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.

This paper was submitted to another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers’ comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

This paper received three reviews from its previous journal but one declined to publish her review.

ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Association of cannabis use with hospital admission and antipsychotic treatment failure in first episode psychosis: an observational study</th>
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<tbody>
<tr>
<td>AUTHORS</td>
<td>Patel, Rashmi; Wilson, Robin; Jackson, Richard; Ball, Michael; Shetty, Hitesh; Broadbent, Matthew; Stewart, Robert; McGuire, Philip; Bhattacharyya, Sagnik</td>
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VERSION 1 - REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Wayne Hall</th>
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<tr>
<td></td>
<td>University of Queensland</td>
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<tr>
<td>REVIEW RETURNED</td>
<td>10-Apr-2015</td>
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<table>
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<tr>
<th>GENERAL COMMENTS</th>
<th>This is an important paper that examines the effects of cannabis use on psychosis outcome in a prospective study of a large representative clinical sample of first episode psychoses (FEPs) in South London. It has the following strengths:</th>
</tr>
</thead>
<tbody>
<tr>
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<td>It reports data on a large sample of first episode cases of psychosis whose symptoms and treatment course are well documented in electronic clinical records that covers the population served by a large clinical health service in South London.</td>
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<td>2.</td>
<td>The outcomes of these cases have been followed for up to 5 years after their first admission, with a minimum of 1 year follow up for all study participants.</td>
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<td>3.</td>
<td>The electronic clinical records provide good measures of psychosis outcomes as reflected in the number of hospitalisations, days spent in hospital and number of changes in antipsychotic medication over the follow up period.</td>
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<tr>
<td>4.</td>
<td>The measure of cannabis use at first admission is reasonable but imperfect for reasons that are clearly acknowledged by the authors, namely, the use of text mining software to search clinical notes for any indications of cannabis use around the time of first admission. Under-reporting of cannabis use is likely and no data were consistently collected on the frequency of use. These limitations mean that the study is more likely to under- than over-estimate the strength of associations between cannabis use at first admission and poorer outcomes of psychosis during the follow up period.</td>
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5. The study is able to throw some light on the possible mechanisms for the observed adverse effects of cannabis use at baseline on treatment outcomes in terms of assessing the indirect contribution of cannabis made by medication failures that, in turn, probably reflect a combination of reduced medication compliance and reduced medication effectiveness.

6. The study reports strong and plausible associations between indications of cannabis use reported in clinical notes around the time of first admission and the number and duration of hospitalisations, the number of different anti-psychotic drugs prescribed and the likelihood of being prescribed clozapine during the follow up period. These associations are substantial and they increase with the duration of follow up.

7. The data limitations are honestly acknowledged by the authors and their possible implications discussed e.g. the effects of multiple clinicians being involved in patient care; the uncertainty as to whether medications were changed after a proper trial of efficacy; and the probable under-estimation of whether cannabis use occurred and uncertainty about its frequency and persistence throughout the follow up period.

<table>
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<th>REVIEWER</th>
<th>Ana González-Pinto</th>
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<td>REVIEW RETURNED</td>
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**GENERAL COMMENTS**

This is a naturalistic study done to investigate whether cannabis use is associated with increased risk of relapse, and whether antipsychotic treatment failure, may mediate this effect in a large dataset of patients with first episode psychosis (FEP). The authors study a very large sample of FEP, using data mining. Natural language processing was used to detect the use of cannabis at admission. Almost 1000 patients were followed up to 5 years. The major finding of this elegant study is the association of cannabis use and treatment failure. And the association of cannabis use and more hospitalizations, mediated by antipsychotic failure.

There are some minor questions that should be considered:
1. Authors explain in the limitations that they it was not possible to systemically ascertain ongoing cannabis use in clinical records analysed in this study. They state that it may be that future long term outcomes were influenced by changes in cannabis use over time. This consideration should be explained more firmly, as it has been demonstrated that quitting cannabis improves functional outcome in FEP (González-Pinto et al., Schizophrenia Bulletin 2011).
2. The authors explain that 70% of patients continue using cannabis after 3 years of treatment. This percentage is high compared with other studies.
3. Authors consider that non compliance can influence the antipsychotic treatment failure. Non compliance can be related also with compulsoty admission. This point must be discussed (Barbeito S, et al. Cannabis use and involuntary admission may mediate long-term adherence in first-episode psychosis patients: a prospective longitudinal study. BMC Psychiatry. 2013).
4. As patients that use cannabis have more treatment failures, they are more frequently treated with clozapine. There is no association...
between clozapine use and cannabis in the multivariate logistic regression models. But it would be interesting to analyse whether use of clozapine diminished relapses in those patients that received it. I suggest that the authors report these analyses.

