Author’s response to reviews

Title: Association between pharmacotherapy for ADHD in offspring and depression-related specialty care visits by parents with a history of depression

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Author’s response to reviews:

Dear editor,

Thank you very much for giving us the opportunity to revise and resubmit our manuscript entitled “Association between pharmacotherapy for ADHD in offspring and depression-related hospital visit in parents with a history of depression” (BPSY-D-18-00713). We would like to thank the editor and the reviewer for the insightful comments and suggestions. We have now carefully revised the manuscript according to the comments as indicated below. We believe both the quality and readability of the manuscript have been considerably improved.

Editor Comments:

1. Please ensure that the manuscript abstract clearly states that this is a registry based study, with data being obtained from a variety of Swedish national registers.

We have added a clear statement regarding the data source in the methods section of the abstract, line 6, page 3.
“Using data from a variety of Swedish national registers, we conducted a cohort study with 8-year follow-up of 5605 parents (3872 mothers and 1733 fathers) who had a history of depression and an offspring diagnosed with ADHD.”

2. Please collate and place Figure Numbers/Titles/Legends in a dedicated section following the references.

The Figure has been placed after the Reference section, on page 21.

3. Please define the contribution of co-author Brian M D’Onofrio in the Authors’ contributions section of the Declarations.

We have revised the section of authors’ contributions as follows:

“… all authors QC, HL, CA, ZC, PL, BMD, JFL were involved in drafting subsequent versions of this article and revising it critically for important intellectual content. All authors gave their final approval of the version to be published.”

4. Please remove the short title on the title page.

The short title has been removed from the title page.

Reviewer report:

Matej Stuhec (Reviewer 1):

The authors have written about an understudied topic. There are few data on this topic and therefore this topic is interesting. This paper also provides important information from large national data. This paper is over well written article, and is easy to read. Although this paper is an interesting one it has some important limitations and questions, which should be addressed before eventual publication. The Methods and Results are easily and well presented. I am in favour for publication if these issues are discussed/responded.

However, in the current form presented, it requires a minor revision before consideration for publication.

The manuscript could be strengthened by attending to the following matters:
General remarks:

Positive:
- Few data on this topic
- New evidence in large national data form
- Important outcomes

Negative:
- Some important limitations

Specific remarks:

Abstract

Background:

1. I suggest to add »very« because effect sizes for ADHD medications are very high (eg=0.5-0.8 etc).

Given a lack of research in the topic understudy, there is no general agreement on how high the effect measured by hazard ratio should be considered high. We therefore decide to report the actual estimates of the rate and hazard ratio to facilitate comparisons with findings in future research.

Visit or visits?

We would like to apologize for the confusion and have rephrased the term “depression-related hospital visits” as “depression-related specialty care visits” or “depression-related visits” for short throughout the manuscript, including the title.

Conclusions

In my opinion conclusions are »too strong«, because there were twice more mothers than fathers included.

Although less fathers than mothers were involved in the current study, the sample sizes are fairly large for both mothers and fathers, which is reflected by the narrow confidence intervals. The conclusions regarding the association in fathers is therefore not strong but an objective summary of the main findings based on a long follow-up of a large sample of fathers. The lack of
statistical significance of the association in mothers is rather reliable considering our study included twice as many mothers than fathers.

BACKGROUND

Page 1:

Lines 2-3: Please use more references for the ADHD epidemiology. In many countries worldwide, ADHD prevalence is far from 5% in children and adolescents. Please use the following papers to cite the prevalence in different countries: The new metaanalysis written by Polanczyk J et al. published in Child Psychol Psychiatry. 2015 Mar;56(3):345-65 and the reference Croat Med J. 2015 Apr;56(2):159-65, where the epidemiology of ADHD in different countries has been cited.

I suggest to the authors to modify their first sentence. .. »worldwide, although data for some countries may be lower etc«.

We have revised the sentence and added the references according to the reviewer’s suggestion.

