PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A COHORT STUDY IN A GENERAL PRACTICE DATABASE ON MORTALITY IN ADULTS ON METHYLPHENIDATE
AUTHORS	Stricker, Bruno; Cheung, Kiki; Verhamme, Katia

VERSION 1 – REVIEW

REVIEWER	ter Horst, P.G.J. Isala Hospitals, Clinical Pharmacy
REVIEW RETURNED	02-Nov-2021

GENERAL COMMENTS	Dear author, I enjoyed reading your manuscript. However, I have some concerns during the whole manuscript. The data came from a large GP database in The Netherlands. Could it be that data from severe cases, eg patients not visiting the GP, but visiting the psychiatrist, are not included in your dataset, and therefore your data are somewhat confounded? As far as I know ADD or ADHD is a disease diagnosed in early childhood and persists during life. How did you manage that in this study? In the first part of the results section, the mean duration of methylphenidate (MPD) therapy was 370 days, which seems not congruent with the diagnose as described above. minor remarks: - How was suicide defined? Is euthanasia also recorded as suicide? And if so, how did it affect your study? - I miss a reference on page 9, line 49 (usually, these types of exposure misclassification …) - The calculations in table 1 on BMI seems not accurate, please check - Table 3a: what was the influence of confounders on the results presented in table 3a, pleaseprovide - Figure 2 (I guess), please provide info on the axes, and here is my point: during the first 3 years, most patients had a suicide. Is this euthanasia, end-of-life decisions? Corrected for age (in case of palliative care), and where are the children? Young adults? Etc etct - The medication possesion ratio was defined in the methods section, however, results of these calculations were not mentioned in the rest of the manuscript

REVIEWER	Magnusson, Frederik Psychiatric Research Unit, Psychiatric Department
REVIEW RETURNED	01-Jan-2022

GENERAL COMMENTS	The manuscript adresses an important concern, namely the safety of methylphenidate which is a very widely used drug.

	After reviewing the manuscript, however, there are several questions which remain to be answered, regarding the design of the study and the statistical methods employed. On page 5 of the manuscript, you mention matching of participants (intervention and non-users) on sex, age, and GP practice. Did you consider matching on other variables? Were non-user participants sampled at the same time-point in the database as intervention group, or were they matched independently of time point? Were non-users sampled from those who had not used methylphenidate up to that point or from those who did not use methylphenidate for the entire study period? They could potentially have been censored at a later time, if they started methylphenidate later in the study period. This is relevant because those individuals who were not using methylphenidate at one point in the study period but began using later are likely the ones that are most like the intervention group. Did you consider matching by propensity scores? On page 7, the authors mention adjusting for intention-to-treat. I am not familiar with the term intention-to-treat in the context of an observational study, and I feel that the method warrants a more in-depth explanation. Please explain, in your own words, what was done, and provide a reference. If this is a novel approach, I think you should reflect that more clearly in the manuscript. On page 7 and 8, the authors mention adjusting for the intervention, which I think is in reference to the same as mentioned above. It is unclear to me how it is possible to adjust for the intervention itself in a study which is ostensibly intended to study the association between intervention and outcome. Again, I think a more in-depth explanation of the method is required. On page 9, you write: " [...] increased risk of psychotic events associated with methylphenidate might be affected by confounding by indication; that is, patients who receive stimulant medication for ADHD are inherently different from those who do not and could have a greater risk of psychotic events independently of stimulant prescription. This type of confounding also played a role in our IPCI-study but by adjusting for independent risk factors and for the intervention we were able to deal with it." The question of confounding by indication is central to observational studies of interventions, and this shows that the authors believe that it is fully addressed by "adjusting for the intervention" as well as other covariates. Again, this calls for an in-depth explanation of how this adjustment was carried out. In summary, the analysis of the paper is not adequately explained by the authors. The authors should also consider employing other methods from pharmacoepidemiology to deal with the risk of confounding by indication. These could include instrumental variable analysis (GP-practice might be a possible instrument), matching by propensity scores, or within-person case-series. Figure 2 and 3 should be revised to include meaningful axis names and units on the axes, as well as titles denoting what is shown in the figure.

