PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	A cross-sectional analysis of the prevalence and predictors of statin utilisation in Ireland with a focus on primary prevention of cardiovascular disease
AUTHORS	Byrne, Paula; Cullinan, John; Murphy, Catriona; Smith, Susan

VERSION 1 – REVIEW

REVIEWER	Jason C. Hsu National Cheng Kung University, Taiwan
REVIEW RETURNED	26-Jul-2017

GENERAL COMMENTS	1. This study described the prevalence of statin utilization by people aged over 50 in Ireland and explored the factors associated with the likelihood of statin use for primary prevention of CVD. The research question is clear and interesting. 2. The authors are suggested to develop more clinical and political implications from the empirical results by comparing the findings and other publications or other ways. 3. This study used TILDA data, which collects data on a nationally representative sample of community living adults aged over 50 in Ireland. It found that the odds of statin usage increased according to age. How about the usage in adults aged less than 50 in Ireland or other countries based on other studies? 4. In terms of the results about socioeconomic factors, the conflicting findings about statin use and socio-economic factors have been reported in studies from other countries. The authors merely addressed the potential reason – differences in access and entitlements within health systems, however, the readers may not know what are the differences and how the differences might contributed to the different findings. 5. This study found that controlling for diagnostic indication, someone receiving five or more medicines would be more likely to receive a statin. Polypharmacy situation exists in patients taking statins, what are the implications (ore suggestions) about this situation?

REVIEWER	Stephen Horgan Morristown Medical Center U.S.A.

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REVIEW RETURNED	10-Aug-2017

GENERAL COMMENTS	(1) The study is reasonably well designed. Recall bias, as outlined by the authors, is a concern. The author points out that good agreement has been previously demonstrated by cross referencing with pharmacy dispensing records. Multivariate logistic regression is an appropriate statistical method to evaluate statin utilization with associated variables. (2) It is unclear how the TILDA survey weights were calculated. More information should be provided - perhaps in the supplemental material. (3) It is not clear why the diagnostic category 'peripheral arterial disease' is not included. Most research studies evaluating the uptake of statins in the community would include this important category and this should have been included in the CAPI. It is stated as a weakness but I suggest that the author elaborate on why it is not included. (4) Some P-values in table 3 are recorded as 0.00. I am uncertain what this means. Either clarify or correct the P-values. The authors should also state in their methods and table legends what P-value they deem to be significant.

REVIEWER	Dr Andrea L Jorgensen, Senior Lecturer in Biostatistics University of Liverpool, UK
REVIEW RETURNED	28-Sep-2017

GENERAL COMMENTS	1. The authors refer to using a 'multivariate logistic regression model' for analysis, however it appears that what was actually used was a 'multivariable logistic regression model' i.e. a logistic regression model including several explanatory variables. I suggest that the authors amend the wording accordingly. 2. The last sentence of the second paragraph in the 'Background' section is confusion,and I recommend the authors review and revise it. In particular, why are two recommended cholesterol levels and two recommended lipoprotein levels stated. To what groups do the two levels relate to ? 3. The authors state that the study used cross-sectional data from 'the baseline wave' of TILDA. Can they please clarify what they mean by 'baseline wave' ? 4. The authors appear to have fitted a multivariable logistic regression model for determining the effect of various factors on statin utilisation without applying any statistical approach to choosing which factors should be included in the model. They state that the 'choice of variables included in the model was influenced by previous research'. It would be beneficial to use a statistical approach such as stepwise variable selection to identify variables to be included in a final model, even if the initial list of variables to consider are informed by previous research. This will allow a parsimonious model to be chosen. Also, the authors should explain what previous research their initial list is based upon. The odds ratios quoted should then be from the final selected model.