Introduction section, line 2, page 4:

“Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder affecting both children and adults [1-3].”

In addition, it is very important how many patients with ADHD are treated (after they have been diagnosed). I suggest to the authors to discuss about this topic, because after they research differences between treated and non-treated patients. This percentage may vary as was published by Stuhec and Locatelli (Eur Psychiatry. 2017 May;42:129-133. & Int J Clin Pharm. 2018 Apr;40(2):341-344.)

More than 77% children with ADHD were treated with ADHD medications. The information required by the reviewer can be found in the last line of Table 1 on page 10.

We have also acknowledged the limitation regarding generalizability of our study in the discussion section on line 4, page 14:

“…the generalizability of the findings to other populations is unclear but worth further investigation.”

We would also like to clarify that the conclusions of the current study were drawn mainly based on the results of within-individual comparisons, in which the same individual was compared with him or herself during on-vs. off-mediation periods.
Lines 24-27: »ADHD medication adherence«. Please explain what you mean under »adherence« …

Given that the precise definition of medication adherence in the study by Fridman et al. (reference #9) is rather complicated, we provided the reference for readers who are interested in the topic.

Medication adherence was originally defined by Fridman et al. as follows:

“Children/adolescents were classified as adherent if their caregivers reported “daily/always” prescriptions with an adherence of ≥80% on weekdays and ≥50% on average for weekends/holidays. In cases where the physician’s recommendation for dosing was “as needed”, caregivers were not asked about the percentage adherence. If the “as needed” recommendation was given for both weekdays and weekends/holidays, such patients were excluded from analyses involving adherence. However, if the “as needed” dosing recommendation, or a recommendation of “never”, was given only for weekends/holidays, adherence was calculated based on weekdays only.”

METHODS

Data sources and study population

Page 5

How is a possibility of this database that patient with existing diagnosis is not included in this database? Are any data on this topic? It would be highly advisable to include this data.

Thanks for pointing this out! We apologize for the confusion and have now clarified the coverage of the National Patient Register in the Method section, line 17, page 5:

“The National Patient Register was established in 1964 and covers almost 100% of inpatient care, with information on psychiatric inpatient care being added since 1973. From 2001 onwards, the register also includes data on outpatient specialty care visits to the public caregivers, whereas data from the private caregivers have been missing.”

Page 6

Lines 2-4: In 1992 there was no ICD-10 used by all member states (I think in 1994). Please re-modify.

The year 1992 was not the time when the offspring received his/her ADHD diagnosis.
In the current study, we adopted two inclusion criteria:

First, the offspring had to be born between January 1, 1992, and December 31, 2003;

Second, the offspring received an ICD-10 diagnosis of ADHD from 1997 onwards.

We have revised the sentence as follows: (in the Method section, line 5, page 6)

“By linking these registers, we identified offspring born between January 1, 1992, and December 31, 2003 and later diagnosed with ADHD according to the International Classification of Disease, 10th, revision (ICD-10 code: F90).”

How the authors checked that kids under 6 didn't receive ADHD medications? In some countries many of them are treated, although it is not supported by treatment guidelines. However, this important issue can change epidemiological values.

Since ADHD medications are only recommended for children at least 6 years old in Sweden, the follow-up of the parents started when their offspring were at least 6 years old. Hence, the parents were not under observation while their offspring were younger than 6 years old regardless of whether the offspring received ADHD medications or not. We did not check the number and proportion of ADHD medication treatment among offspring younger than 6, since this information is beyond the scope of the current study.

How was with possible »linking errors« when comparing more databases? This should be mentioned within limitations.

Every resident in Sweden is assigned a unique personal identity number (PIN). The PIN was pseudonymized and used for unambiguous linkage between the registers. A small number of duplicated PINs are removed by the database administrators before the data are used for research. The rate of linking error is therefore extremely low, if any. The low rate constitutes a major strength of the study rather than a limitation.