REVIEWER	Storebø, Ole Jakob

	University of Southern Denmark, Psychiatric Research Unit
REVIEW RETURNED	01-Jan-2022

GENERAL COMMENTS	Peer review of the manuscript INCREASED MORTALITY ASSOCIATED WITH METHYLPHENIDATE IN ADULTS. This seems to be a well-planned and conducted study. In a study as this, there is a risk of confounding factors affecting the association between methylphenidate and psychiatric events. In this study the authors seems to have considered many relevant confounding factors. The objective of this research article is to assess whether methylphenidate in adults was associated with an increased risk of psychiatric events such as depression, and suicide attempt, and overall mortality. The design of the study is a cohort study including data from the general practitioners (GP) database in the Netherlands with a source population of 2.5 million inhabitants. During the period 1 st June 1996 to 1st January 2018 8905 adults started methylphenidate and each of these were matched to 10 non-users on sex, age, GP practice, and prescription date. Introduction: The introduction lacks a short description of the disease and also some references to studies investigating the benefits and harms of methylphenidate for adults eg. 1. Cândido RCF, Menezes de Padua CA, Golder S, Junqueira DR. Immediate-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults. Cochrane Database of Systematic Reviews 2021, Issue 1. Art. No.: CD013011. DOI: 10.1002/14651858.CD013011.pub2. Accessed 31 December 2021. and this: 2. Elliott J, Johnston A, Husereau D, Kelly SE, Eagles C, Charach A, Hsieh SC, Bai Z, Hossain A, Skidmore B, Tsakonas E, Chojecki D, Mamdani M, Wells GA. Pharmacologic treatment of attention deficit hyperactivity disorder in adults: A systematic review and network meta-analysis. PLoS One. 2020 Oct 21;15(10):e0240584. doi: 10.1371/journal.pone.0240584. PMID: 33085721; PMCID: PMC7577505. In the Netherlands Methylphendiate is prescribed by a GP, but in other countries ADHD medication can only be described by a medical doctor specialized in psychiatry. Perhaps the author could discuss what it means that methylphenidate is prescribed by non-specialized doctors? One concern about this practice is whether the ADHD diagnosis given by the GPs can be considered valid? I wonder how was ADHD assessed by the GPs? By a rating scale only? Or only by a short clinical interview? Please include more information about this. In the result section the author describes clearly that most of the risks for psychiatric symptoms and diseases, were non-significant when adjusted for confounding factors. The risk for suicide attempts was, however, significantly increased (after full adjustment) for the age group of 18 to 40 years. The risk for mortality was increased also after adjustment (HR 1.3 95% CI 1.1 – 1.6). This were partly explained by “of label use” of methylphenidate in palliative care. I find this study to be well conducted and scientific sound. The authors have clearly described the strength and limitations of the study and I find that these findings should be published, as it is an important study.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. P.G.J. ter Horst, Isala Hospitals
Comments to the Author:
Dear author, I enjoyed reading your manuscript. However, I have some concerns during the whole manuscript. The data came from a large GP database in The Netherlands. Could it be that data from severe cases, eg patients not visiting the GP, but visiting the psychiatrist, are not included in your dataset, and therefore your data are somewhat confounded? As far as I know ADD or ADHD is a disease diagnosed in early childhood and persists during life. How did you manage that in this study? In the first part of the results section, the mean duration of methylphenidate (MPD) therapy was 370 days, which seems not congruent with the diagnose as described above.

