

**Manuscript ID: BMJ.2015.029971.R1**

**TITLE: Cardiovascular safety of methylphenidate among pediatric patients with ADHD: a nationwide self-controlled case series study**

Dear Editor-in-Chief:

We express our gratitude to the editor and reviewers for taking their time to review our manuscript, referenced as Manuscript ID BMJ.2015.029971.R1. The reviewers' constructive comments and suggestions helped us to refine and polish this manuscript. We have addressed all comments from the reviewer, and we believe that the manuscript has improved substantially. We have enclosed the revised manuscript with the changes highlighted, together with point-by-point responses to the reviewer's comments.

Thank you for your ongoing consideration, and we are looking forward to hearing good news from you soon. Please feel free to contact me if you have any questions related to this manuscript.

Sincerely yours,

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## **Response to the comments of committee meeting**

1. We thought your study addresses an interesting and potentially important research question. We had the following concerns: The 'event' or outcome you use is a very broad composite one. In addition to arrhythmia, you lump in MI, hypertension, stroke and heart failure. The mechanism of arrhythmia differs from the others. There is a comparability issue here - we were surprised to see hypertension alongside MI, stroke and heart failure. A closer inspection of the rate ratio's for the components seems to point to arrhythmia as the only significant component.

**Author's response:** *Thank you for your thorough review of our manuscript. We intended to explore the broad cardiovascular events from mild to serious event and to explore the temporal association between exposure and outcome. As you indicated, the composite outcome was influenced by the results of arrhythmias and as you say mechanisms of action may differ across the outcomes. We have omitted the analysis of the composite outcome and present each 5 events separately. The manuscript has been amended to reflect this.*

2. A dose response curve would be desirable

**Author's response:** *We presented differential risk according to the low and high dose of methylphenidate in table 3. We divided daily dose into low (less than 27 mg per day) and high (more than 27 mg per day), because 27mg is the median value based on the dose distribution. Due the limited number of study subjects, we could not categorize dose into more refined groups. These were also added in the methods and results. We found that stratifying by dose made little impact on our overall risk estimates.*

3. The flowchart does not run logically.

**Author's response:** *Thank you for the careful review. We have amended our flowchart. Please see*

*figure 1.*

4. If you can provide data on congenital heart disease that would be value adding, the ACC/AHA statements all call for this, with subgroup analysis.

**Author's response:** *Thank you for the constructive comment. We have conducted a sub-group analysis according to the presence of congenital heart disease. This has been included in the methods, results, and discussion (table3). The Results presented in Table 3 indicate that while the risk of arrhythmia was lower in those without congenital heart disease a significant risk is still present. No difference in risk of hypertension was observed in those with congenital heart disease and those without. Congenital heart disease was rare in patients with MI, ischaemic stroke and heart failure.*

5. Case-control studies do not quantify the absolute risk in the overall MF-taking pediatric population. It is probably very low; might you add a remark on this?

**Author's response:** *We chose to use the self-controlled case series method to minimize comparability issues and because the rate of cardiovascular outcomes was expected to be low in the adolescent population. This methodology does not allow the estimation of absolute risk and we have made comment regarding this. "While we did find an increased relative risk the absolute risk is likely to be low".*

6. It would be useful to have a few more details about the duration of the unexposed and exposed periods before and after the cardiac outcome (eg. median and range).

**Author's response:** *We have included the median and range for the duration of exposure before and after the outcome in table 1. As would be expected the range of exposure durations is variable over time, overall the median exposure time is 6 months with the majority of the exposure occurring*

*after the event.*

7. Table 1. Why is the median age at first outcome 2 years below that of the first exposure? We would have thought that it should be the other way round?

**Author's response:** *After re-running the analysis we have confirmed that the age at first exposure and first outcome are similar, except for heart failure where the age at first exposure is 12 yrs and age at first outcome is 13 . (Table 1)*

8. In the sensitivity analysis where pre-exposure risk periods are included, the rate ratios prior to medication are very high (Table 3), and even higher than that during exposure to the drug. This is of concern. What is the explanation for this? It could be suggested that initiation of the drug occurs when the risk of cardiac outcomes is very high ie. there are some changes in the subject's health? If so, then the study does not provide strong evidence of an increased risk of a cardiac event with drug use.