5. Other comments: in "what is already known" authors say "However the association of cannabis use with clinical outcomes in people with first episode psychosis is less well established". I consider that there are important data in the literature about the influence of continuing cannabis use in psychosis.

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1

Recommendation:

Comments:

This is an important paper that examines the effects of cannabis use on psychosis outcome in a prospective study of a large representative clinical sample of first episode psychoses (FEPs) in South London. It has the following strengths:

1. It reports data on a large sample of first episode cases of psychosis whose symptoms and treatment course are well documented in electronic clinical records that covers the population served by a large clinical health service in South London.

2. The outcomes of these cases have been followed for up to 5 years after their first admission, with a minimum of 1 year follow up for all study participants.

3. The electronic clinical records provide good measures of psychosis outcomes as reflected in the number of hospitalisations, days spent in hospital and number of changes in antipsychotic medication over the follow up period.

4. The measure of cannabis use at first admission is reasonable but imperfect for reasons that are clearly acknowledged by the authors, namely, the use of text mining software to search clinical notes for any indications of cannabis use around the time of first admission. Under-reporting of cannabis use is likely and no data were consistently collected on the frequency of use. These limitations mean that the study is more likely to underestimate than over-estimate the strength of associations between cannabis use at first admission and poorer outcomes of psychosis during the follow up period.

5. The study is able to throw some light on the possible mechanisms for the observed adverse effects of cannabis use at baseline on treatment outcomes in terms of assessing the indirect contribution of cannabis made by medication failures that, in turn, probably reflect a combination of reduced medication compliance and reduced medication effectiveness.

6. The study reports strong and plausible associations between indications of cannabis use reported in clinical notes around the time of first admission and the number and duration of hospitalisations, the number of different anti-psychotic drugs prescribed and the likelihood of being prescribed clozapine during the follow up period. These associations are substantial and they increase with the duration of follow up.

7. The data limitations are honestly acknowledged by the authors and their possible implications discussed e.g. the effects of multiple clinicians being involved in patient care; the uncertainty as to whether medications were changed after a proper trial of efficacy; and the probable under-estimation
of whether cannabis use occurred and uncertainty about its frequency and persistence throughout the follow up period.

/*We thank the reviewer for their supportive comments.*/

Reviewer: 2
Recommendation:
Comments:

This is a naturalistic study done to investigate whether cannabis use is associated with increased risk of relapse, and whether antipsychotic treatment failure, may mediate this effect in a large dataset of patients with first episode psychosis (FEP). The authors study a very large sample of FEP, using data mining. Natural language processing was used to detect the use of cannabis at admission. Almost 1000 patients were followed up to 5 years.

The major finding of this elegant study is the association of cannabis use and treatment failure. And the association of cannabis use and more hospitalizations, mediated by antipsychotic failure.

/*Thank you for your supportive comments*/

There are some minor questions that should be considered:

1. Authors explain in the limitations that they it was not possible to systemically ascertain ongoing cannabis use in clinical records analysed in this study. They state that it may be that future long term outcomes were influenced by changes in cannabis use over time. This consideration should be explained more firmly, as it has been demonstrated that quitting cannabis improves functional outcome in FEP (González-Pinto et al., Schizophrenia Bulletin 2011).

/*We agree that changes in cannabis use are likely to be associated with varying clinical outcomes. We acknowledge we were unable to investigate this but have updated the manuscript to refer to this helpful study.*/

2. The authors explain that 70% of patients continue using cannabis after 3 years of treatment. This percentage is high compared with other studies.