Reply:
We would like to thank the reviewer for his comment. Indeed, in a general practice [GP] database such as IPCI, not all encounters with the specialist are recorded. However, in most cases where methylphenidate is started by a psychiatrist, the first prescription will not be registered but in the majority of patients the continuation of methylphenidate treatment goes through the GP, especially because of the central role that Dutch GPs have in patient care. Therefore, we think that we will have enrolled also most of the severe cases, albeit somewhat later in their treatment course. However, even if we miss some of the most severe cases, it is likely that this has led to conservative instead of inflated estimates.
We clarified this in the Discussion as follows:
"Also, we might have missed the most severe cases of ADHD/ADD, initially treated by the psychiatrist. However, in the majority of patients the continuation of methylphenidate treatment goes through the GP. Therefore, we think that we will have enrolled also most of the severe cases, albeit somewhat later in their treatment course. And even if we missed some of the most severe cases, it is likely that this has led to conservative instead of inflated estimates."

minor remarks:
- How was suicide defined? Is euthanasia also recorded as suicide? And if so, how did it affect your study?
Reply:
All cases of suicidal ideation/attempt/suicide were checked by reference to the free text of the medical record. In all cases, the text was very specific and could be distinguished from euthanasia [unless the GP or patient would deliberately have chosen another term but, of course, this can not be verified in these anonymized data]. Similarly, we checked all death by reference to the medical history and found that the strong increase of mortality in the old were mostly 'end-of-life' problems as a consequence of cancer and euthanasia was often mentioned in these records. However, methylphenidate was not prescribed with the indication 'euthanasia' but because of depression and exhaustion in people who were about to die. Hence, we do not expect that there is much mutual misclassification between the terms suicide and euthanasia.

- I miss a reference on page 9, line 49 (usually, these types of exposure misclassification …)
Reply:
We clarified this as follows:
Usually, these types of exposure misclassification lead to an underestimation of the true risk because

the group of non-exposed actually includes exposed individuals [28].

- The calculations in table 1 on BMI seems not accurate, please check
Reply:
The figures on BMI in table 1 are accurate but may have confused the reviewer because of the large number of missing values. That is why the percentages in each category do not add up to 100%

- Table 3a: what was the influence of confounders on the results presented in table 3a, please provide

Reply:
The crude risk of suicide is given in table 2: HR 5.5 [95%CI: 3.5-8.6] which goes down to 2.0 [95%CI: 1.1-3.6] after adjustment.

- Figure 2 (I guess), please provide info on the axes, and here is my point: during the first 3 years, most patients had a suicide. Is this euthanasia, end-of-life decisions? Corrected for age (in case of palliative care), and where are the children? Young adults? Etc etc

Reply:
We added more info in the legends of figures 2A and 2B [frequency represents number of cases]. The majority of patients with suicide was young [fig 2A] while almost all cases of euthanasia/'end-of-life' notifications were old and had multiple comorbidities. Children [<18 years] were excluded from this study population.

- The medication possesion ratio was defined in the methods section, however, results of these calculations were not mentioned in the rest of the manuscript

Reply:
The medication possession ratio was given as a descriptive but indeed not used. We deleted this paragraph from the methods section.

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Reviewer: 2
Mr. Frederik Magnusson, Psychiatric Research Unit
Comments to the Author:
The manuscript adresses an important concern, namely the safety of methylphenidate which is a very widely used drug.

After reviewing the manuscript, however, there are several questions which remain to be answered, regarding the design of the study and the statistical methods employed.

On page 5 of the manuscript, you mention matching of participants (intervention and non-users) on sex, age, and GP practice. Did you consider matching on other variables?
Reply:
We have a preference for direct adjustment without matching but here that would be inefficient because most people start as young adult in the study and most of them are men and without matching relatively many controls from a practice might be older and female. Furthermore, in a dynamic database with healthcare data, there may be relevant but difficult to recognize differences between general practices in the way they register their healthcare data. Therefore, we matched on sex, age, and general practice but adjusted for other covariables.

Were non-user participants sampled at the same time-point in the database as intervention group, or were they matched independently of time point?
Reply:
Yes, users and controls were followed from the same time point. So, each starter was matched to up to 10 controls which were followed as of the calendar date of prescription in the user/starter. This was clarified in the methods as follows: " For each matched set of 1 user and [mostly] 10 nonusers during the study period, follow-up started at the day of first prescription of methylphenidate and this date was also allocated to the 10 non-users. All participants were eligible for GP healthcare during the study period."

