PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Are primary care factors associated with hospital episodes for adverse drug reactions? A national observational study
AUTHORS	McKay, Ailsa; Newson, Roger; Soljak, Michael; Riboli, Elio; Car, Josip; Majeed, Azeem

VERSION 1 - REVIEW

REVIEWER	Narjes Saheb Sharif-Askari Universiti Sains Malaysia, Penang, Malaysia
REVIEW RETURNED	13-Aug-2015

GENERAL COMMENTS	Comments to the Author General comments; In this manuscript entitled “Are primary care factors associated with hospital episodes for adverse drug reactions? A national observational study ”, the authors identified primary care factors associated with the hospital admissions for adverse drug reactions. This study is novel and it has two important distinctions: Firstly, to control confounding factors, the authors employed some modern statistical procedures. Secondly, it uses large sample size with national coverage across the UK. Specific comments; 1- Please rewrite the following sentences from the introduction and add citations to them. ‘’Occurrence is influenced by prescribing practice, drug monitoring, drug interactions and patient factors. They are caused by both over-the-counter and prescription medications.’’ 2- Please reconsider the following sentence. This sentence is repeated and has no citation. “Their continuation is anticipated as the population continues to age.” 3-In the study objectives, there was no report of association of patient factors with ADR-related hospital admission; while patient’s age, sex, ethnicity, and patient morbidity status was extensively studied. This can create some confusion among readers. I think the word patient factors should be added beside other study objectives such as practice demographics, measures of primary care supply, and performance indicators. 4- In the ethics statement, you reported that no ethical approval was required for your study. Please give more details or name any hospital or institution that allows such practice.

	Any research project involving human participants, including the use of existing records for secondary analysis of personal data, irrespective of whether or not the data are publicly available, whether or not the data originally collected are intended for research purposes and whether the personal data from existing records will be extracted for secondary analysis, should need ethical approval prior to collection or use of data. Please note that exclusion from ethical approval will only apply to anonymous surveys for improving teaching and learning (not for research) exclusively for the university's internal usage. 5- Elaborate what you mean by the sentences in the lines 264-266, it can be confusing to the readers. "….., comparing ADR rates between the real-world scenario and a hypothetical scenario where that factor was at the base level for all subjects." 6- What do you mean by giving reference points to the predictors. Is table No.1 essential enough to be included in the study? 7- In Table No. 5, why is patient's age and sex not included in the patient population factor section. I think variables in table No.5 should be similar to the variables in table No.3. 8- Based on your findings, please explain more about the interventions which can be done to reduce the occurrence of ADR related hospitalization.

REVIEWER	Khedidja Hedna Institution of Medical and Health Sciences Division of Drug Research Linköping University Linköping Sweden
REVIEW RETURNED	17-Aug-2015

GENERAL COMMENTS	The paper "Are primary care factors associated with hospital episodes for adverse drug reactions? A national observational study" has the novelty to study the factors associated with ADRs out of hospital settings, which is rarely raised in the actual literature. While the paper is interesting, some points need to be discussed more, or clarified. - The definition of ADRs was based on ICD codes. This should be stated in the abstract. Moreover, this method to define ADRs is often criticised because of the low quality of coding of ADRs. More references should be added to discuss this aspect. This angle should also be considered when discussing the findings, such as the increase of ADRs with increased QOF. As the quality of monitoring of ADRs and their coding may be better with a better QOF. - Does the study exclude ADRs responsible of an emergency visit without hospital admission? - Regarding the national survey: for the variables PE 07 and PE08. It would be informative to include what is the answer rate to this survey. Who were included in the survey? - For the population ethnicity. Can the authors describe more what they mean by white? (Which ethnicities are included) - For the variable: GP with non UK qualifications is rather a very heterogeneous group. As it includes for example, both those