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	5.There is lack of clarity in terms of what the six categories of income and six categories of social class represent, since they are just listed in Table 3 as numbers. I would recommend that the authors describe the categories in more detail. 6. I am surprised to see the footnote to Table 3 which explains how a variable was omitted due to co-linearity, since there is no mention in the methods section of assessing variables for co-linearity or excluding them on the basis of co-linearity. The authors should revise the methods section to include an explanation of the approach taken in this regard. 7.The authors comment that the likelihood of utilising a statin did not exactly follow the order of prescribing priority, and they appear to base this conclusion on the point estimates of odds ratios obtained from the logistic regression model. Relying on the point estimates alone can be misleading, and the authors should also take note of the 95% confidence intervals for the odds ratios, many of which overlap. The unexpected ordering of odds ratios may well be due to the numbers being small in some categories of indication for statin, leading to wide confidence intervals, and the disparity in ordering should not be over-interpreted. 8. For completion, table 2 could do with actual numbers to accompany the percentages summarised. 9. Several of the variables included in the regression model are not statistically significant, as Table 3 illustrates, again emphasizing why a variable selection method should be applied to achieve a parsimonious model.

REVIEWER	Henrik Støvring Department of Public Health Aarhus University Denmark
REVIEW RETURNED	02-Oct-2017

GENERAL COMMENTS	The paper in general has a well-defined rationale and aim: Estimate the prevalence of statin use among persons aged >50 in Ireland and relate the prevalence to an indication hierarchy and various individual characteristics (sex, age, etc). The data have been collected in a face-to-face computer-aided personal interview at home, and it appears to have good validity, also when compared with external sources such as pharmacy data. The statistical analysis is generally transparent and clear to follow, although I have a couple of somewhat minor comments: Only ORs are accompanied by 95% CIs - I would think it preferable that prevalences were also reported with CIs. Not least, because prevalences are the main outcomes. Authors could consider using splines to report relationships with age or cholesterol levels, since these are in essence continuous variables. A couple of times authors refer to a bell-curve shape. This has in statistics become somewhat synonymous with the normal distribution shape, which is perhaps a distracting connotation here.

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	Further, a bell-curve is to me by definition strictly symmetric in shape, which I am not sure actually matches the verbal description provided by authors. Please rephrase. My final comments concern the discussion, where authors in the Strengths and Limitations state that their study contributes useful information regarding "...the patterns by which these drugs are prescribed." (p11, l33-5) This does not square with the stated objective, and indeed I think authors would need longitudinal data to study patterns. All other places authors make a clear point that their data are indeed cross-sectional and should be interpreted as such. The main weakness of the paper is indeed the fact that it is cross-sectional, which precludes analyses of changes and trends. Yet, at the same time the main contribution is to look at an important public health issue, use of statin, by use of a survey. This provides an important supplement to a field, which has otherwise predominantly used prescription registries as the main data source.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1. This study described the prevalence of statin utilization by people aged over 50 in Ireland and explored the factors associated with the likelihood of statin use
for primary prevention of CVD. The research question is clear and interesting.

Resposne: Thank you for your review of our paper and for your helpful comments, which we address below.

2. The authors are suggested to develop more clinical and political implications from the empirical results by comparing the findings and other publications or other ways.

Resposne: We agree that our paper has clinical and political implications. In our opinion, the most significant finding is that a large proportion of statins were used by people who did not have established CVD. We now have expanded on the implications of this and how it ties in to the current debate on appropriateness of statin prescribing in primary prevention in our conclusion. In particular we have added the following:

“There have been concerns about the medicalisation of risk factors such as mild hypercholesterolaemia. (44) Various commentators have pointed out that the benefits of prescribing a medicine must outweigh the harms (45) and that the budget impact of thresholds for treatment needs to be considered. (46) However, uncertainties abound when deciding upon cost-effective treatment thresholds. (47, 48)”

and

“The debate on the appropriate use of statins for primary prevention of CVD is on-going and highly topical. (17, 42, 50-53) At the heart of this debate is the question as to whether the benefits of taking statins outweigh the harms and costs for patients in the primary prevention category. The first step

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towards answering this question is to consider current utilisation and indication for use, as we have done, which provide important contextual information for the debate on statin use."

Despite the addition of these statements, we are nonetheless also wary of making claims in the paper that are beyond the scope of our cross-sectional analysis. In another study, yet to be completed, we are examining attitudes and behaviours of physicians who prescribe statins. We hope that this second paper will build on and complement our findings here and will allow us to more deeply consider the implications for clinicians in their day-to-day prescribing.

3. This study used TILDA data, which collects data on a nationally representative sample of community living adults aged over 50 in Ireland. It found that the odds of statin usage increased according to age. How about the usage in adults aged less than 50 in Ireland or other countries based on other studies?