/*It is likely that variation in continuation or discontinuation of cannabis depends on a complex interaction of patient and environmental factors and we will update the manuscript to discuss this further.*/

3. Authors consider that non compliance can influence the antipsychotic treatment failure. Non compliance can be related also with compulsory admission. This point must be discussed (Barbeito S, et al. Cannabis use and involuntary admission may mediate long-term adherence in first-episode psychosis patients: a prospective longitudinal study. BMC Psychiatry. 2013).

/*This is an important point which we have discussed further.*/

4. As patients that use cannabis have more treatment failures, they are more frequently treated with clozapine. There is no association between clozapine use and cannabis in the multivariate logistic regression models. But it would be interesting to analyse whether use of clozapine diminished relapses in those patients that received it. I suggest that the authors so these analyses.
This is a very interesting question which merits further study. Unfortunately, we do not have sufficient data to perform this analysis, partly because of the small sample size of people started on clozapine and also because of limited temporal follow-up (as clozapine is usually initiated after failure of at least two other antipsychotics). However, we agree this is an important area to address and we have updated the manuscript to discuss this further and suggest options for future research.

5. Other comments: in "what is already known" authors say "However the association of cannabis use with clinical outcomes in people with first episode psychosis is less well established". I consider that there are important data in the literature about the influence of continuing cannabis use in psychosis.

"We agree that there are important data and this statement refers to the fact that there are relatively fewer studies investigating clinical outcomes in FEP compared to risk of developing psychosis in relation to cannabis use."

**VERSION 2 – REVIEW**

| REVIEWER | Wayne Hall  
| University of Queensland  
| Australia |
| I have a visiting appointment at Kings College London but have not worked with any of the authors. |
| REVIEW RETURNED | 16-Oct-2015 |

**GENERAL COMMENTS**

I remain of the view that the revised paper is important paper in documenting an association between cannabis use and psychosis outcome in a prospective study of a large representative clinical sample of first episode psychoses (FEPs) in South London.

The paper reports data on a large sample of first episode cases of psychosis whose symptoms and treatment course are well documented in electronic clinical records on a population served by a large clinical health service in South London. The clinical outcomes have been followed for up to 5 years after their first admission, with a minimum of 1 year follow up. The electronic clinical records provide valid measures of psychosis outcomes as reflected in the number of hospitalisations, days spent in hospital and number of changes in antipsychotic medication over the follow up period.

The measure of cannabis use at first admission is imperfect for reasons that are clearly acknowledged in the paper, namely, the use of text mining software to search clinical notes for any indications of cannabis use at first admission. This makes under-reporting of cannabis use likely, as reflected in the lower prevalence reported in this study than in other London studies of first episode psychoses. There were no data collected on the frequency of cannabis use at either baseline or during the follow up period. These limitations mean that the study is more likely to under- than over-estimate the strength of associations between cannabis use at first admission and poor clinical outcomes during the follow up period.

The study is also able to throw some light on the mechanisms for the observed association of cannabis use at baseline with treatment outcomes by assessing the indirect contribution of cannabis to poor
outcome via medication failures that, in turn, probably reflect a combination of reduced medication compliance and reduced medication effectiveness.

The data limitations are honestly acknowledged by the authors and their possible implications discussed e.g. the effects of multiple clinicians being involved in patient care; the uncertainty as to whether medications were changed after a proper trial of efficacy; and the probable under-estimation of whether cannabis use occurred and uncertainty about its frequency and persistence throughout the follow up period. These limitations are likely to have worked against finding associations between cannabis use at first admission and poor psychosis outcomes during follow up.

Given that the study is an observational one, critics can argue about whether these associations indicate that cannabis use is a cause (direct or indirect) of poor clinical outcomes. It is difficult to argue, however, that cannabis use is not associated with poorer clinical outcomes. This is an important contribution made by this study in a large cohort of first episode psychoses that warrants publication.

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<td>REVIEW RETURNED</td>
<td>02-Nov-2015</td>
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**GENERAL COMMENTS**

This is an interesting manuscript about the relationship between cannabis use and resistance to treatment. The authors design an innovative method to analyze some of the variables used in a large sample of first psychotic episodes. The method is very well described. The results are useful for clinical practice. The discussion is well organized.

The authors are not able to distinguish between resistance due to non-adherence to medication, or to poor response to treatment. They include this difficulty in the limitations. The manuscript is good enough for being published in the journal.

