnicity, more older persons and increasing social deprivation being significant predictors of reduced prescribing rates of statins for primary prevention.”

15) "Estimates of prescribing rates were lower than anticipated given the prevalence of diabetes, hypertension and the population over 65 years." What
rate did the authors anticipate and what were these anticipated rates based on?

**Response:** This point was raised by both reviewers. Although we felt the statement was likely to be true (given that most patients with diabetes and most of those over 65 years will be at high risk of CVD), it is not possible to draw these conclusions from our data alone, so we have removed this sentence.

16) Tables 1 and 2 present GP practice characteristics but some are included only in Table 1 and not in Table 2 and some only in Table 2 and not in Table 1. Also, the order of presentation of the common characteristics is different. The authors seemed to have used the standardized coefficients to order the characteristics. However, given that there are positive and negative coefficients this order of the numerical value doesn't reflect the effect size.

**Response:** we have revised table 1, including the descriptive statistics for the full regression model. We have re ordered table 1 and 2 by the effect size of the standardised coefficients.

I would invite the authors to address these issues - and perhaps a few more that I did not list - in order to increase the quality of the paper.

**Response:** we have extensively copyedited the paper using BMC guidelines to help improve the quality.

**Level of interest:** An article of importance in its field

**Quality of written English:** Not suitable for publication unless extensively edited
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests: I don’t have any competing interests.