Resposne: TILDA is a longitudinal study focusing on those aged 50 and over in Ireland. Wave 1 data collection included only 329 participants who were aged less than 50 years and this relatively small sub-sample was not adequate to undertake an analysis of under 50s. In fact, we are not aware of any suitable dataset for Ireland that would allow such an analysis. Moreover, the aim of our study was to examine statin use in over-50s and, as a result, these younger participants were excluded from our analysis. We agree that it would be interesting to examine the use of statins in younger patients, but this was not the focus of our study and in any case we are limited by the data available. A recent US Preventive Task Force (USPTF) (Bibbins-Domingo et al. 2016) recommendation statement found there was insufficient evidence to screen children and teens for lipid disorders and that those aged 40 to 75 were most likely to benefit from statin treatment. The USPTF found insufficient evidence that screening for dyslipidaemia before the age of 40 had an effect on short or long-term CVD outcomes. The USPTF found no studies that evaluated the effects of screening vs. no screening, treatment vs. no treatment, or delayed vs. earlier treatment in adults in this age group. The USPSTF found 4 trials of statin use for primary prevention that enrolled patients younger than 40 years. However, results were not reported separately for this age group.

4. In terms of the results about socioeconomic factors, the conflicting findings about statin use and socio-economic factors have been reported in studies from other countries. The authors merely addressed the potential reason – differences in access and entitlements within health systems, however, the readers may not know what are the differences and how the differences might contributed to the different findings.

Resposne: We have expanded our explanation on the differences in socio-economic factors and described and referenced the following factors on page 13: reimbursement regulation; types of insurance cover; clinical guideline recommendations; local medical and patient culture; political contexts and difference in demand from patients in differing socio-economic groups. In particular, we now state the following:

"Conflicting findings about statin utilisation and socio-economic factors have been reported in studies from other countries.(4, 10, 11, 20, 28, 29) These differences may be a result of differences in access and entitlements within health systems, as well as differing social, political and cultural contexts.(32) Countries may vary in reimbursement regulation,(1, 28, 29) type of insurance cover (such as Medicaid, Medicare and private insurance in the US),(11) clinical guideline recommendations,(14) local medical and patient culture, as well as differences in demand from patients in differing socio-economic groups.(1, 29)"

5. This study found that controlling for diagnostic indication, someone receiving five or more medicines would be more likely to receive a statin. Polypharmacy situation exists in patients taking statins, what are the implications (ore suggestions) about this situation?

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Resposne: Our study observed an association between polypharmacy and statin use. The reasons for this association are not clear and further work would need to be done in the context of statins. In a separate qualitative analysis, we have interviewed GPs and patients about statin use and it is possible this work, once completed, will shed some light on the association.

Factors contributing to polypharmacy, in general, include the growing prevalence of multi-morbidity and the use of single condition-focused treatment guidelines, but as our models accounted for diagnostic indication, it would seem unlikely this is the reason. We have also controlled for number of GP visits, so increased access to the doctor would seem an unlikely reason too. It is possible there are treatment decision heuristics at play.

As a result of your comment, we have searched for papers on the association between polypharmacy, potentially inappropriate prescribing and statins. We found some evidence of an association between polypharmacy and statin use or adherence to statin therapy. One paper found that patients subject to polypharmacy were less likely to be adherent to statins and other medications. We have added this information to the section entitled 'Polypharmacy' on page 14. In particular, we now state:

"Some studies have found an association between polypharmacy and increased likelihood of statin use (36, 37) and adherence to statins, (38, 39) while others found that people subject to polypharmacy were less likely to adhere to medicines, including statins. (40) Further qualitative research is recommended to explore this finding."

Overall, however, the question over doctors' decision making processes remains. For example, do doctors find it more acceptable to prescribe statins to patients who are already on a number of drugs? Unfortunately this current paper can merely make the observation that this is happening and further qualitative research is necessary to explain the reasons why. Nonetheless our finding is an important one in the context of the literature on statin utilisation.

Reviewer: 2

(1) The study is reasonably well designed. Recall bias, as outlined by the authors, is a concern. The author points out that good agreement has been previously demonstrated by cross referencing with pharmacy dispensing records. Multivariate logistic regression is an appropriate statistical method to evaluate statin utilization with associated variables.

Resposne: Thank you for your review of our paper and for your helpful comments, which we address below.

