PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Exposure to selective serotonin reuptake inhibitors and the risk of congenital malformations: a nation-wide cohort study
AUTHORS	Espen Jimenez-Solem, Jon Trærup Andersen, Morten Petersen, Kasper Broedbaek, Jonas Krogh Jensen, Shoaib Afzal, Gunnar Gislason, Christian Torp-Pedersen, Henrik Enghusen Poulsen

VERSION 1 - REVIEW

REVIEWER	Heli Malm, MD, PhD Teratology information, HUSLAB and Helsinki University Central Hospital PBOX 790 00029 HUS Finland I have no potential conflicts of interest
REVIEW RETURNED	02/04/2012

GENERAL COMMENTS	This manuscript is clearly written, based on the ever-continuing debate of the possible teratogenicity of SSRIs. The authors have compared exposure during organogenesis to exposure only before concep-tion or after pregnancy – a welcome methodology in trying to separate confounding by indication. The results suggest that confounding by indication may play a major role. Comments: Throughout the text, the authors use: ..'pausing exposure during pregnancy'. For the reader, it would be more clear to say: ..'pausing exposure before conception'. The dose: What was the basis for the low vs. high dose? This could be shortly commented. For exam-ple, for paroxetine, the starting dose in major depression is often 20mg/d. One possible explanation could be that the women using SSRIs have had a previous pregnancy with complications including fetal malformation, increasing anxiety and use of SSRis. These women would then easily stop the medication before a planned pregnancy but their offspring would possibly be at an increased risk on hereditable basis. Is there a possibility to check on previous pregnancies in this database? Table 1. As the numbers of unexposed are high, all differences are likely to be statistically significant. I suggest to delete the P-values from the table. Major: Table 2. and Figure 1. As ventricular septal defects and limb

	defects are more common in the 'paused exposure' group than in the exposed group, this raises the serious question about the possible explanation. The first question to rise is if these women are then more prone to use other psychotropic drugs or alcohol when they stop SSRI treatment and continue to suffer from depressive/ anxiety symptoms. The authors mention in the Results that including other psychiatric drugs did not significantly change the results. However, it would have been interesting to have this information included (adjusment made for other psych drug use) in the Table 2 and the Figure 1 results. The issue I am most worried about and which is not discussed at all in the text is that in supplement A, of severe congenital malformations there is only one neural tube defect among the over 4,000 SSRI exposed. This is naturally due to the fact that most pregnancies with a NTD fetus are terminated as prenatal diagnostics reach most pregnant women (practically all in Scandinavian countries). Therefore data on pregnancies ending in birth today are not a reliable source of information on the prevalence of severe congenital anomalies, as most of these pregnancies are electively terminated. This study material did not include data on elective pregnancy terminations due to fetal congenital anomaly, and may therefore give rise to false safety evaluation. This issue should be discussed. Few registers include data on pregnancy terminations but in the Finnish study (Malm et al. 2011) also elective terminations due to major fetal anomaly were included. Minor: Page 18. The authors falsely comment on the Finnish study that exposure was defined as redemption of the SSRI prescription between one month before pregnancy and birth. In that study, congenital anomalies were analyzed in the fetuses/ infants of mothers purchasing the drug during the first trimester (1 month before until 12 weeks post LMP). Page 18. In the Swedish material, most pregnant women are interviewed during the first trimester and major recall bias is therefore unlikely. Page 18. In both the Swedish (Reis and Källen 2010) and the Finnish study (Malm et al 2011), adjustments were made with smoking, which is a strong proxy for socioeconomic status in these countries. The situation may be different in Denmark and it may therefore be justified to include both smoking and SES in the analysis, contrary to Sweden and Finland.