	graduated from other EU countries with a legislation and education close to the UK, and others from other continents. - For the discussion: o The effects of some variables on ADRs should be discussed more, such as the effect of the number of GPs on ADRs. If the reasoning of authors is followed, having less practitioners in the population would help to reduce occurrence of ADRs because of increased continuity of care. It is hard to draw a conclusion of the number of practitioner for an individual patient (continuity of care) based on the number of GPs/1000 patients. We may also think that having more GPs in the population would will allow them to improve the monitoring of medication safety and report more ADRs. o The results of the effects of age and sex on ADRs were not discussed. - Some general comments: o Please check that all abbreviations were defined while used the first time (e.g. TIA) o I suggest to define ADR as is stated by the WHO (ref 1), to report clearly that ADRs are occurring at normal doses (exclude overdose and under dosing). o It is not common to have the reference in examples between brackets. o Be consistent in the number of decimals of CI, and p-values when reporting results. o The conclusion in the abstract and the manuscript should be similar. Please check and correct. o The statistics were clearly described. However, being not very familiar with some analysis, I asked for a statistician review.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name Narjes Saheb Sharif-Askari
Institution and Country Universiti Sains Malaysia, Penang, Malaysia
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
Comments to the Author
General comments; In this manuscript entitled "Are primary care factors associated with hospital episodes for adverse drug reactions? A national observational study ", the authors identified primary care factors associated with the hospital admissions for adverse drug reactions.
This study is novel and it has two important distinctions: Firstly, to control confounding factors, the authors employed some modern statistical procedures. Secondly, it uses large sample size with national coverage across the UK.

Specific comments;
1- Please rewrite the following sentences from the introduction and add citations to them.
''Occurrence is influenced by prescribing practice, drug monitoring, drug interactions and patient factors. They are caused by both over-the-counter and prescription medications.''

These sentences have been rewritten and references included (lines 80-83).

2- Please reconsider the following sentence. This sentence is repeated and has no citation.
"Their continuation is anticipated as the population continues to age."

This sentence has been removed.

3-In the study objectives, there was no report of association of patient factors with ADR-related hospital admission; while patient's age, sex, ethnicity, and patient morbidity status was extensively studied. This can create some confusion among readers. I think the word patient factors should be added beside other study objectives such as practice demographics, measures of primary care supply, and performance indicators.

This has been added (line 112).

4- In the ethics statement, you reported that no ethical approval was required for your study. Please give more details or name any hospital or institution that allows such practice.
Any research project involving human participants, including the use of existing records for secondary analysis of personal data, irrespective of whether or not the data are publicly available, whether or not the data originally collected are intended for research purposes and whether the personal data from existing records will be extracted for secondary analysis, should need ethical approval prior to collection or use of data. Please note that exclusion from ethical approval will only apply to anonymous surveys for improving teaching and learning (not for research) exclusively for the university's internal usage.

The following statement has been added (lines 121-127):

This was a secondary use of administrative data. The only patient-level data used was Hospital Episode Statistics (HES) data provided by provided by the Health and Social Care Information Centre (HSCIC). The remainder of the data were publicly available practice-level data from HSCIC (http://www.hscic.gov.uk/home). HSCIC provides ethical approval as part of the process of approving release of the HES data. This is also the case with other published UK analyses which have used HES data.

5- Elaborate what you mean by the sentences in the lines 264-266, it can be confusing to the readers. "….., comparing ADR rates between the real-world scenario and a hypothetical scenario where that factor was at the base level for all subjects."

Further explanation has been added (lines 283-289).

6- What do you mean by giving reference points to the predictors. Is table No.1 essential enough to be included in the study?

Table 1 describes the baseline and additional reference points used in the analyses. The baseline points are the hypothetical scenario used to calculate the PAFs, as per the information added at lines 283-289.

7- In Table No. 5, why is patient's age and sex not included in the patient population factor section. I think variables in table No.5 should be similar to the variables in table No.3.

Table 3 is used to describe the study sample. Patient age and sex are not included in Table 5 as models were fitted to the ADR data for each combination of practice, age and sex (see lines 265-269). Episode rates by age and sex are displayed in Table 4.