Were non-users sampled from those who had not used methylphenidate up to that point or from those who did not use methylphenidate for the entire study period? They could potentially have been censored at a later time, if they started methylphenidate later in the study period. This is relevant because those individuals who were not using methylphenidate at one point in the study period but began using later are likely the ones that are most like the intervention group.
Reply:
Controls were chosen from those who did not receive methylphenidate during the entire study period. See our answer to the previous question.

Did you consider matching by propensity scores?

Reply:
We prefer multivariable adjustment here because with a stepwise introduction in the model, the contribution of each variable to the risk estimates can be assessed. Propensity scores may be more difficult to interpret because they may have a completely different set of risk factors for being treated with methylphenidate but nevertheless have an identical propensity score. Hereby, they can introduce confounding which may be difficult to recognize. Unless multivariable adjustment is not possible, we favor it over propensity scores. We analyzed also with a baseline [start of methylphenidate] propensity score but results were grossly similar and therefore not given. This is not surprising because propensity scores in this study were composed of the same determinants as we used in our multivariable analyses.

On page 7, the authors mention adjusting for intention-to-treat. I am not familiar with the term intention-to-treat in the context of an observational study, and I feel that the method warrants a more in-depth explanation. Please explain, in your own words, what was done, and provide a reference. If this is a novel approach, I think you should reflect that more clearly in the manuscript.

Reply:
Except for the randomization, our study had a similar design as a clinical trial because a group of exposed/unexposed was followed over an identical period of calendar time. But of course, the lack of randomization in our study requires adjustment for potential confounding factors, notably for confounding by intervention/indication. In a clinical trial, both an intention-to-treat as well as an as-treated analysis is performed because people in the treated arm may stop using the drug while the placebo group remains untreated. Here, we had the same situation because in the treated arm, study participants having the outcome of interest [e.g. suicide] may be user or have already stopped methylphenidate. That is why we used a Cox regression model for time-varying determinants [i.e.methylphenidate use].

On page 7 and 8, the authors mention adjusting for the intervention, which I think is in reference to the same as mentioned above. It is unclear to me how it is possible to adjust for the intervention itself in a study which is ostensibly intended to study the association between intervention and outcome. Again,

I think a more in-depth explanation of the method is required.
On page 9, you write: " [...] increased risk of psychotic events associated with methylphenidate might be affected by confounding by indication; that is, patients who receive stimulant medication for ADHD are inherently different from those who do not and could have a greater risk of psychotic events independently of stimulant prescription. This type of confounding also played a role in our IPCI-study but by adjusting for independent risk factors and for the intervention we were able to deal with it."
The question of confounding by indication is central to observational studies of interventions, and this shows that the authors believe that it is fully addressed by "adjusting for the intervention" as well as other covariates. Again, this calls for an in-depth explanation of how this adjustment was carried out.
Reply:
Confounding by intervention refers to the basic decision to intervene while confounding by indications refers to a specific indication. Assumedly, either ADHD or ADD was supposed to be the reason for prescribing methylphenidate but there may be other indications, as can be seen from our study ['end-of-life' exhaustion], albeit off-label. But we do not know the quality of diagnosis, nor do we know which other reasons the prescribers had in mind. The only thing we know for sure is that the GP intervened by prescribing methylphenidate. That is why we use the intervention [yes/no] as an instrumental variable which is easier to understand than a propensity score, and which adjusts for those with the event suicide/death who were unexposed [no longer exposed] on the day of the event but had been in the intervention group [but stopped taking methylphenidate].

In summary, the analysis of the paper is not adequately explained by the authors. The authors should also consider employing other methods from pharmacoepidemiology to deal with the risk of confounding by indication. These could include instrumental variable analysis (GP-practice might be a possible instrument), matching by propensity scores, or within-person case-series.

Reply:
As explained above, we decided to match on GP-practice to guarantee the same type and quality of healthcare information for each user-10 controls combination. Multivariable adjustment with adjustment for intervention worked best.