(2) It is unclear how the TILDA survey weights were calculated. More information should be provided - perhaps in the supplemental material.

Resposne: We have now explained the estimation of the weights used in Appendix 2.2: Estimation of the Health Assessment Survey Weights.

(3) It is not clear why the diagnostic category 'peripheral arterial disease' is not included. Most research studies evaluating the uptake of statins in the community would include this important category and this should have been included in the CAPI. It is stated as a weakness but I suggest that the author elaborate on why it is not included.

Resposne: The reviewer is correct that the diagnostic category 'peripheral arterial disease' (PAD) is an important category and it is a limitation that it was not included. PAD is a broad term describing

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diseases of the blood vessels outside of the heart and brain caused by inflammation, atherosclerosis and thrombus. However, as this paper was based on a secondary analysis of Wave 1 TILDA data, we were limited to the data already collected. The diagnostic hierarchy was created using the information gleaned from a computer assisted personal interview (CAPI) used in Wave 1 TILDA data collection. During the CAPI, participants were asked if a doctor had ever diagnosed them with the following CVD related conditions; 'high blood pressure or hypertension'; 'angina'; 'heart attack'; 'congestive heart failure'; 'stroke'; 'mini-stroke'; 'high cholesterol'; 'heart murmur'; 'any other heart trouble' or; 'none of these'. No further detail was included that would allow us to classify a participant as having PAD, therefore, it was considered the best option to exclude the category and state this clearly in our 'Strengths and Limitations' section as follows:

"Also, the diagnostic category 'Peripheral Arterial Disease' could not be ascertained due to limitations of the data gathered in TILDA."

(4) Some P-values in table 3 are recorded as 0.00. I am uncertain what this means. Either clarify or correct the P-values. The authors should also state in their methods and table legends what P-value they deem to be significant.

Resposne: We now report p-values to three decimal places and use "<0.000" (instead of 0.000) to indicate a p-value of less than 0.000 e.g. 0.0002. We now also state as a footnote to Table 3 that:

"Note: The model is a stepwise (backward selection) multivariable binary logit model, applying a 10% significance level for removal. This means that only variables found to be statistically significant at the 10% level are included in the final model."

Reviewer: 3

1. The authors refer to using a 'multivariate logistic regression model' for analysis, however it appears that what was actually used was a 'multivariable logistic regression model' i.e. a logistic regression model including several explanatory variables. I suggest that the authors amend the wording accordingly.

Resposne: Thank you for your review of our paper. We hope we have addressed all of your comments. Yes, it is correct that we have estimated a multivariable logistic regression model and we have corrected the terminology throughout the manuscript.

2. The last sentence of the second paragraph in the 'Background' section is confusing and I recommend the authors review and revise it. In particular, why are two recommended cholesterol levels and two recommended lipoprotein levels stated? To what groups do the two levels relate to?

Resposne: We agree this sentence is confusing. The 2007 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice recommend that… "In the highest risk subjects, especially those with clinically established CVD and patients with diabetes….
The treatment goals should be … total cholesterol of <4.5 mmol/l, with an option of <4mmol/l if feasible, and LDL cholesterol<2.5mmol/l with an option of <2mmol/l if feasible" (page 2397). For clarity, we have now removed the lower levels of TC and LDL.

3. The authors state that the study used cross-sectional data from 'the baseline wave' of TILDA. Can they please clarify what they mean by 'baseline wave' ?

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Resposne: Our use of the term ‘baseline wave’ was confusing here. TILDA data, to date, have been gathered across four waves. The first wave of data was collected between 2009-2011 and it is this data we use in our analysis. We have changed the term ‘baseline wave’ to ‘Wave 1’ throughout the document to clarify this.

4. The authors appear to have fitted a multivariable logistic regression model for determining the effect of various factors on statin utilisation without applying any statistical approach to choosing which factors should be included in the model. They state that the 'choice of variables included in the model was influenced by previous research'. It would be beneficial to use a statistical approach such as stepwise variable selection to identify variables to be included in a final model, even if the initial list of variables to consider are informed by previous research. This will allow a parsimonious model to be chosen. Also, the authors should explain what previous research their initial list is based upon. The odds ratios quoted should then be from the final selected model.