**Author's response:** *We observed a higher rate ratio prior for arrhythmia stroke and heart failure but not myocardial infarction in the time period prior to initiating methylphenidate. As you indicated, it suggests prescribing occurred when children had a cardiovascular event which would be contraindicated prescribing. We have discussed this issue as follows:*

*“The increased risk in the pre-initiation exposure risk period suggests that children with cardiovascular events, except MI, were initiated on methylphenidate. This may reflect prescribing in contraindicated patients and itself is of concern and may indicate prescribers only consider MI to be a contraindication to methylphenidate use. Additionally an increased risk of cardiovascular outcomes was observed in the washout period. There are a number of possible explanations for this. Firstly, the exposure duration may have been underestimated, that is patients may have still been taking the medicine for longer than the expected supply due to non-compliance. Secondly,*

*methylphenidate comes in slow release preparations and is metabolized by the liver, either of which could have implications for persons who are slow metabolisers where there may be some potential for medicine activity beyond the expected supply.”*

### **Response to the comments of reviewer #1**

This is a rather interesting and well written study with an adequate design to pick up rare adverse events following the use of central stimulants as treatment for ADHD in children and adolescents. I think it would be of interest to the readers of BMJ if it was revised. I have some major concerns, but rally mostly minor concerns

### **Major concerns**

1. I think they could have use for a language consultant.

**Author’s response:** *We have edited the manuscript substantially to address this issue.*

2. The first paragraph of the introduction is a bit messy

**Author’s response:** *We have re-worded the first paragraph focusing on the safety issues of methylphenidate. (Page 3)*

3. In the second paragraph on page 3 they say that the design eliminates confounding – is this totally true?

**Author’s response:** *We have amended this sentence. The advantage of the within person study design is that it eliminates time-constant patient-specific confounding, however it is possible that results may still have residual confounding due to time-varying confounding. To account for this we adjusted for conditions and co-medications using time-varying confounding adjustment. We have*

*modified the expression to read ‘thus minimizing confounding caused by comparing different patients, by study design’. (Page 3)*

4. Second paragraph page 5: The events included in each cluster of diagnosis range from something that is very mild disease and something that is very severe disease. This is a major problem with the paper: different things are clustered together

**Author’s response:** *On the request of reviewer’s comments, we deleted composite outcome, and focused on each outcome separately.*

5. Page 12: strength and limitations: they need to work on the limitations bit: Something about the wash out period needs to be discussed in limitations. Likewise Diagnostic accuracy (high of course from previous study, but not 100% - how does this influence results. They don’t know if prescribed drugs are taken: what could noncompliance do to these findings. And what about the placebo effect? If patients take amphetamine or methylphenidate they will notice this. Any event will more readily be viewed as a consequence of this intake. Thus increasing the chance of having any episodes after the intake of these drugs.

**Author’s response:** *Thank for your helpful review. We have amended our discussion of the limitations as follows.*

*“Additionally an increased risk of cardiovascular outcomes was observed in the washout period. There are a number of possible explanations for this. Firstly, the exposure duration may have been underestimated, that is patients may have still been taking the medicine for longer than the expected supply due to non-compliance. Secondly, methylphenidate comes in slow release preparations and is metabolized by the liver, either of which could have implications for persons who are slow metabolisers where there may be some potential for medicine activity beyond the expected supply.”*

## Minor concerns

6. I think it would be more appropriate if they were to call it adverse events or events than outcome. I think it would be more appropriate to call it cardiovascular adverse event rather than cardiac when they include stroke

**Author's response:** *We changed terms from 'outcome' to 'cardiovascular adverse events' in the revised manuscript.*

7. Line 47 page 2: “particularly in children with mild disease” – what disease?

**Author's response:** *We meant mild ADHD disease. We have included this to clarify.*

8. Line 50 page 3: “confounding between individuals” – correct phrasing?

**Author's response:** *We have amended this. We rewrote as follow: 'thus minimizing confounding caused by comparing different patients, by study design'. (Page 3)*

9. Line 30 page 4: I would make a paragraph between “....Tenth Revision (ICD-10)” and “All researchers...”

**Author's response:** *We have amended this paragraph according to your suggestion. (Page 4)*

10. The previous study they refer to in line 45 page 4 has measured diagnosis to “actual diagnosis” – what gold standard is this?

**Author's response:** *A validation study compared the diagnoses derived from the HIRA database with the gold standard as actual diagnoses in the patient medical records from hospital or clinics chart review. (Page 4) We have clarified this in the text*

11. Line 38, page 8: “partitioned” – a good word?

**Author's response:** *We have removed this word.*

## **Response to the comments of reviewer #2**

This is a well written paper on an interesting topic - the effects of methylphenidate on arrhythmia, hypertension, MI, ischaemic stroke and heart failure. The rationale is clear and well justified and the data and methods are mostly well described. The assumptions underpinning the SCCS method have been discussed and I agree with the authors on their assessment of these. I have a number of specific comments as detailed below:

Major comments:

1. In Table 3 we see the sensitivity analysis where a pre-exposure period has been added into the analysis to account for the possibility that the event affects the probability of future exposure. Here we see that this seems to be the case. There is a strongly increased risk of all outcomes in the 2 month period before exposure, of a similar or greater magnitude than seen during exposure, e.g. for MI, there is a 7-fold increased risk in the 31-60 days before methylphenidate starts. This suggests to me that the time of methylphenidate initiation seems to co-incide with a time when the risk of these events is raised, but that the medication initiation is not having any impact on this increased risk (it isn't getting any higher after starting the drug). This seems to suggest the association with methylphenidate is unlikely to be causal.