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<td>UCLA</td>
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**GENERAL COMMENTS**

For a count outcome, the effect estimate is the rate ratio of count, not the incidence rate ratio, which is used for a binary outcome of event. Please correct.

As the mediation analysis has not been used widely in the clinic studies and the majority readers of BMJ might not be interested in the technical details about the mediation analysis, it would be helpful for the authors to provide more details about their mediation analysis in a supplement, as shown in the questions related to mediation.
One of the key assumptions of mediation analysis is no unmeasured confounders, including temporal ordering, in all the path ways. It seems that there are many unmeasured confounders in this study, and there was a temporal ambiguity between the mediator and outcome variables, as they were calculated over the same time period. So, the validity of the mediation analysis is questionable, and the authors should discuss about this.

The number of unique antipsychotic medications might not be a good indication for treatment failure as a subject could have a high number of medications at the time of cannabis use. It might be better to use the change (or increase) in the number of medications from the time of cannabis use.

Although statistically significant, the effect of exposure on mediator was just a 10% increase in the number of antipsychotic medications among cannabis users. This also raises some concerns about the choice of mediator in this study as the mediator is expected to have a strong relationship with the exposure and outcome.

For a continuous outcome in a linear regression model, the total effect is defined as the sum of direct and indirect effects, but for a binary or count outcome, the total effect is calculated as the product of direct and indirect effects (rather than the sum). So, the indication “total effect = NDE + NIE” in Figure 1 is misleading as it is only correct for the continuous outcome the authors used. Also, the percentage of total effect mediated by indirect effect is not well-defined for a binary or count outcome, as it is equivalent to the inverse of direct ratio effect based on the ratio of indirect ratio effect to the total ratio effect. One possible solution is to transform odds ratio estimates to risk differences, and calculate the percentage of total effect mediated by indirect effect on risk difference scales. However, there are serious concerns in this method, especially when there is a weak association between exposure and outcome variables. It is not clear how the authors calculated the percentage of total effect mediated by indirect effect in their analysis for the ratio effects as the percentage of total effect in the last column of Table 3 was definitely not the ration of NIE to total effect, and the authors should describe this in the methods as the description “The percentage of the total effect mediated by cannabis use was estimated by dividing the natural indirect effect estimate by the total effect” was incorrect.
The “paramed” command in STATA only supports linear and logistic regression models for the mediator model. Did the authors use an updated version supporting regression models for a count mediator? Otherwise, please clarify how a negative binomial regression model for a count mediator variable (number of unique antipsychotic medications) is specified in the mediation analysis and how the indirect and total effects are calculated based on a count mediator.

Did the authors allow for the interactions between mediator and exposure variables?

According to the authors, the cannabis use is the exposure variable and the treatment failure (number of unique antipsychotics) is the mediator. However, in several occasions, the authors used the term “mediated by cannabis use”, which should be changed to “mediated by number of unique antipsychotics”.

The indirect and direct estimates in the mediation analysis for a binary outcome are based on the assumption of rare outcome. However, the percentage of patients admitted to hospital compulsorily appeared to be high with more than 40% at 4 and 5 years, so that the odds ratio estimates for the admission to hospital compulsorily cannot be used to approximate risk ratio and this would also lead to the bias in the indirect and direct estimates. A log link function, instead of a logit link function, should be used in the “logistic” regression model for the admission to hospital compulsorily.

As the authors mentioned that it is impossible to conduct a randomized study of cannabis use, it is therefore a good recommendation and meaningful to perform a propensity score analysis in this study. A propensity score analysis is not restricted to examine intervention effects, and it is commonly used to assess the relationship between an exposure and an outcome after controlling for selection bias and/or other confounding effects. It is different from a multivariable regression analysis assuming linear and additive (or multiplicative) effects of confounders. However, it seems that the authors have limited number of baseline variables which are needed to estimate propensity scores (weighting) of cannabis use. Hence, unless the authors can collect more baseline information, a propensity score analysis might not add much to the results using the existing data, and the authors can choose not to run the propensity score analysis (but not for the reasons authors provided – propensity score analysis is inappropriate). On the other hand, a mediation analysis is used to explore possible pathways of the relationship between an exposure and an outcome, which is built
based on the “fact” that such relationship exists. Similarly, and one can choose not to run the mediation analysis in this study as the relationship between the exposure and the outcome has not been well established.