Resposne: Thank you for your suggestion. We have now re-estimated our multivariable logistic regression model using a stepwise (backward selection) approach. In particular, we applied a 10% significance level for removal, but also tested the robustness of our findings by applying a 5% significance level for removal, as well as by estimating a number of backward stepwise models with 5% and 10% significance levels for removal and addition. Overall our main findings were robust across these different approaches. As suggested by the reviewer, the statistical approach to model selection now adopted in the paper provides a parsimonious model which is the one we now discuss.

Finally in relation to this comment, we now explain what previous research our initial list of variables is based upon in the section entitled “Factors associated with statin utilisation”.

5. There is lack of clarity in terms of what the six categories of income and six categories of social class represent, since they are just listed in Table 3 as numbers. I would recommend that the authors describe the categories in more detail.

Resposne: We now describe the income and social class categories in Table 1 and have extended the description and derivation of the categories from the TILDA CAPI in Appendix 2.

6. I am surprised to see the footnote to Table 3 which explains how a variable was omitted due to co-linearity, since there is no mention in the methods section of assessing variables for co-linearity or excluding them on the basis of co-linearity. The authors should revise the methods section to include an explanation of the approach taken in this regard.

Resposne: This footnote has been removed and the SCORE analysis is now clarified in the main text in the Results section. In particular, we now state that:

“In a separate multivariable model using the subsample of those without CVD or diabetes whose LDL and/or TC levels were above the recommended thresholds, SCORE risk category was not found to be statistically significantly related to taking a statin (results not presented).”

7.The authors comment that the likelihood of utilising a statin did not exactly follow the order of prescribing priority, and they appear to base this conclusion on the point estimates of odds ratios obtained from the logistic regression model. Relying on the point estimates alone can be misleading, and the authors should also take note of the 95% confidence intervals for the odds ratios, many of which overlap. The unexpected ordering of odds ratios may well be due to the numbers being small in some categories of indication for statin, leading to wide confidence intervals, and the disparity in ordering should not be over-interpreted.

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Resposne: We now state in the Discussion: Key Results section that:

“However, it should be noted that this may be due to the numbers being small in some indication categories, leading to wide confidence intervals, and thus the disparity in ordering should not be over-interpreted”

while in the Indication Hierarchy sub-section in the Discussion we add:

“though again we acknowledge the caveat that this may be due to small numbers for some indication categories”.

8. For completion, table 2 could do with actual numbers to accompany the percentages summarised.

Resposne: We are not entirely sure what specifically this comment relates to. We would note that the percentages included in Table 2 are calculated/based on numbers reported in the table e.g. 74.0% of those with MI are taking statins and this is calculated using numbers reported i.e. 185/250. We are happy to revisit this comment if necessary or if we have misunderstood the comment. We would also note that following a comment by another reviewer, we have now added 95% CIs for all of the estimated prevalences in this table.

9. Several of the variables included in the regression model are not statistically significant, as Table 3 illustrates, again emphasizing why a variable selection method should be applied to achieve a parsimonious model.

Resposne: We have, as suggested, now applied a statistical approach to model selection and used a stepwise (backward selection) approach for the multivariable logistic regressions, applying a 10% significance level for removal. Thus, all variables included in the final model are statistically significant at a 10% level of significance. All bar Social Class (Farmers) are statistically significant at a 5% level of significance.

Reviewer: 4

The paper in general has a well-defined rationale and aim: Estimate the prevalence of statin use among persons aged >50 in Ireland and relate the prevalence to an indication hierarchy and various individual characteristics (sex, age, etc). The data have been collected in a face-to-face computer-aided personal interview at home, and it appears to have good validity, also when compared with external sources such as pharmacy data. The statistical analysis is generally transparent and clear to follow, although I have a couple of somewhat minor comments:

Resposne: Thank you for reviewing our paper and for your helpful comments. We hope that we have addressed all issues raised below to your satisfaction.

Comment: Only ORs are accompanied by 95% CIs - I would think it preferable that prevalences were also reported with CIs. Not least, because prevalences are the main outcomes.

Resposne: We have now added 95% CIs for all prevalences reported in Table 2 and in Tables A3.1 and A3.2 in Appendix 3.

Comment: Authors could consider using splines to report relationships with age or cholesterol levels, since these are in essence continuous variables.