8- Based on your findings, please explain more about the interventions which can be done to reduce the occurrence of ADR related hospitalization.

We feel this would be difficult without a developed understanding of the factors underlying the associations identified. A sentence stating this has been added (lines 515-16).

Reviewer: 2

Reviewer Name Khedidja Hedna
Institution and Country Institution of Medical and Health Sciences
Division of Drug Research
Linköping University
Linköping
Sweden
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
Dear Editor,
The paper “Are primary care factors associated with hospital episodes for adverse drug reactions? A national observational study” has the novelty to study the factors associated with ADRs out of hospital settings, which is rarely raised in the actual literature. While the paper is interesting, some points need to be discussed more, or clarified.
- The definition of ADRs was based on ICD codes. This should be stated in the abstract. Moreover, this method to define ADRs is often criticised because of the low quality of coding of ADRs. More references should be added to discuss this aspect. This angle should also be considered when discussing the findings, such as the increase of ADRs with increased QOF. As the quality of monitoring of ADRs and their coding may be better with a better QOF.

The use of ICD10 codes has been indicated in the abstract (lines 40-41). Further references and information regarding under-estimates of ADRs in HES data has been added to the discussion of limitations (lines 478-481).

Where factors that could reflect primary care quality have been noted to have potentially unexpected positive correlation with ADR episode rates, the possibility that they are associated with better identification and reporting of ADRs, rather than ADR occurrence, has been discussed (lines 421-424 and 446-449).

- Does the study exclude ADRs responsible of an emergency visit without hospital admission?

Yes, information indicating this has been added (lines 137-139).

- Regarding the national survey: for the variables PE07 and PE08. It would be informative to include what is the answer rate to this survey. Who were included in the survey?

This information has been added (lines 223-227).

- For the population ethnicity. Can the authors describe more what they mean by white? (Which ethnicities are included)

This information has been added (lines 246-247).

- For the variable: GP with non UK qualifications is rather a very heterogeneous group. As it includes for example, both those graduated from other EU countries with a legislation and education close to

the UK, and others from other continents.

Only non-UK qualification data are easily available for use. We have added this comment to the discussion of limitations (lines 489-90).

- For the discussion:
o The effects of some variables on ADRs should be discussed more, such as the effect of the number of GPs on ADRs. If the reasoning of authors is followed, having less practitioners in the population would help to reduce occurrence of ADRs because of increased continuity of care. It is hard to draw a conclusion of the number of practitioner for an individual patient (continuity of care) based on the number of GPs/1000 patients. We may also think that having more GPs in the population would will allow them to improve the monitoring of medication safety and report more ADRs.

These suggestions have been added (lines 421-424).

o The results of the effects of age and sex on ADRs were not discussed.

Please see Reviewer 1, point 7, above.

- Some general comments:
o Please check that all abbreviations were defined while used the first time (e.g. TIA)

We have aimed to define all abbreviations.

o I suggest to define ADR as is stated by the WHO (ref 1), to report clearly that ADRs are occurring at normal doses (exclude overdose and under dosing).

A comment to indicate this has been added (line 79)

o It is not common to have the reference in examples between brackets.

These references have been modified to be consistent with the rest.

o Be consistent in the number of decimals of CI, and p-values when reporting results.

The tables have been edited so that this is the case, except in the case of p-values so that the actual figures can be reported.

o The conclusion in the abstract and the manuscript should be similar. Please check and correct.

These have both been edited for consistency.

o The statistics were clearly described. However, being not very familiar with some analysis, I asked for a statistician review.

The study statistician (Dr R Newson) has reviewed all statistical comments.

VERSION 2 – REVIEW

REVIEWER	Khedidja Hedna Division of Drug Research Department of Medical and Health Sciences Linköping University Linköping Sweden
REVIEW RETURNED	18-Oct-2015

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.