REVIEWER	Lars Henning Pedersen Assistant professor, MD, PhD Dept. ObGyn, Institute of Clinical Medicine Aarhus University Aarhus, Denmark
REVIEW RETURNED	03/04/2012

THE STUDY	The limitation of one of the two exposure groups is not adequately described
RESULTS & CONCLUSIONS	The limitation of one of the two exposure groups is not adequately described
GENERAL COMMENTS	Review:

	"Exposure to selective serotonin reuptake inhibitors and the risk of congenital malformations: a nation-wide cohort study." (Manuscript ID bmjopen-2012-001148) The paper use information from a very large dataset in order to further describe the potential association between SSRIs and malformation, with specific focus on confounding by indication. The method used by the authors is indeed intelligent with parallels to e.g. Samy Suissas work. The results are very intriguing and may corroborate that confounding by indication is an important part of the causal relation. This is far from a new thought but the paper is one of the few studies that might provide evidence for such an explanation. However, there are some important limitations to the method that needs to be discussed in more details than provided in the current version of the paper. The main new result in the paper is based on the interpretation of women that “paused” SSRI use during pregnancy. It is crucial for the interpretation that these women are not exposed during pregnancy. Had the women in the pause group used SSRIs e.g. up to the point in time of a positive pregnancy test, the interpretation would be difficult, as heart malformations may be caused by exposure very early in pregnancy prior to the normal timing of an early pregnancy test (e.g. one week after a missed period). The authors use no redemption to prescriptions 3 months or more prior to the beginning of gestation as the “wash-out” period. This may be too short for a number of reasons: 1) Many SSRIs tablets have a scoreline. In a scenario where a women redeems a prescription 3 months prior to gestation for e.g. citalopram 40 mg and her symptoms diminishes one month later, her doctor may half the dose. That would change the treatment to ½ pill a day and the prescription would then overall imply exposure for 5 months in total and thus exposure during early pregnancy (or until a postitive pregnancy test, see 4) below). Such change would not be detectable in the registry. 2) Women may get prescriptions to 100 units of SSRIs. If a treatment is ongoing, and the women were already in treatment 3 months prior to gestation, few would redeem the prescription when they take the last pill of the prior batch. 3) The half-life of the active metabolite of fluoxetine is more than 14 days (and may be even longer due to dose dependent metabolism). Again, in the scenario of a prescription 3 months prior to the beginning of gestation, the embryo could be exposed to SSRIs during heart development even is the woman stops immediately after their intended last period. 4) In many cases women would use medication until they get pregnant and stop after a positive pregnancy test. The method used in the paper suggest a scenario were the women that redeem a prescription 3 months prior to pregnancy stop before or just after intended last period and get pregnant. This is of cause possible but again it does suggest the possibility that the 3 months wash-up period is to short. 5) The women may have used the medication differently from the prescriptions, e.g. paused during the prescription period and started again (e.g. overlapping with pregnancy). This is always a problem in studies using prescription data but when data is used to define a

	non-exposure group, misclassification may lead to bias away from unity (in the analysis “paused” vs. unexposed). This limitation needs to be discussed in detail and it would be of interest to see the analysis with wash-out periods of 6 and 9 months. Furthermore, the limitations in my mind call for more careful wording in both the abstract, the Key Messages and especially in the conclusion (p.21). Specific comments: Introduction: p.5, l.11: “…studies including up to a million pregnancies indicate little risk of congenital malformations”, the references must be for the first part of the sentence, as many of the studies do suggest associations with malformations, including neural tube defects (Malm 2011) and heart malformations (Berard 2007 and Pedersen 2009). p.5, l.16: Given the limitations, maybe the authors could describe the method (e.g. “did not redeem a prescription 3 months prior to pregnancy”) instead of using the word paused. Method: p.7, l.19: Why did the authors limit the group to the same SSRI? The guidelines recommend paroxetine or sertraline (citalopram as 3rd choice) during breast feeding, that could limit the group unnecessarily. p.7, l.21: There are limitations to the interpretation of the dosage, see above comment. Discussion: p.17, l. 20: The sentence is somewhat misleading as the references describe associations between specific SSRIs and malformations (Malm, Berard, Källen). It seems that the sentence describes, that several studies have found no associations between SSRIs and major malformations overall. p.20, l.4: The described information bias is very important. p.20. l.9: However, misclassification of the paused group may lead to bias away from unity, as described above. p.21: Confounding by indication may be one explanation but information bias is also a potential part of the potential causal relation as described. Overall, I agree with the authors that the association between SSRIs and heart malformation may be caused by systematic error. However, the intelligent method used in the paper deserves a more thorough discussion of the limitations, also when concluding on the data. Alternatively, the authors may provide analyses with longer wash-out periods. Such analyses may attenuate the potential confounding by indication but would make the results less prone to the described misclassification in the pause group central to this paper.