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Resposne: We did consider the use of splines for age but this did not add any additional useful insights to our analysis and thus we chose to report the simpler model without splines.

Comment: A couple of times authors refer to a bell-curve shape. This has in statistics become somewhat synonymous with the normal distribution shape, which is perhaps a distracting connotation here. Further, a bell-curve is to me by definition strictly symmetric in shape, which I am not sure actually matches the verbal description provided by authors. Please rephrase.

Resposne: The reference to a bell-curve has been removed.

Comment: My final comments concern the discussion, where authors in the Strengths and Limitations state that their study contributes useful information regarding "...the patterns by which these drugs are prescribed." (p11, l33-5) This does not square with the stated objective, and indeed I think authors would need longitudinal data to study patterns. All other places authors make a clear point that their data are indeed cross-sectional and should be interpreted as such.

Resposne: Thank you for this observation. We now realise that the use of the term 'pattern' could be confusing. We have removed this term on pages 8, 11 and 14.

Comment: The main weakness of the paper is indeed the fact that it is cross-sectional, which precludes analyses of changes and trends. Yet, at the same time the main contribution is to look at an important public health issue, use of statin, by use of a survey. This provides an important supplement to a field, which has otherwise predominantly used prescription registries as the main data source.

Resposne: Thank you. We agree that cross-sectional data has its limitations but that our paper offers a good insight into real life usage that can supplement data from prescription registries and provides motivation for further research.

1. Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW, García FA, et al. Statin use for the primary prevention of cardiovascular disease in adults: US Preventive Services Task Force recommendation statement. Jama. 2016;316(19):1997-2007.

References

Finnikin, S., Ryan, R. & Marshall, T. 2017. Statin initiations and QRISK2 scoring in UK general practice: a THIN database study. Br J Gen Pract, bjgp17X693485.

Bibbins-Domingo, K., Grossman, D. C., Curry, S. J., Davidson, K. W., Epling, J. W., García, F. A., Gillman, M. W., Kemper, A. R., Krist, A. H. & Kurth, A. E. 2016. Statin use for the primary prevention of cardiovascular disease in adults: US Preventive Services Task Force recommendation statement. Jama, 316, 1997-2007.

VERSION 2 – REVIEW

REVIEWER	Stephen Horgan Morristown Medical center U.S.A.
REVIEW RETURNED	17-Nov-2017

GENERAL COMMENTS	Please add a line in the methods regarding participant consent and ethics approval.

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REVIEWER	Dr Andrea L Jorgensen University of Liverpool, UK
REVIEW RETURNED	22-Nov-2017

GENERAL COMMENTS	1. It is important to include effect estimates and corresponding 95% CIs in the results section of the abstract when you are describing factors significantly associated with outcome. Please add these. 2. In the background section, second line of the second paragraph, please make it clear whether diabetes and familial hypercholesterolaemia are classified as primary preventions - currently it is ambiguous. 3. In the analysis section you state "The likelihood that an individual was taking a statin was estimated using a multivariable logistic regression model, controlling for cardiovascular indication and socio-demographic factors". This is incorrect. What the multivariable model will give you is, for each covariate, the odds of statin use for one category of the covariate relative to another category, adjusting for all other covariates in the model. Please correct how you describe the analysis. 4. In the analysis section it is also important that you describe what variables you included in the initial model prior to stepwise selection, and how you decided on those initial variables. 5. When describing your variable selection method what do you mean by 'applied a 10% significance level for removal'. Typically when using backward elimination you remove the variable with the greatest p-value, one at a time, until all remaining variables have a p-value less than a given threshold. Please clarify what you mean here. 6.The paragraph The choice of variables considered in the model was influenced by previous research, some of which had found significant associations between statin use and educational status, (28) gender, (14, 20, 28) age, (4, 29) socio-economic status, (10, 20, 29) number of GP visits, (10) and indication, (10, 14). Other research found non-significant associations between statin use and marital status. (28) A stepwise (backward selection) approach was used, applying a 10% significance level for removal, meaning that only variables found to be statistically significant at the 10% level were included in the final model" in the results section belongs in the methods section (analysis subsection). Also, the final sentence is duplicated from the methods section and should be deleted. 7. In the results section you state "Table 3 presents the estimated odds ratios from a multivariable logistic regression of utilising a statin controlling for a wide range of variables including". This is a little unclear, and suggest you change to "Table 3 presents the odds ratios obtained for each variable included in the final multivariable logistic regression model, adjusting for all other variables in the model." 8. Some of the results quoted in the results section are not consistent with Table 3. For example, you state that living alone is

