PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	”Use of corticosteroids during pregnancy and risk of asthma in offspring: A nationwide Danish cohort study”
AUTHORS	Byrjalsen, Anna; Frøslev, Trine; Telén Andersen, Ane Birgitte; Olsen, Morten; Toft Sørensen, Henrik

VERSION 1 - REVIEW

REVIEWER	Jason D. Pole Scientist, Pediatric Oncology Group of Ontario (POGO) Assistant Professor, Dalla Lana School of Public Health Adjunct Scientist, Hospital for Sick Children Research Institute Adjunct Scientist, Institute for Clinical Evaluative Sciences Canada
REVIEW RETURNED	21-Mar-2014

GENERAL COMMENTS	- In the methods section, I am a little confused about when the corticosteroid exposure is being measured. The authors indicate that the exposure period starts 30 days prior to pregnancy. Two issues arise when the authors indicate further categorization. One, it is not clear if first trimester exposure includes the 30 days before pregnancy? Two, the definition of former use provided indicates exposures any time prior to the pregnancy. It is not clear if this includes the 30 days discussed above and if previous pregnancies are included as part of the ‘former’ period. Given corticosteroid exposure is main exposure of the study clarity with regard to this definition is paramount. - The authors note that in Denmark the RMPS records all prescription reimbursement for prescribed medications from pharmacies. I wonder if pharmacies within hospitals (pharmacies not available to the public) are included in this system? Could patients have been exposed in hospital and the RMPS not recorded it? - It is curious that the authors elected to examine first trimester exposure to corticosteroids without consider other potentially critical time points during gestation. There is a body of work that has examined the development of asthma from a perinatal origin standpoint and this work focus on the placental polarization to Th2 dominance in late gestation. Widening the exposure window from other similar studies could alone provide for attenuated measures of association. It would be good to see different exposure windows or at a minimum for the authors to discuss the potential impact. - The authors use a novel definition of asthma. This definition would allow a patient to be classified as asthmatic with as little as a single outpatient record. The authors support their definition by referencing a previous validity study that used prescription information. I think this manuscript would be strengthened by knowing how each

	asthmatic subject was identified (number of inpatient, outpatient and ER visits and number of prescriptions). I would agree that many of the subjects would be identified by multiple prescriptions, but the decision of including some subjects with minimal evidence of asthma may bias the results. - With this novel definition of asthma, the authors do not mention how time may impact the definition. There could be differing amounts of time between the two prescriptions for example, or how long from birth a subject is diagnosed with asthma. How does time impact the definition? What does the distribution of asthmatics relative to time look like? - The within-mother-between-pregnancy analysis is a clever way to try and untangle the association being examined. Given corticosteroid administration is often related to chronic health conditions; wouldn't the order of the dis-concordant pairs potentially provide different results? I wonder if the authors could discuss a stratified analysis that examines the relationship in those who were exposed to corticosteroids with their first delivery as opposed to second delivery. - The authors discuss little potential for bias with regard to either the definition of exposure or outcome. Given there is no validity with regard to these definition presented, I think the authors need to acknowledge and discuss the potential for bias more fully. - The authors reference my work in the area incorrectly. The aHR for the later time period was not 0.75, it was 0.74 and the reference they provide for these estimates is not the manuscript that discusses the time varying effects. Please correct. - It is interesting that of the 43093 mothers who were diagnosed with asthma, only 10 % had corticosteroid exposure. This seems low and is worth a comment in the discussion. - The rate of corticosteroid exposure among pre-term infants seems very low. I am not sure if Denmark has different policies with regard to antenatal corticosteroid administration for per-term birth, but the proportion is not comparable to that in various parts of Canada. With that in mind, I am not sure if exposures are missed (see previous comment about hospital delivery of corticosteroid and capture in the administrative data) or if there are other reasons. This requires further investigation and comments by the authors.