**Author's response:** *Thanks for your constructive comments. We did observe a higher incidence rate ratio in the pre-exposure period for arrhythmia, stroke and heart failure which does suggest that some subjects experienced a cardiovascular event prior to initiating methylphenidate. Of note,*



*we did not find a significantly increased risk of MI in pre-exposure risk-periods while we did find a significant increased risk after 1 week on treatment. We have discussed this as follows:*

*“The increased risk in the pre-initiation exposure risk period suggests that children with cardiovascular events, except MI, were initiated on methylphenidate. This may reflect prescribing in contraindicated patients and itself is of concern and may indicate prescribers only consider MI to be a contraindication to methylphenidate use”.*

2. A secondary analysis looking at atomoxetine exposure might be helpful since it is used in similar patients but has a different mechanism of action (though I realise there is also some overlap in action). It might help better inform whether this is a non-drug specific phenomenon related to the peri-diagnostic time for ADHD?

**Author’s response:** *Thanks for your constructive comments. At first, we planned the analysis with atomoxetine exposure, however, atomoxetine, non-stimulants for ADHD treatment, is only approved for the secondary treatment. We could not find single atomoxetine users in our study population. All records of atomoxetine were prescribed after methylphenidate.*

3. I don't think the statement in the discussion about a higher incidence in the pre-exposure period being consistent with a higher prevalence of ADHD in children with heart disease is justified. For this, we would need data on people with and without CVD to make a comparison. This just shows there is an increased risk of CVD before and after the start of methylphenidate.

**Author’s response:** *Thank you for your comment. We have deleted the sentence. We only acquired data for children with a diagnosis of ADHD, therefore, we were unable to compare the prevalence of CVD in children with and without ADHD. We have cited previous literature which showed a different distribution of risk factors for cardiovascular disease between children with and without*

*ADHD. We have also presented our analysis according to the presence of congenital heart disease in Table3.*

Minor Comments:

4. The overall PPV of diagnoses in the NHIS data is quoted as 83.4%. This is likely to vary considerably depending on the specific diagnosis - can the authors tell us more about the PPV for outcomes included in this study?

**Author's response:** *All diagnoses had been coded according to the International Classification of Disease, Tenth Revision (ICD-10). A previous validation study compared the diagnoses derived from the HIRA database with the gold standard as actual diagnoses in the patient medical records from hospital or clinics chart review. These studies reported that the positive predictive value of the diagnoses was 83.4% for ischemic stroke (I63), and >70% for MI (I21).<sup>12-14</sup> The overall positive predictive value of the diagnosis was approximately 70%.<sup>12</sup>*

5. People with pre-existing cardiac disease in the preceding year to index date were excluded. To clarify, were people still eligible if they had a known CV event >12 months previously?

**Author's response:** *People with pre-existing cardiac disease between January 2007 and December 2007 only were excluded.*

6. For the exposure assessment, the first exposed risk period is days 1-3, but people with events on day 1 were excluded, so should this be days 2-3 instead? I think it may be better to keep those with events on day 1, but to have day 1 as a separate category in the analysis.

**Author's response:** *Thanks for careful comments. We re-selected study subjects, and re-presented in table 3 the analysis including outcome and exposure events that occurred on the same day (Day 0). Day 1 counted as the day after initiation of methylphenidate. (Page 22)*

7. As the authors note, there is possibly a timing issue for the recording of events like heart failure, hypertension and arrhythmia compared with when the events were truly incident. This leads to misclassification in a SCCS which could affect the results in either direction.

**Author's response:** *We agree with the concern you have raised. We have discussed this issue as follows:*

*'It is possible that a form of detection bias may have influenced the results for hypertension as it is a condition that is non-symptomatic and may only been detected through routine tests at a scheduled follow-up appointments with healthcare providers. We did find that there was a significantly increased risk of hypertension in the 4-7 day risk period which would correspond to the first follow-up visit after initiating treatment. In contrast, all the other cardiovascular events assessed were symptomatic events, the symptoms of which would precipitate attendance independent of a planned visit, hence a more accurate timing assessment of the event.'*

### **Response to the comments of reviewer #3**

The authors used a self-controlled case series (SCCS) design to rule out between-person confounding e.g. differing risk factor distributions between groups that use the drug vs. do not use the drug. The authors state that prior literature did not use a case only design like SCCS, and they cite this difference as why their study results diverge from previous studies. But there are other aspects of the SCCS design that are relevant, which I will focus on here.