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	not significantly associated with outcome, however the p-value in the final model is <0.05. 9. In table 3, why are only categories 1 and 4 of Social Class reported ? Either all categories or not categories of a single variable should be retained in the final model - you cannot just remove some categories, since they all relate to the same variable. Please re-fit the model, but this time retaining all categories of a single variable if it is statistically significant. The same may be true for the indication variable (I cannot see the IHD category in table 3) and 'living with' status. 10. In the 'key results' section of the Discussion section the sentence "Polypharmacy, frequency of GP visits and living arrangements were also significantly associated with the likelihood of taking a statin, while controlling for indication" is not entirely correct, since other variables were also controlled for eg age, social class. 11. I do not understand the justification given for different findings in terms of effect of medical card eligibility (Interpretation section - "Medical card eligibility varies significantly across age groups in this cohort and this may account for this difference." Can you please explain this with more clarity. 12. In the 'Number of GP visits' subsection of the 'Interpretation' section, you state "In their study of factors influencing...". Who's study are you referring to ? Please clarify. 13. In table 1, please clarify that income levels are per annum. 14. In the footnotes of Table 3, it would be more correct to call the model 'logistic' than 'logit'.

REVIEWER	Henrik Støvring Department of Public Health Aarhus University Denmark
REVIEW RETURNED	13-Nov-2017

GENERAL COMMENTS	My concerns have been addressed satisfactorily - nothing further to add.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 4 Henrik Støvring

My concerns have been addressed satisfactorily - nothing further to add.

Resposne: Thank you for your review.

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Reviewer: 2 Stephen Horgan

Please add a line in the methods regarding participant consent and ethics approval.

Thank you for your review. We have now added the following line at the outset of the Methods section: “Ethical approval for the TILDA study was received from the Trinity College Research Ethics Committee and all participants provided written informed consent. As our study comprised secondary analysis of TILDA data, which is anonymised, further participant consent or ethical approval was not required.”

Reviewer: 3 Dr Andrea L Jorgensen

1. It is important to include effect estimates and corresponding 95% CIs in the results section of the abstract when you are describing factors significantly associated with outcome. Please add these.

Resposne: Thank you for your review. We have now included estimated odds ratios and their associated 95% CIs in the results section of the abstract.

2. In the background section, second line of the second paragraph, please make it clear whether diabetes and familial hypercholesterolaemia are classified as primary preventions - currently it is ambiguous.

Resposne: We have now clarified that diabetes and familial hypercholesterolaemia are classified as primary prevention.

3. In the analysis section you state "The likelihood that an individual was taking a statin was estimated using a multivariable logistic regression model, controlling for cardiovascular indication and socio-demographic factors". This is incorrect. What the multivariable model will give you is, for each covariate, the odds of statin use for one category of the covariate relative to another category, adjusting for all other covariates in the model. Please correct how you describe the analysis.

Resposne: We now state “A multivariable logistic regression model of whether an individual was taking a statin or not was estimated, controlling for cardiovascular indication and socio-demographic factors. This provides, for each covariate, the odds of statin use for one category of the covariate relative to another category, adjusting for all other covariates in the model.”

4. In the analysis section it is also important that you describe what variables you included in the initial model prior to stepwise selection, and how you decided on those initial variables.

Resposne: We now state in the analysis section that: “The choice of variables included in the initial model was influenced by the data available in TILDA, as well as previous research, some of which had found significant associations between statin use and educational status,(27) gender,(14, 20, 27) age,(4, 28) socio-economic status,(10, 20, 28) number of GP visits,(10), polypharmacy, (37, 38) and indication,(10, 14). Other research found non-significant associations between statin use and marital status.(27)”

5. When describing your variable selection method what do you mean by 'applied a 10% significance level for removal'. Typically when using backward elimination you remove the variable with the

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greatest p-value, one at a time, until all remaining variables have a p-value less than a given threshold. Please clarify what you mean here.