VERSION 1 – AUTHOR RESPONSE

AUTHOR RESPONSE

We would like to thank the reviewers for their thorough comments and constructive criticism. In the following we respond to their observations point-by-point and indicated where in the text of the article changes have been made, where appropriate. Reference to page (p.) and line (l.) numbers refer to

the new main document.

Reviewer 1

Reviewer: Heli Malm, MD, PhD
Teratology information, HUSLAB and Helsinki University Central Hospital

Comment
Throughout the text, the authors use: ..'pausing exposure during pregnancy'. For the reader, it would be more clear to say: ..'pausing exposure before conception'.

Response
We agree with the reviewer that the phrasing used can be misleading. We have therefore changed the word 'pausing' with 'paused' where appropriate. We have chosen not to use the reviewer's suggestion of 'pausing exposure before conception' since we want to emphasize that this group of women not only paused exposure before conception, but furthermore had no exposure during the whole pregnancy, and then restarted exposure after pregnancy. Changes were made in the following places of the article: p. 2, l. 14 and 19; p. 4, l. 5 and 10; p. 7, l. 16; p. 12, l. 13 and 15; p. 17, l. 7 and p. 18, l. 19.

Comment
The dose: What was the basis for the low vs. high dose? This could be shortly commented. For example, for paroxetine, the starting dose in major depression is often 20mg/d.

Response
The cut-off values for low and high doses chosen for the different SSRIs were based on the recommended standard dose. On p. 8, l 4, we state that the cut-off value for paroxetine is 10 mg. This is regrettably a typo and it has been corrected to 20 mg. We have furthermore added the word 'recommended' on p. 8, l. 2.

Comment
One possible explanation could be that the women using SSRIs have had a previous pregnancy with complications including fetal malformation, increasing anxiety and use of SSRis. These women would then easily stop the medication before a planned pregnancy but their offspring would possibly be at an increased risk on hereditable basis. Is there a possibility to check on previous pregnancies in this database?

Response
We agree with the reviewer's comment. We have the possibility to check for previous pregnancies in our cohort. We find that no woman exposed to an SSRI (during the first trimester or paused during pregnancy) and giving birth to a child with a malformation had had a previous pregnancy ending in a child with a malformation or other serious birth outcome (stillbirth or neonatal death).

Comment
Table 1. As the numbers of unexposed are high, all differences are likely to be statistically significant. I suggest to delete the P-values from the table.

Response
We agree that such a large population will frequently yield covariates that are statistically significantly

different between groups. Still, we find it important to emphasize differences and similarities in basic characteristics between women exposed to an SSRI during pregnancy, and unexposed women or women with paused exposure during pregnancy. As an example, women with exposure during the first trimester do not differ from women with paused exposure in smoking habits and BMI. We believe that the p-values in table 1 help the reader discover these comparisons in an otherwise very busy table. We have therefore chosen not to delete the p-values from Table 1.

Comment
Major: Table 2. and Figure 1. As ventricular septal defects and limb defects are more common in the 'paused exposure' group than in the exposed group, this raises the serious question about the possible explanation. The first question to rise is if these women are then more prone to use other psychotropic drugs or alcohol when they stop SSRI treatment and continue to suffer from depressive/ anxiety symptoms. The authors mention in the Results that including other psychiatric drugs did not significantly change the results. However, it would have been interesting to have this information included (adjusment made for other psych drug use) in the Table 2 and the Figure 1 results.

Response
We have added an additional table as Supplement B where we show our analyses further adjusted for psycholeptics (ATC code N05) and antidiabetics (ATC code A10). We did not add this information in Table 2 because we feel the table would be too busy. No information was added to Figure 1 since it only includes rates with no adjustments. We have added a reference to Supplement B on p. 16, l. 9. The word 'benzodiazepines' on p. 16, l 6, has been removed, because benzodiazepines are categorized under psycholeptics.

Comment
The issue I am most worried about and which is not discussed at all in the text is that in supplement A, of severe congenital malformations there is only one neural tube defect among the over 4,000 SSRI exposed. This is naturally due to the fact that most pregnancies with a NTD fetus are terminated as prenatal diagnostics reach most pregnant women (practically all in Scandinavian countries). Therefore data on pregnancies ending in birth today are not a reliable source of information on the prevalence of severe congenital anomalies, as most of these pregnancies are electively terminated. This study material did not include data on elective pregnancy terminations due to fetal congenital anomaly, and may therefore give rise to false safety evaluation. This issue should be discussed. Few registers include data on pregnancy terminations but in the Finnish study (Malm et al. 2011) also elective terminations due to major fetal anomaly were included.