REVIEWER	Laila Tata University of Nottingham, UK
REVIEW RETURNED	21-Mar-2014

GENERAL COMMENTS	A well written paper – my main concern is that the corticosteroid exposure is generalised to one exposure (as there are actually many forms of delivery and strength and uses). Despite excellent use of covariates (e.g. comorbidities) in relation to this, consideration is needed for description and breakdown rather than including all (from topical to oral) in the exposure. There is a separation of local and systemic, but this is not assessed across most of the analyses (including the different types of analysis such as the sibling pairs), which assess only steroid use in general. Different analytical

	methods will not help if different corticosteroids potentially have a different associated risk with asthma. Of course, I acknowledge that these breakdowns require statistical power that often goes beyond the large numbers already available – I would just like to see more discussion of this in the Discussion section (and some further breakdown in the results where feasible). Intro – whilst there is on specific sentence on ACSs, which have a very specific use, there needs to be further distinction in this in terms of which types of corticosteroids are being discussed (with respect to risks). ACS are very distinct from inhaled or oral corticosteroids (in use and indication) so it would be useful to clarify related risks, and provide a more specific definition of what is meant by 'maternal corticosteroid therapy' at the end of the introduction (and whether or not, this may, for example, include ACSs). Methods – There is considerable assumption that the reader knows about the structure of the Danish data linkages. Whilst I have knowledge about this, for an international journal, this needs description in the paper that is specific to this study for the reader to understand the linkages (and thus representativeness of the data). E.g. at the moment the first paragraph includes '…to perform unambiguous linkage among registries.' Yet there is no previous or subsequent mention of what the CRN was linked to (or from) or other registries. Description of how it links mothers to children, children to their diagnostic records and also women to drug dispensing records/registry is what is specifically needed for this study. I.e. it would be useful to say that the RMPS was linked using the CRN… -Discussion section needs information regarding local corticosteroids not all being included in the dispensing registry and whether this could have affected findings. -clarification of the timing of maternal diagnoses and covariates is needed in relation to the pregnancy (i.e. which were during/before pregnancy, were any subsequent to pregnancy/later in life). This needs explaining somewhat in relation to the results – for example, it is quite surprising that even 0.6% of women using and 0.3% not using had COPD – confirmation that this is before or during pregnancy would be helpful. -Could the reason for the additional"within-parents-between-pregnancy"analysis be justified – is there reason to believe that differing fathers could modify the corticosteroid-asthma relationship? Results and discussion -Much more detail is needed of what local and systemic corticosteroids were used (for example, to what extent did these include topical forms?) –I realised at the end that these are in the appendices, but within the paper there is only minimal breakdown to systemic and local in the analyses. The methods imply that they are analysed separately but most analyses are just 'any' corticosteroid. Despite adjustments for use, the individual corticosteroids could have varied use (frequency, mode of delivery) and strength. If some corticosteroids do have an effect, including others that do not within the exposure will lead towards a null finding across all the types of analytical approaches in the paper. This is not addressed in the results or at least should be a large part of the discussion.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name: Jason D. Pole
Institution and Country Scientist, Pediatric Oncology Group of Ontario (POGO)
Assistant Professor, Dalla Lana School of Public Health
Adjunct Scientist, Hospital for Sick Children Research Institute
Adjunct Scientist, Institute for Clinical Evaluative Sciences
Canada
Please state any competing interests or state 'None declared': None declared

- In the methods section, I am a little confused about when the corticosteroid exposure is being measured. The authors indicate that the exposure period starts 30 days prior to pregnancy. Two issues arise when the authors indicate further categorization. One, it is not clear if first trimester exposure includes the 30 days before pregnancy? Two, the definition of former use provided indicates exposures any time prior to the pregnancy. It is not clear if this includes the 30 days discussed above and if previous pregnancies are included as part of the 'former' period. Given corticosteroid exposure is main exposure of the study clarity with regard to this definition is paramount.

1) Authors respond:
The first trimester are the first 12 weeks of pregnancy, as children cannot be exposed until they are conceived. If the mother redeem a prescription for a corticosteroid 30 days prior to pregnancy, the child will be classified as exposed during the first trimester.
Former use was defined as corticosteroid use prior to the 30 before pregnancy. Former use was defined as any former use and as such also during previous pregnancies.
We have tried to clarify this page 7, line 16-20.

- The authors note that in Denmark the RMPS records all prescription reimbursement for prescribed medications from pharmacies. I wonder if pharmacies within hospitals (pharmacies not available to the public) are included in this system? Could patients have been exposed in hospital and the RMPS not recorded it?

2) Authors respond:
We do not have information on in hospital drug use. However, as corticosteroids are typically used to treat chronic inflammatory diseases and as admissions in relation to labour are rarely long lasting, we do think that we have captured the vast majority of mothers exposed to corticosteroids.
Included at page 13, line 5-12.