Resposne: We now clarify this is follows: “In particular, we estimated a stepwise (backward selection) model and applied a 10% significance level for removal. This means that we removed the variable with the greatest p-value, one at a time, until all remaining variables had a p-value less than the 10% threshold.”

6.The paragraph The choice of variables considered in the model was influenced by previous research, some of which had found significant associations between statin use and educational status, (28) gender, (14, 20, 28) age, (4, 29) socio-economic status, (10, 20, 29) number of GP visits, (10) and indication, (10, 14). Other research found non-significant associations between statin use and marital status. (28) A stepwise (backward selection) approach was used, applying a 10% significance level for removal, meaning that only variables found to be statistically significant at the 10% level were included in the final model" in the results section belongs in the methods section (analysis subsection). Also, the final sentence is duplicated from the methods section and should be deleted.

Resposne: We have moved this paragraph to the Methods Section (Analysis Sub-section) and deleted the final sentence as suggested.

7. In the results section you state "Table 3 presents the estimated odds ratios from a multivariable logistic regression of utilising a statin controlling for a wide range of variables including". This is a little unclear, and suggest you change to "Table 3 presents the odds ratios obtained for each variable included in the final multivariable logistic regression model, adjusting for all other variables in the model."

Resposne: We have changed this sentence as suggested.

8. Some of the results quoted in the results section are not consistent with Table 3. For example, you state that living alone is not significantly associated with outcome, however the p-value in the final model is <0.05.

Resposne: We have now carefully checked that all results quoted in the results section are consistent with Table 3. For example, we have added the following sentence to the results section: “People who were living with a spouse or partner were more likely than those living alone to be taking a statin (OR 1.35; CI 1.10 to 1.65).”

9. In table 3, why are only categories 1 and 4 of Social Class reported ? Either all categories or not categories of a single variable should be retained in the final model - you cannot just remove some categories, since they all relate to the same variable. Please re-fit the model, but this time retaining all categories of a single variable if it is statistically significant. The same may be true for the indication variable (I cannot see the IHD category in table 3) and 'living with' status.

Resposne: This has now been corrected to include all categories of variables found to be statistically significant.

10. In the 'key results' section of the Discussion section the sentence "Polypharmacy, frequency of GP visits and living arrangements were also significantly associated with the likelihood of taking a statin, while controlling for indication" is not entirely correct, since other variables were also controlled for eg age, social class.

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Resposne: We have changed the sentence to: ‘Polypharmacy, frequency of GP visits and living arrangements were also significantly associated with the likelihood of taking a statin, while controlling for all other variables in the model.’

11. I do not understand the justification given for different findings in terms of effect of medical card eligibility (Interpretation section - "Medical card eligibility varies significantly across age groups in this cohort and this may account for this difference." Can you please explain this with more clarity.

Resposne: We have now removed this statement.

12. In the 'Number of GP visits' subsection of the 'Interpretation' section, you state "In their study of factors influencing...". Who's study are you referring to ? Please clarify.

Resposne: We have changed the sentence to: “In their study of factors influencing the prescribing of statins in the UK, Wu et al. (10) found that statin prescribing increased with number of blood pressure measurements, a proxy for GP visits and perception of CVD risk.”

13. In table 1, please clarify that income levels are per annum.

Resposne: We have now clarified in Table 1 that income is per annum.

14. In the footnotes of Table 3, it would be more correct to call the model 'logistic' than 'logit'.

Resposne: We have now corrected this term.

VERSION 3 – REVIEW

REVIEWER	Andrea L Jorgensen University of Liverpool, UK
REVIEW RETURNED	15-Dec-2017

GENERAL COMMENTS	I am happy that all comments from my previous review have been addrssed, and would recommend that the paper is accepted for publication. However, please ask the authors to address the following: Abstract – results section, where you are quoting OR for factors with more than two levels please make it clear what the assumed baseline level was (i.e. age categories and GP visits).

VERSION 3 – AUTHOR RESPONSE

Reviewer: 3

I am happy that all comments from my previous review have been addressed, and would recommend that the paper is accepted for publication. However, please ask the authors to address the following:

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Abstract – results section, where you are quoting OR for factors with more than two levels please make it clear what the assumed baseline level was (i.e. age categories and GP visits).

Resposne: We have now included the base categories for all categorical variables with more than two levels in the Abstract.

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