Response
We thank the reviewer for pointing out this important piece of missing information. The reviewer is correct to point out the lack of discussion regarding one of the important limitations of the study. Regrettably we do not have access to information on electively terminated pregnancies due to malformations. We will investigate this issue further and try to include it in future studies. On the basis of the reviewers comment we have added a section in the article's discussion under the heading 'Strengths and limitations'; p. 20, l. 9-12.

Comment
Minor: Page 18. The authors falsely comment on the Finnish study that exposure was defined as redemption of the SSRI prescription between one month before pregnancy and birth. In that study, congenital anomalies were analyzed in the fetuses/ infants of mothers purchasing the drug during the first trimester (1 month before until 12 weeks post LMP).

Response
We deeply regret this misunderstanding and thank the reviewer for pointing it out. The mistake is now corrected and the interpretation of this exposure time changed on p. 18, l. 13-16.

Comment
Page 18. In the Swedish material, most pregnant women are interviewed during the first trimester and major recall bias is therefore unlikely.

Response
We agree with this comment and added the term 'although unlikely' on p. 18, l. 6.

Comment
Page 18. In both the Swedish (Reis and Källen 2010) and the Finnish study (Malm et al 2011), adjustments were made with smoking, which is a strong proxy for socioeconomic status in these countries. The situation may be different in Denmark and it may therefore be justified to include both smoking and SES in the analysis, contrary to Sweden and Finland.

Response
We agree that smoking is a marker for socioeconomic status, but smoking may affect pregnancy on its own. Since we had access to both socioeconomic status and smoking we included both in the analyses.

Reviewer 2
Reviewer: Lars Henning Pedersen
Assistant professor, MD, PhD
Dept. ObGyn, Institute of Clinical Medicine
Aarhus University
Aarhus, Denmark

Comment
The main new result in the paper is based on the interpretation of women that "paused" SSRI use during pregnancy. It is crucial for the interpretation that these women are not exposed during pregnancy. Had the women in the pause group used SSRIs e.g. up to the point in time of a positive pregnancy test, the interpretation would be difficult, as heart malformations may be caused by exposure very early in pregnancy prior to the normal timing of an early pregnancy test (e.g. one week after a missed period). The authors use no redemption to prescriptions 3 months or more prior to the beginning of gestation as the "wash-out" period. This may be too short for a number of reasons:

1) Many SSRIs tablets have a scoreline. In a scenario where a women redeems a prescription 3 months prior to gestation for e.g. citalopram 40 mg and her symptoms diminishes one month later, her doctor may half the dose. That would change the treatment to ½ pill a day and the prescription would then overall imply exposure for 5 months in total and thus exposure during early pregnancy (or until a postitive pregnancy test, see 4) below). Such change would not be detectable in the registry.

2) Women may get prescriptions to 100 units of SSRIs. If a treatment is ongoing, and the women were already in treatment 3 months prior to gestation, few would redeem the prescription when they take the last pill of the prior batch.
3) The half-life of the active metabolite of fluoxetine is more than 14 days (and may be even longer

due to dose dependent metabolism). Again, in the scenario of a prescription 3 months prior to the beginning of gestation, the embryo could be exposed to SSRIs during heart development even is the woman stops immediately after their intended last period.

4) In many cases women would use medication until they get pregnant and stop after a positive pregnancy test. The method used in the paper suggest a scenario were the women that redeem a prescription 3 months prior to pregnancy stop before or just after intended last period and get pregnant. This is of cause possible but again it does suggest the possibility that the 3 months wash-up period is to short.

5) The women may have used the medication differently from the prescriptions, e.g. paused during the prescription period and started again (e.g. overlapping with pregnancy). This is always a problem in studies using prescription data but when data is used to define a non-exposure group, misclassification may lead to bias away from unity (in the analysis "paused" vs. unexposed).

This limitation needs to be discussed in detail and it would be of interest to see the analysis with wash-out periods of 6 and 9 months. Furthermore, the limitations in my mind call for more careful wording in both the abstract, the Key Messages and especially in the conclusion (p.21).