Figure 2 and 3 should be revised to include meaningful axis names and units on the axes, as well as titles denoting what is shown in the figure.

Reply:
The legends of these figures have been clarified.

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Reviewer: 3
Prof. Ole Jakob Storebø, University of Southern Denmark
Comments to the Author:
Peer review of the manuscript INCREASED MORTALITY ASSOCIATED WITH METHYLPHENIDATE IN ADULTS.

This seems to be a well-planned and conducted study. In a study as this, there is a risk of confounding factors affecting the association between methylphenidate and psychiatric events. In this study the authors seems to have considered many relevant confounding factors.
The objective of this research article is to assess whether methylphenidate in adults was associated with an increased risk of psychiatric events such as depression, and suicide attempt, and overall mortality. The design of the study is a cohort study including data from the general practitioners (GP) database in the Netherlands with a source population of 2.5 million inhabitants. During the period 1 st

June 1996 to 1st January 2018 8905 adults started methylphenidate and each of these were matched to 10 non-users on sex, age, GP practice, and prescription date.

Introduction:
The introduction lacks a short description of the disease and also some references to studies investigating the benefits and harms of methylphenidate for adults eg.

1. Cândido RCF, Menezes de Padua CA, Golder S, Junqueira DR. Immediate-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults. Cochrane Database of Systematic Reviews 2021, Issue 1. Art. No.: CD013011. DOI: 10.1002/14651858.CD013011.pub2. Accessed 31 December 2021. and this:
2. Elliott J, Johnston A, Husereau D, Kelly SE, Eagles C, Charach A, Hsieh SC, Bai Z, Hossain A, Skidmore B, Tsakonas E, Chojecki D, Mamdani M, Wells GA. Pharmacologic treatment of attention deficit hyperactivity disorder in adults: A systematic review and network meta-analysis. PLoS One. 2020 Oct 21;15(10):e0240584. doi: 10.1371/journal.pone.0240584. PMID: 33085721; PMCID: PMC7577505.
Reply:
Thank you for this suggestion. We amended the introduction as follows [1st para, line 4]:
Attention deficit hyperactivity disorder (ADHD) is defined as a mental health disability, which usually begins before 12 years of age, and is characterized by three main symptoms: inattention, impulsivity, and hyperactivity. The intensity of the symptoms tends to decrease with ageing, but in 40% to 50% of people diagnosed with ADHD in childhood, symptoms may persist during adolescence and adulthood [3,4].

In the Netherlands Methylphendiate is prescribed by a GP, but in other countries ADHD medication can only be described by a medical doctor specialized in psychiatry. Perhaps the author could discuss what it means that methylphenidate is prescribed by non-specialized doctors? One concern about this practice is whether the ADHD diagnosis given by the GPs can be considered valid? I wonder how was ADHD assessed by the GPs? By a rating scale only? Or only by a short clinical interview? Please include more information about this.

Reply:
There is a specific guideline for GPs on the diagnosis and treatment of ADHD/ADD but admittedly, it is likely that there is misclassification of the diagnosis by GPs. Unfortunately, there is no information in the database on how the diagnosis was made although the patients of whom medication is only continued after an initial diagnosis by a psychiatrist might be validly diagnosed. Moreover, not for all prescriptions, a diagnosis was available in the GP-records.

In the result section the author describes clearly that most of the risks for psychiatric symptoms and diseases, were non-significant when adjusted for confounding factors. The risk for suicide attempts was, however, significantly increased (after full adjustment) for the age group of 18 to 40 years. The risk for mortality was increased also after adjustment (HR 1.3 95% CI 1.1 – 1.6). This were partly explained by “of label use” of methylphenidate in palliative care.
I find this study to be well conducted and scientific sound. The authors have clearly described the strength and limitations of the study and I find that these findings should be published, as it is an important study.

Reply:
We highly appreciate this supportive comment.