**VERSION 2 – AUTHOR RESPONSE**

Reviewer: 1
Reviewer Name: Wayne Hall
Institution and Country: University of Queensland, Australia.

Please leave your comments for the authors below

I remain of the view that the revised paper is important paper in documenting an association between cannabis use and psychosis outcome in a prospective study of a large representative clinical sample of first episode psychoses (FEPs) in South London.

The paper reports data on a large sample of first episode cases of psychosis whose symptoms and treatment course are well documented in electronic clinical records on a population served by a large clinical health service in South London. The clinical outcomes have been followed for up to 5 years after their first admission, with a minimum of 1 year follow up. The electronic clinical records provide valid measures of psychosis outcomes as reflected in the number of hospitalisations, days spent in hospital and number of changes in antipsychotic medication over the follow up period.

The measure of cannabis use at first admission is imperfect for reasons that are clearly acknowledged in the paper, namely, the use of text mining software to search clinical notes for any indications of cannabis use at first admission. This makes under-reporting of cannabis use likely, as reflected in the lower prevalence reported in this study than in other London studies of first episode psychoses. There were no data collected on the frequency of cannabis use at either baseline or during the follow up period. These limitations mean that the study is more likely to under- than over-estimate the strength of associations between cannabis use at first admission and poor clinical outcomes during the follow up period.

The study is also able to throw some light on the mechanisms for the observed association of cannabis use at baseline with treatment outcomes by assessing the indirect contribution of cannabis to poor outcome via medication failures that, in turn, probably reflect a combination of reduced medication compliance and reduced medication effectiveness.

The data limitations are honestly acknowledged by the authors and their possible implications discussed e.g. the effects of multiple clinicians being involved in patient care; the uncertainty as to whether medications were changed after a proper trial of efficacy; and the probable under-estimation of whether cannabis use occurred and uncertainty about its frequency and persistence throughout the follow up period. These limitations are likely to have worked against finding associations between cannabis use at first admission and poor psychosis outcomes during follow up.

Given that the study is an observational one, critics can argue about whether these associations indicate that cannabis use is a cause (direct or indirect) of poor clinical outcomes. It is difficult to argue, however, that cannabis use is not associated with poorer clinical outcomes. This is an important contribution made by this study in a large cohort of first episode psychoses that warrants publication.
Thank you for your supportive comments.

Reviewer: 2
Reviewer Name: Ana Gonzalez Pinto
Institution and Country: Hospital Santiago, Spain.

Please leave your comments for the authors below

This is an interesting manuscript about the relationship between cannabis use and resistance to treatment. The authors design an innovative method to analyze some of the variables used in a large sample of first psychotic episodes. The method is very well described. The results are useful for clinical practice. The discussion is well organized.

The authors are not able to distinguish between resistance due to non-adherence to medication, or to poor response to treatment. They include this difficulty in the limitations. The manuscript is good enough for being published in the journal.

Thank you for your supportive comments.

Reviewer: 3
Reviewer Name: Fei Yu
Institution and Country: UCLA, USA.

For a count outcome, the effect estimate is the rate ratio of count, not the incidence rate ratio, which is used for a binary outcome of event. Please correct.

"We acknowledge that rate ratio of count variables may be described using varying terminology but we have chosen to express this in our paper using the terminology “incidence rate ratio” as this is the terminology used by the statistical analysis software (STATA) we have employed in our study (http://www.ats.ucla.edu/stat/stata/dae/nbreg.htm)."

As the mediation analysis has not been used widely in the clinic studies and the majority readers of BMJ might not be interested in the technical details about the mediation analysis, it would be helpful for the authors to provide more details about their mediation analysis in a supplement, as shown in the questions related to mediation analysis below.

"We agree that mediation analysis is not widely used in clinical studies. While some readers may not be interested in the technical details of the analysis, we feel it is important to include these in the main manuscript rather than in a supplement in order to facilitate access to information on the methods we have employed. However, we have delineated the methods section into separate sections to make it easier for the reader to focus on or skip through the descriptions of the various statistical methods employed in our study."