The issues surrounding SCCS designs and their target of inference can and should be addressed in the Discussion as it is very relevant for placing this study in context. The issue about residual and unmeasured time-varying confounding in this SCCS design can only be partially addressed, because symptoms and precipitating factors are usually unmeasured in claims data. Nonetheless, the study could motivate future studies with better clinical data.

#### **MAJOR POINTS:**

1. The SCCS design changes the research question in an important way. By comparing exposure during the case period and control periods, it focuses on the question of how these risk periods differ among persons who ultimately developed the outcome. In the words of Malcom Maclure, it focuses on "why now" instead of "why me" (see Maclure *Pharmacoepidemiol Drug Saf.* 2007 Aug;16(8):850-3.) Thus, the study really appears to be asking whether or not methylphenidate use is a triggering event among children who eventually did experience cardiovascular events. This may not be the same question addressed in earlier cohort studies: whether children who take methylphenidate have higher risk of cardiovascular events compared to those who do not. It is important that the reader understand this difference.

**Author's response:** *Thanks for your constructive comments. We revised our research questions as follows: 'To explore whether or not methylphenidate use is a triggering event among children who experienced cardiovascular events' and discussed all issues you indicated. '*

*"Our study, however, determines whether methylphenidate use 'triggers' the occurrence of a cardiovascular adverse event within a patient. The population included is only those children who had the exposure and the event during the study period. As described by Maclure et al, the analysis of a within-person study design can be summarized by the expression 'why now' rather than 'why me' as in a cohort or case control study.<sup>22</sup>" (Page 11)*

2. Another issue with comparing results from SCCS designs with those from cohort studies is that the populations differ (not just the comparison of persons vs. times). In the SCCS design everyone experiences a cardiovascular event. They may have already been at very high risk for cardiovascular events which begs the question of whether the results apply to children who are healthier. To be clear, this isn't an issue of bias but of generalizability. It's not possible to ascertain this population's cardiovascular risk from the author's Table 1 because it does not report distributions of cardiovascular risk factors. We cannot tell whether this population is high risk or even how it differs from the populations that appear in earlier cohort studies. The authors attribute their unique findings to between-person confounding, but it is very plausible that both sets of studies are reasonably correct, but the populations have different distributions of effect modifiers (i.e. which by definition must be associated with risk factors for cardiovascular events...see VanderWeele TJ Epidemiology. 2009 Nov;20(6):863-71).

**Author's response:** *Thanks for your constructive comments. We agree with your comments. A previous study reported ADHD patients had higher prevalence of heart disease than in the general pediatric population. This means that ADHD patients may already have high possibility of*

*cardiovascular adverse events independent of drug exposure. This is why we chose to use the self-controlled case series design so that we would control for baseline level of cardiovascular disease in a child – that is it would be the same in periods of exposure compared to unexposure.*

3. As the authors point out, SCCS designs are subject to time-varying confounding. That is, risk factor distributions differ between exposed periods and unexposed periods of time. Although their models control for psychiatric diagnoses and co-medications, this is probably insufficient. There may be residual differences in ADHD symptom severity (along with symptoms of other disorders), medication dose, substance use, and precipitating factors.

**Author's response:** *Thank you for your constructive comments. We added a sentence to explain potential limitations of this study. (Page 13)*

*'Second, we performed a self-controlled case series study, which controls for non-time varying patient-specific measured and unmeasured confounders and has previously been shown to produce similar risk estimates to a new-user cohort study design.<sup>21</sup> While the self-controlled case series design adjusts implicitly for constant patient specific confounders, it is possible that the association observed may be biased due to time-varying confounders. Antidepressants, antipsychotics or antiepileptics are frequently co-prescribed with methylphenidate and may explain some of the association found with cardiovascular adverse events.<sup>29 30</sup> We adjusted all our analyses for time-varying comorbidities and co-medications however it is possible that other unmeasured time-varying confounders could have influenced our results. For example, there may be differences in ADHD symptom severity (along with symptoms of other disorders), substance use, and precipitating factors that may have influenced both the occurrence of a cardiovascular adverse event and methylphenidate exposure.'*

MINOR POINT:

4. It was difficult for me to assess whether the SCCS design was bi-directional or unidirectional.

Figure 2 did not resolve this issue for me. Perhaps a bit more detail is needed, like those in Maclure et al. Pharmacoepidemiol Drug Saf. 2012 Jan;21 Suppl 1:50-61.

**Author's response:** *Thank you for your constructive comments. We applied bi-directional SCCS design and modified the figure 2 according to your suggestion. (Page 17)*