- It is curious that the authors elected to examine first trimester exposure to corticosteroids without consider other potentially critical time points during gestation. There is a body of work that has examined the development of asthma from a perinatal origin standpoint and this work focus on the placental polarization to Th2 dominance in late gestation. Widening the exposure window from other similar studies could alone provide for attenuated measures of association. It would be good to see different exposure windows or at a minimum for the authors to discuss the potential impact.

3) Authors respond:
We set out to investigate the exposure to corticosteroids during pregnancy and not only the perinatal period. The authors are aware of the work focusing on the perinatal period however corticosteroids are often used during the perinatal period to ensure lung maturation and thus administered to premature children who already have a higher risk of respiratory deficits. The first trimester was singled out as this is the period during gestation when organ development is mainly happening.
We discuss this in the section of the Discussion were we compare our results with the excellent work of the reviewer (the Canadian study by Pole et al., page 12, line 14-22).

- The authors use a novel definition of asthma. This definition would allow a patient to be classified as asthmatic with as little as a single outpatient record. The authors support their definition by referencing a previous validity study that used prescription information. I think this manuscript would be strengthened by knowing how each asthmatic subject was identified (number of inpatient, outpatient and ER visits and number of prescriptions). I would agree that many of the subjects would be identified by multiple prescriptions, but the decision of including some subjects with minimal evidence of asthma may bias the results.

4) Authors respond:
We acknowledge that this may be an issue, and have tried to address this in page 14 line 1-8.

- With this novel definition of asthma, the authors do not mention how time may impact the definition. There could be differing amounts of time between the two prescriptions for example, or how long from birth a subject is diagnosed with asthma. How does time impact the definition? What does the distribution of asthmatics relative to time look like?

5) Authors respond:
We did not look at time as a factor, except for the redemption of prescriptions for corticosteroids in mothers, which is how we defined the exposure. In theory there could be long periods of time in between the redemption of asthma medication in the children.

- The within-mother-between-pregnancy analysis is a clever way to try and untangle the association being examined. Given corticosteroid administration is often related to chronic health conditions; wouldn't the order of the dis-concordant pairs potentially provide different results? I wonder if the authors could discuss a stratified analysis that examines the relationship in those who were exposed to corticosteroids with their first delivery as opposed to second delivery.

6) Authors respond:
We agree with the reviewer that the order of exposed and unexposed pregnancies may be an issue. We believe we have addressed this in the analysis comparing unexposed firstborns with exposed secondborns. This analysis rendered similar results to the analysis in which the order of exposure status was random.

- The authors discuss little potential for bias with regard to either the definition of exposure or outcome. Given there is no validity with regard to these definition presented, I think the authors need to acknowledge and discuss the potential for bias more fully.

7) Authors respond:
Page 13, line 5-12, and page 14, line 1-8.

- The authors reference my work in the area incorrectly. The aHR for the later time period was not 0.75, it was 0.74 and the reference they provide for these estimates is not the manuscript that discusses the time varying effects. Please correct.

8) Authors respond:
This has been corrected.

- It is interesting that of the 43093 mothers who were diagnosed with asthma, only 10 % had corticosteroid exposure. This seems low and is worth a comment in the discussion.

9) Authors respond:
Page 13, line 13-18.

- The rate of corticosteroid exposure among pre-term infants seems very low. I am not sure if Denmark has different policies with regard to antenatal corticosteroid administration for per-term birth, but the proportion is not comparable to that in various parts of Canada. With that in mind, I am not sure if exposures are missed (see previous comment about hospital delivery of corticosteroid and capture in the administrative data) or if there are other reasons. This requires further investigation and comments by the authors.

10) Authors respond:
We do not have information on in hospital administered corticosteroids, and thus neither of antenatal corticosteroid therapy. Please see under the ”corticosteroids” section of the methods section (page 8, line 2-3).