Reviewer: 1

Competing interests of Reviewer: none

Reviewer: 2
Competing interests of Reviewer: I have no competing interests to declare

Reviewer: 3
Competing interests of Reviewer: No competing interests

VERSION 2 – REVIEW

REVIEWER	ter Horst, P.G.J. Isala Hospitals, Clinical Pharmacy
REVIEW RETURNED	17-Feb-2022

GENERAL COMMENTS	dear authors, thanks for the revised manuscript. I do not have any comments on the revised version.

REVIEWER	Storebø, Ole Jakob University of Southern Denmark, Psychiatric Research Unit
REVIEW RETURNED	06-Mar-2022

GENERAL COMMENTS	I am mostly satisfied with the author response. However, since the author admits that there likely is misclassification of the diagnosis by GPs this should also be described as an limitation in the "Strength and limitations" section

REVIEWER	Magnusson, Frederik Psychiatric Research Unit, Psychiatric Department
REVIEW RETURNED	20-Mar-2022

GENERAL COMMENTS	I thank the authors for their diligent and thorough response to all reviewers' comments. I still have outstanding questions about the analysis, however. The presence of confounding by indication/intervention, it seems to me, would imply that assignment to intervention is not an obvious candidate for instrumental variable. I am not an expert in the use of the Cox proportional hazard model but it seems to me that there may be problems with adjusting for the assignment to intervention (prescribing) to remove confounding by indication/intervention. I would be very appreciative if the authors provided a reference to a discussion of this approach. My chief concern is that this adjustment removes a true causal relationship between methylphenidate use and the outcomes of interest, or underestimates the size of such a relationship. I would be very interested to see how collinear the assignment to intervention variable and use of methylphenidate are.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Dr. P.G.J. ter Horst, Isala Hospitals
Comments to the Author:
dear authors, thanks for the revised manuscript. I do not have any comments on the revised version.

No changes requested

Reviewer: 3
Prof. Ole Jakob Storebø, University of Southern Denmark
Comments to the Author:
I am mostly satisfied with the author response. However, since the author admits that there likely is misclassification of the diagnosis by GPs this should also be described as an limitation in the "Strength and limitations" section

We added to the Discussion:

"Although there is a specific guideline for GPs on the diagnosis and treatment of ADHD/ADD, it is likely that there is some misclassification of the diagnosis by GPs"

Reviewer: 2
Mr. Frederik Magnusson, Psychiatric Research Unit
Comments to the Author:
I thank the authors for their diligent and thorough response to all reviewers' comments.

I still have outstanding questions about the analysis, howeverThe presence of confounding by indication/intervention, it seems to me, would imply that assignment to intervention is not an obvious candidate for instrumental variable.

I am not an expert in the use of the Cox proportional hazard model but it seems to me that there may be problems with adjusting for the assignment to intervention (prescribing) to remove confounding by indication/intervention. I would be very appreciative if the authors provided a reference to a discussion of this approach.

My chief concern is that this adjustment removes a true causal relationship between methylphenidate use and the outcomes of interest, or underestimates the size of such a relationship. I would be very interested to see how collinear the assignment to intervention variable and use of methylphenidate are.

This is a very important point and we are not completely reassured by our own results. Therefore, we added the following paragraph to the discussion:

"Obviously, there is collinearity between the intervention at baseline and actual use during follow-up. People may decide not to fill a prescription for methylphenidate, fail to use it, stop it early or use it continuously. Although we adjusted for the intervention at baseline to adjust for non/registered mental co-morbidity, changes during follow-up might have led to underestimation of the true risk, for instance, because patients with a lower vulnerability to suicidal thoughts stopped methylphenidate early during follow-up. Consequently, the risk of suicidal thoughts and attempts may have been underestimated. Therefore, it is important that our findings must be a starting point for further research."

VERSION 3 – REVIEW

REVIEWER	Magnusson, Frederik Psychiatric Research Unit, Psychiatric Department
REVIEW RETURNED	06-Jun-2022

GENERAL COMMENTS	I thank the authors for their revisions. I have no further comments.