One of the key assumptions of mediation analysis is no unmeasured confounders, including temporal ordering, in all the pathways. It seems that there are many unmeasured confounders in this study, and there was a temporal ambiguity between the mediator and outcome variables, as they were calculated over the same time period. So, the validity of the mediation analysis is questionable, and the authors should discuss about this.

"We agree that an assumption of mediation analysis (and, indeed, any inferential statistical analysis based on observational data) is the lack of unmeasured confounders and that the exposure and any
potential mediators precede the outcome. We cannot exclude unmeasured confounders in our study and have updated the discussion section to clarify this (page 16, paragraph 2). With respect to the temporal ambiguity between the mediator and outcome variable, we agree that it is possible that switch in antipsychotic treatment may have occurred after hospital admission, although hospital admission is likely to have occurred secondary to treatment failure. This may have affected the validity of mediation analysis. We have updated the discussion section to clarify this (page 16, paragraph 1).∗

The number of unique antipsychotic medications might not be a good indication for treatment failure as a subject could have a high number of medications at the time of cannabis use. It might be better to use the change (or increase) in the number of medications from the time of cannabis use.

∗To clarify, in our study the number of unique antipsychotic medications refers to the number of different antipsychotics prescribed at any point during a particular time period. We were unable to ascertain information related to dose or concomitant prescription of multiple antipsychotic medications, although it is unlikely that an individual presenting with a first episode of psychosis would be prescribed more than one antipsychotic concurrently. We agree that this limitation means that the number of unique antipsychotics may not truly reflect failure or treatment as there are a number of reasons why an individual may be prescribed several different antipsychotics during a particular time period (e.g. poor tolerability or poor medication adherence) rather than a genuine lack of response to treatment. We have described this issue in the discussion section (page 15).

Although statistically significant, the effect of exposure on mediator was just a 10% increase in the number of antipsychotic medications among cannabis users. This also raises some concerns about the choice of mediator in this study as the mediator is expected to have a strong relationship with the exposure and outcome.

∗We acknowledge that although there is a statistically significant relationship between cannabis exposure and increase in number of unique antipsychotics, the absolute difference is modest. This is likely to reflect the fact that there are a number of unmeasured confounding genetic and environmental factors other than cannabis use which may predict an increase in number of unique antipsychotics prescribed. Furthermore, the use of routinely recorded electronic health record data in our study means that we were unable to obtain detailed information on response to antipsychotic treatment and we chose to analyse number of unique antipsychotics as this represents an objective measure which is available for all patients.

For a continuous outcome in a linear regression model, the total effect is defined as the sum of direct and indirect effects, but for a binary or count outcome, the total effect is calculated as the product of direct and indirect effects (rather than the sum). So, the indication “total effect = NDE + NIE” in Figure 1 is misleading as it is only correct for the continuous outcome the authors used. Also, the percentage of total effect mediated by indirect effect is not well-defined for a binary or count outcome, as it is equivalent to the inverse of direct ratio effect based on the ratio of indirect ratio effect to the total ratio effect. One possible solution is to transform odds ratio estimates to risk differences, and calculate the percentage of total effect mediated by indirect effect on risk difference scales. However, there are serious concerns in this method, especially when there is a weak association between exposure and outcome variables. It is not clear how the authors calculated the percentage of total effect mediated by indirect effect in their analysis for the ratio effects as the percentage of total effect in the last column of Table 3 was definitely not the ration of NIE to total effect, and the authors should describe this in the methods as the description “The percentage of the total effect mediated by cannabis use was estimated by dividing the natural indirect effect estimate by the total effect” was incorrect.

∗For number of admissions to hospital (negative binomial regression – incidence rate ratio) and
compulsory admission to hospital (logistic regression – odds ratio) we obtained the percentage of total effect mediated by number of unique antipsychotics using the coefficients derived by the natural logarithm of the incidence rate ratio for negative binomial regression and odds ratio for binary logistic regression. We have updated the methods section to clarify this point (page 11). We agree that the percentage mediated may not accurately reflect the magnitude of mediation where there is a small absolute difference between NDE, NIE and total effect and that this means care should be taken in interpreting these results for number of admissions in hospital and compulsory admission to hospital."