Reviewer Name: Laila Tata
Institution and Country University of Nottingham, UK
Please state any competing interests or state ‘None declared’:non declared

Overall comments:
A well written paper – my main concern is that the corticosteroid exposure is generalised to one exposure (as there are actually many forms of delivery and strength and uses). Despite excellent use of covariates (e.g. comorbidities) in relation to this, consideration is needed for description and breakdown rather than including all (from topical to oral) in the exposure. There is a separation of local and systemic, but this is not assessed across most of the analyses (including the different types of analysis such as the sibling pairs), which assess only steroid use in general. Different analytical methods will not help if different corticosteroids potentially have a different associated risk with asthma. Of course, I acknowledge that these breakdowns require statistical power that often goes beyond the large numbers already available – I would just like to see more discussion of this in the Discussion section (and some further breakdown in the results where feasible).

11) Authors respond:
We have discussed this a lot amongst the authors and do recon that this is an issue. We have not divided the sibling analysis into local or systemic due to lack of statistical power and as the main results (divided into local and systemic) render almost the same estimate, we do not believe that such a subdivision will alter the results markedly. The analysis can be done if required.
Page 13, line 19-24.

Intro – whilst there is one specific sentence on ACSs, which have a very specific use, there needs to be further distinction in this in terms of which types of corticosteroids are being discussed (with respect to risks). ACS are very distinct from inhaled or oral corticosteroids (in use and indication) so it would be useful to clarify related risks, and provide a more specific definition of what is meant by ‘maternal corticosteroid therapy’ at the end of the introduction (and whether or not, this may, for example, include ACSs).

12) Authors respond:
Page 5, line 16-20.

Methods
– There is considerable assumption that the reader knows about the structure of the Danish data linkages. Whilst I have knowledge about this, for an international journal, this needs description in the paper that is specific to this study for the reader to understand the linkages (and thus representativeness of the data). E.g. at the moment the first paragraph includes '…to perform unambiguous linkage among registries.' Yet there is no previous or subsequent mention of what the CRN was linked to (or from) or other registries. Description of how it links mothers to children, children to their diagnostic records and also women to drug dispensing records/registry is what is specifically needed for this study. I.e. it would be useful to say that the RMPS was linked using the CRN…

13) Authors respond:
Page 8, line 2.

-Discussion section needs information regarding local corticosteroids not all being included in the dispensing registry and whether this could have affected findings.

14) Authors respond:
Page 13, line 5-9.

-clarification of the timing of maternal diagnoses and covariates is needed in relation to the pregnancy (i.e. which were during/before pregnancy, were any subsequent to pregnancy/later in life). This needs explaining somewhat in relation to the results – for example, it is quite surprising that even 0.6% of women using and 0.3% not using had COPD – confirmation that this is before or during pregnancy would be helpful.

15) Authors respond:
Diagnoses included were diagnoses given before/during pregnancy.

-Could the reason for the additional"within-parents-between-pregnancy"analysis be justified – is there reason to believe that differing fathers could modify the corticosteroid-asthma relationship?

16) Authors respond:
The rationale of this analysis was to make sure that the siblings had the exact same genetic background, thus if one father had severe asthma and father number 2 did not, the genetic background for the siblings would be somewhat different.

Results and discussion
-Much more detail is needed of what local and systemic corticosteroids were used (for example, to what extent did these include topical forms?) –I realised at the end that these are in the appendices, but within the paper there is only minimal breakdown to systemic and local in the analyses. The methods imply that they are analysed separately but most analyses are just 'any' corticosteroid. Despite adjustments for use, the individual corticosteroids could have varied use (frequency, mode of delivery) and strength. If some corticosteroids do have an effect, including others that do not within the exposure will lead towards a null finding across all the types of analytical approaches in the paper. This is not addressed in the results or at least should be a large part of the discussion.

17) Authors respond:
Page 5, line 16-20.
Page 13, line 5-12.

VERSION 2 – REVIEW

REVIEWER	Jason D. Pole Scientist, Pediatric Oncology Group of Ontario (POGO) Assistant Professor, Dalla Lana School of Public Health Adjunct Scientist, Hospital for Sick Children Research Institute Adjunct Scientist, Institute for Clinical Evaluative Sciences Canada
REVIEW RETURNED	08-May-2014

GENERAL COMMENTS	Two minor edits. (1) Page 7, Line 44, I think you need to add 'days' after '30'. (2) Page 13, Line 42, I think 'does' should be 'do'.

REVIEWER	Laila Tata University of Nottingham, UK
REVIEW RETURNED	28-Apr-2014

- The reviewer completed the checklist but made no further comments.