Response
We thank the reviewer for this detailed and constructive comment and we agree with the reviewer about what he rightfully points out. However, we defined exposure periods based on an algorithm, and not solely on date of redemption. This algorithm calculates exposure periods based on the redeemed drug; its strength, the recommended dosage and number of pills redeemed. It estimates the daily dosage at each new dispensing by calculating an average dosage from up to seven consecutive prescriptions prior to the actual prescription, constituting a treatment interval. We included women in the group with 'paused exposure' if their treatment interval ended before three months before conception.
This means, that if a woman redeemed a prescription of an SSRI, for example, 6 months before pregnancy we would calculate her treatment interval based on the number of pills redeemed and her prior prescriptions. If her treatment interval would stretch beyond three months before conception she would not be included in the group with paused exposure. On the contrary, if her treatment interval ended before three months before conception and she didn't redeem any SSRI until after pregnancy she would be included in the group with paused exposure. Most of these women (depending on their estimated dosage and the number of redeemed pills) redeemed their last prescription at least 6 months before conception. We believe that this ensured no exposure during pregnancy in the four first scenarios mentioned by the reviewer
Regarding scenario number 5. Due to the observational nature of the study we cannot account for the women's compliance. We agree with the reviewers comment that the women could have stopped treatment and started again during pregnancy. We believe that this scenario would apply to very few of our cases due to the chosen, long drug-free period of three months before conception.
We hope that our response answers the questions raised by the reviewer, and we choose therefore not to perform further analyses with wash-out periods of 6 or 9 months as suggested. Furthermore, we believe that the theoretical limitations concerning the definition of 'paused exposure' do not call for changes in the abstract, key message and conclusion.

Specific comments:
Introduction:
p.5, l.11: "…studies including up to a million pregnancies indicate little risk of congenital malformations", the references must be for the first part of the sentence, as many of the studies do suggest associations with malformations, including neural tube defects (Malm 2011) and heart

malformations (Berard 2007 and Pedersen 2009).

Response
We agree that the references might be misleading and we have therefore changed the positioning of the references to the first part of the sentence on p. 5, l. 11.

Comment
p.5, l.16: Given the limitations, maybe the authors could describe the method (e.g. “did not redeem a prescription 3 months prior to pregnancy”) instead of using the word paused.

Response
We refer to our response of reviewer 2’s first comment which we believe answers the present question.

Comment
Method:
p.7, l.19: Why did the authors limit the group to the same SSRI? The guidelines recommend paroxetine or sertraline (citalopram as 3rd choice) during breast feeding, that could limit the group unnecessarily.

Response
We agree with the reviewer that this limitation is very conservative. We did not allow for change in type of SSRI in order to ensure comparability between women exposed during the first trimester and women with paused exposure. Furthermore, we believe that we increase the probability of a more correctly defined pause by limiting exposure to the same SSRI. As the reviewer rightfully points out, this could limit the group unnecessarily, and increase the uncertainty of our estimates. On the other hand, we did find statistically increased risks for women with paused exposure. We have added a more detailed explanation of our choice on p. 7, l. 20-21.

Comment
p.7, l.21: There are limitations to the interpretation of the dosage, see above comment.

Response
The definition of the daily dosage was based on the mean dose for the corresponding treatment interval. The study is though based on registers, and therefore we could not account for lack of compliance. Compliance has though been estimated to be 80% among pregnant women in Denmark, and we believe that misclassification into low and high dose is minimal.

Comment
Discussion:
p.17, l. 20: The sentence is somewhat misleading as the references describe associations between specific SSRIs and malformations (Malm, Berard, Källen). It seems that the sentence describes, that several studies have found no associations between SSRIs and major malformations overall.

Response
We thank the reviewer for pointing this misleading sentence. We have added the word ‘overall’ at the end of the sentence (p. 17, l. 20) to clarify that these studies have found no association with major malformations overall and not with specific major malformations.

Comment
p.20, l.4: The described information bias is very important.

Response
We agree with the reviewer that information bias (diagnostic suspicion bias) could be part of the explanation of our findings, and that it should be emphasized more in the article. We have therefore expanded the discussion on the issue on p. 20, l. 6-8.

Comment
p.20. l.9: However, misclassification of the paused group may lead to bias away from unity, as described above.