The “paramed” command in STATA only supports linear and logistic regression models for the mediator model. Did the authors use an updated version supporting regression models for a count mediator? Otherwise, please clarify how a negative binomial regression model for a count mediator variable (number of unique antipsychotic medications) is specified in the mediation analysis and how the indirect and total effects are calculated based a count mediator.

"We used the 26-04-2013 version of paramed available here: https://ideas.repec.org/c/boc/bocode/s457581.html. This version permits mediation analysis for the outcome variable using negative binomial regression but only linear or logistic regression for the mediator variable. We therefore analysed number of unique antipsychotics as a linear variable for the purposes of mediation analysis. We have updated the methods section to clarify this (page 11)."

Did the authors allow for the interactions between mediator and exposure variables?

"We did allow for interactions between the exposure and mediator variables and have updated the methods section to clarify this (page 11)."

According to the authors, the cannabis use is the exposure variable and the treatment failure (number of unique antipsychotics) is the mediator. However, in several occasions, the authors used the term "mediated by cannabis use", which should be changed to "mediated by number of unique antipsychotics".

"Thank you highlighting this – we have updated the nomenclature throughout the manuscript accordingly."

The indirect and direct estimates in the mediation analysis for a binary outcome are based on the assumption of rare outcome. However, the percentage of patients admitted to hospital compulsorily appeared to be high with more than 40% at 4 and 5 years, so that the odds ratio estimates for the admission to hospital compulsorily cannot be used to approximate risk ratio and this would also lead to the bias in the indirect and direct estimates. A log link function, instead of a logit link function, should be used in the “logistic” regression model for the admission to hospital compulsorily.

"We agree that odds ratio approximates relative risk for rare outcomes but not for common outcomes. However, as paramed does not permit the use of log link for outcome variables, we chose to analyse compulsory hospital admission using logistic regression."

As the authors mentioned that it is impossible to conduct a randomized study of cannabis use, it is therefore a good recommendation and meaningful to perform a propensity score analysis in this study. A propensity score analysis is not restricted to examine intervention effects, and it is commonly used to assess the relationship between an exposure and an outcome after controlling for selection bias and/or other confounding effects. It is different from a multivariable regression analysis assuming linear and additive (or multiplicative) effects of confounders. However, it seems that the authors have limited number of baseline variables which are needed to estimate propensity scores (weighting) of
cannabis use. Hence, unless the authors can collect more baseline information, a propensity score analysis might not add much to the results using the existing data, and the authors can choose not to run the propensity score analysis (but not for the reasons authors provided – propensity score analysis is inappropriate). On the other hand, a mediation analysis is used to explore possible pathways of the relationship between an exposure and an outcome, which is built based on the “fact” that such relationship exists. Similarly, and one can choose not to run the mediation analysis in this study as the relationship between the exposure and the outcome has not been well established.

"We agree that, under the right circumstances, a propensity score adjusted analysis may be a useful method to employ for observational data and may provide additional information beyond a multivariable regression analysis. In our study we analysed routinely recorded electronic health record data which permitted the analysis of data from a large number of patients but balanced with limits in the depth of data available for each patient. We agree that this limits the possibility to generate a meaningful propensity score as there are a number of unmeasured factors which may affect exposure to cannabis, such as genetic factors and availability of cannabis. We also agree an assumption of mediation analysis is a relationship between the exposure and outcome. In the introduction, we cite a number of studies which suggest a relationship between cannabis exposure and poor outcomes in first episode psychosis, albeit with limitations of sample size and duration of follow-up. Moreover, in our study we demonstrate a clear association of cannabis with poor clinical outcomes in a large sample of patients with first episode psychosis. We therefore feel that these are reasonable grounds for performing a mediation analysis but acknowledge that there are several limitations with respect to interpreting the results of our analysis which we have already described in the discussion section."
Association of cannabis use with hospital admission and antipsychotic treatment failure in first episode psychosis: an observational study

Rashmi Patel, Robin Wilson, Richard Jackson, Michael Ball, Hitesh Shetty, Matthew Broadbent, Robert Stewart, Philip McGuire and Sagnik Bhattacharyya

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