Treatment status by ADHD medication

Did the authors check that medications were used only for ADHD (e.g. for example methyphenidate is used for different purposes including sleeping problems)

In the current study, we restricted offspring to those diagnosed with ADHD. In extremely rare cases, they might have received diagnoses such as narcolepsy [4] in addition to ADHD. This, however, should not affect the results very much.

How the authors define patients treated with medications? (e.g. only one dose at least etc).

Unfortunately, data on dosage of medication is not readily usable for the current study.
Treatment status by ADHD medication is defined in the Method section, line 16, page 6:

“In the current study, we identified all dispensing dates of four stimulants (methylphenidate [N06BA04], amfetamine [N06BA01], dexamfetamine [N06BA02], and lisdeamfetamin [N06BA12]) and one non-stimulant (atomoxetine [N06BA09]) for treatment of ADHD. In accordance with prior research [5, 6], we divided the follow-up into time periods when offspring were on and off medication for treatment of ADHD. An offspring was considered on medication during the time interval between two consecutive ADHD medication dispensations no longer than 6-month (183 days) apart. An on-medication period started on the date of first dispensation and ended on the date of last dispensation. The remaining time periods were off-medication periods. A detailed description of the definition of exposed period can be found elsewhere [7].”

What about drug holidays patients? In the study period treatment guidelines have been changed from »favour« to »non-favour« drug holidays.

Unfortunately, information on drug holiday is not available in the register. An offspring was considered on medication during the time interval between two consecutive ADHD medication dispensations no longer than 6 months (183 days) apart. If a drug holiday is misclassified as on-medication period, it is likely to bias the estimated results towards null.

Outcome events:

What about if patient was already diagnosed with depression before the study period?

In the current study, all mothers and fathers were diagnosed with depression either before or at the start of follow-up. The start of follow up was defined as January 1, 2006, the offspring’s 6th birthday, or the first depression-related hospital visit, whichever came last. Time since prior depression-related hospital visit was selected as the underlying time scale in the Cox regression models to ensure perfect adjustment of the time scale. It should be noted that, in Cox models, the start of follow-up does not have to be the origin of the selected underlying time scale.

Covariates:

OK

Thank you!

Statistical analyses:

What about missing variables? How the authors defined them?
The absolute numbers and proportions of missingness on parental highest achieved education, civil status, and employment at baseline are displayed in Table 1 (all below 0.5%). Other variables had no missing values. It is reasonable to assume such extremely low proportions of missingness should not affect the between-individual analyses, and not at all influence the within-individual analyses given that these variables were constant for the same individuals and all time-constant factors were automatically adjusted for by within-individual comparisons.

Results:

Very clear presented.

Thank you!

Discussion:

It would be interesting to discuss about different impact on parents' depression according to different ADHD medications used.

Many limitations should be discussed according to the previous comments.

Given that the parents were not the actual patients who were treated by ADHD medications, our interest is primarily in exploring the impact of pharmacotherapy for ADHD in general among the children on depression in their parents. In addition, the vast majority of ADHD medications dispensed in Sweden are methylphenidate. Subgroup analysis by type of ADHD medication would therefore be largely underpowered except for methylphenidate. However, we agree with the reviewer that this is an interesting topic for future research.

(Skoglund et al., 2014) reference?

Thanks for pointing this out! The mistake has now been corrected. Please see reference #38 on page 20.

If medications were dispensed it is not necessary that they were taken. I think this is also an important issue, because more than 50% patients with ADHD do not take their medications.

We have acknowledged the limitation in the Discussion section, line 18, page 15:

“Although used in many studies, the definition might not precisely reflect the actual consumption of ADHD medications by the offspring.”

It is unclear to us based on what evidence the reviewer believes that more than 50% patients with ADHD do not take their medications. It is also unclear if the reviewer meant that 50% patients
do not take the medications at all. We would be happy to revise our manuscript if this issue is clarified.

References