Response
Please refer to our response of reviewer 2's first comment which we believe answers the present question.

Comment
p.21: Confounding by indication may be one explanation but information bias is also a potential part of the potential causal relation as described.

Response
We agree that the conclusion should include the importance of information bias. This has been added on p. 21, l. 15-17.

Other changes made by the authors.
Typos
In table 1 and table 3, some places where the second decimal of a number was '0' it was omitted. This has now been corrected.

VERSION 2 – REVIEW

REVIEWER	Lars Henning Pedersen Assistant professor, MD, PhD Dept. ObGyn, Institute of Clinical Medicine Aarhus University Aarhus, Denmark
REVIEW RETURNED	18/04/2012

GENERAL COMMENTS	This is an excellent study but it needs to acknowledge the limitations of the method or provide evidence that proves otherwise. The women in the paused group might be exposed during pregnancy in spite of the algorithm. The paper uses a method described by Fosbøl et al. That paper analyses NSAID use. SSRI exposure is different. Importantly, due to the risk of discontinuation symptoms, patients need to taper the dose. As a result, even in the case of a woman with up to 7 consecutive redemptions to SSRIs, you would not expect the dose stated in the last prescription to hold.

	Further, the dose-effect relation is more complex than for NSAIDs. A redeemed prescription to 100 pills 20 mg fluoxetine or citalopram would probably suggest 3 months exposure in the algorithm. Yet, if the dose is later tapered to 10 mg, the exposure period may overlap with early heart development if the prescription is redeemed even 6 months prior to gestation (due to the other issues pointed out previously, e.g. latency to use a new prescription, half-life etc.). The problem is the subsequent potential bias away from the null in this scenario. Additionally, as the authors acknowledge, some women might have stopped treatment and started again overlapping with pregnancy, which would also lead to bias away from unity. The above scenarios are not common but the point is that it will be the case for some (that's an observation from at least one Danish obstetric dept.) and the magnitude of the resulting bias is undetermined. The response from the authors that "most" women redeemed at least 6 months prior to gestation is not an entirely valid epidemiological argument. Further, for the potential stop-start women, they reply "[…] this scenario would apply to very few of our cases due to the chosen, long drug-free period of three months before conception". That faith may be wrong given the above and at least, even in an observational study, limitations of this nature needs to be discussed in the paper. For a hands-on approach to the magnitude of see e.g. Grzeskowiak et al 2011 (1). In conclusion, this great study needs analyses with e.g. a longer wash out period to further describe the potential exposure misclassification. Alternatively, the discussion and conclusion need to be moderated to reflect the potential bias away from the null in the specific group (in contrast to the bias toward the null in the other group). 1. Grzeskowiak LE, Gilbert AL, Morrison JL. Exposed or not exposed? Exploring exposure classification in studies using administrative data to investigate outcomes following medication use during pregnancy. Eur J Clin Pharmacol 2011.

REVIEWER	Heli Malm, MD, PhD Teratology information, Helsinki University Central Hospital and HUSLAB, Helsinki, Finland and Department of Clinical Pharmacology, Helsinki University and Helsinki University Central Hospital, Helsinki, Finland No competing interests
REVIEW RETURNED	18/04/2012

GENERAL COMMENTS	I would still argue with the discussion part of including socioeconomic factors in the analyses. As smoking is strongly asscoiated with lower socioeconomic status, including only one of these variables in the analyses - like smoking in the Swedish and the Finnish studies - should be considered sufficient.

VERSION 2 – AUTHOR RESPONSE

We would like to thank the reviewers again for their constructive suggestions and thorough comments. In the following we respond to their observations and indicated where in the text of the article changes have been made, where appropriate. Reference to page (p.) and line (l.) numbers refer to the new main document.

Reviewer 1

Reviewer: Lars Henning Pedersen, MD, PhD.
Assistant professor, Dept. ObGyn, Institute of Clinical Medicine, Aarhus University Aarhus, Denmark & Research Fellow, Dept. Fetal Medicine, Royal Prince Alfred Hospital, Sydney, Australia

Comment
This is an excellent study but it needs to acknowledge the limitations of the method or provide evidence that proves otherwise.

The women in the paused group might be exposed during pregnancy in spite of the algorithm. The paper uses a method described by Fosbøl et al. That paper analyses NSAID use. SSRI exposure is different. Importantly, due to the risk of discontinuation symptoms, patients need to taper the dose. As a result, even in the case of a woman with up to 7 consecutive redemptions to SSRIs, you would not expect the dose stated in the last prescription to hold. Further, the dose-effect relation is more complex than for NSAIDs.

A redeemed prescription to 100 pills 20 mg fluoxetine or citalopram would probably suggest 3 months exposure in the algorithm. Yet, if the dose is later tapered to 10 mg, the exposure period may overlap with early heart development if the prescription is redeemed even 6 months prior to gestation (due to the other issues pointed out previously, e.g. latency to use a new prescription, half-life etc.). The problem is the subsequent potential bias away from the null in this scenario.

Additionally, as the authors acknowledge, some women might have stopped treatment and started again overlapping with pregnancy, which would also lead to bias away from unity.

The above scenarios are not common but the point is that it will be the case for some (that's an observation from at least one Danish obstetric dept.) and the magnitude of the resulting bias is undetermined. The response from the authors that "most" women redeemed at least 6 months prior to gestation is not an entirely valid epidemiological argument. Further, for the potential stop-start women, they reply "[…] this scenario would apply to very few of our cases due to the chosen, long drug-free period of three months before conception". That faith may be wrong given the above and at least, even in an observational study, limitations of this nature needs to be discussed in the paper.

For a hands-on approach to the magnitude of see e.g. Grzeskowiak et al 2011 (1).

In conclusion, this great study needs analyses with e.g. a longer wash out period to further describe the potential exposure misclassification. Alternatively, the discussion and conclusion need to be moderated to reflect the potential bias away from the null in the specific group (in contrast to the bias toward the null in the other group).

1. Grzeskowiak LE, Gilbert AL, Morrison JL. Exposed or not exposed? Exploring exposure classification in studies using administrative data to investigate outcomes following medication use during pregnancy. Eur J Clin Pharmacol 2011.

Response

We thank the reviewer for his detailed comment and agree with his observations. On the basis of the comment, we acknowledge the need for further analyses to assess a possible exposure misclassification of women pausing treatment before conception. As the reviewer suggests we have performed additional analyses including women exposed to an SSRI who paused treatment six and nine months before conception. A table containing these results has been added as a supplementary table, and additional text has been added to the manuscript in the results section; p.12, l 19-21, and the discussion section; p. 20, l. 23, and p.21, l. 1-5.

Reviewer 2

Reviewer: Heli Malm, MD, PhD
Teratology information, Helsinki University Central Hospital and HUSLAB, Helsinki, Finland
and Department of Clinical Pharmacology, Helsinki University and Helsinki University Central Hospital, Helsinki, Finland

Comment
I would still argue with the discussion part of including socioeconomic factors in the analyses. As smoking is strongly asscoiated with lower socioeconomic status, including only one of these variables in the analyses - like smoking in the Swedish and the Finnish studies - should be considered sufficient.

Response
We thank the reviewer for this very interesting comment.
In our a priori hypothesis we included smoking, education and household income as independent variables. In this particular cohort, in our adjusted statistical analysis both education and income were statistically significant associated with our outcomes, and therefore we conclude that both education (p=0.002) and income (p=0.001) have a predictive value in spite of adjustment for smoking. On the basis of these results we believe that education and income can be included in the model together with smoking in this study. We have consulted this matter with the Copenhagen University's Biostatistics Department. In addition, we have performed analyses without education and income as covariates, and the results yielded nearly identical estimates and confidence intervals as our primary analyses: Major malformations overall; adjusted OR=1.33 (95% CI, 1.15-1.53), malformations of the heart; adjusted OR=2.04 (95% CI, 1.63-2.57). We have added a sentence in the manuscript, p.18, l. 22-23 and p.19, l. 1.

Other changes made by the authors.
A sentence has been added under Acknowledgments, p. 22, l. 9-12.

VERSION 3 – REVIEW

REVIEWER	Lars Henning Pedersen Assistant professor, MD, PhD Dept. ObGyn, Institute of Clinical Medicine Aarhus University Aarhus, Denmark
REVIEW RETURNED	18/04/2012

GENERAL COMMENTS	The authors have sufficiently addressed my comments. The paper is well written and the results are of both clinical and theoretical importance.