

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Use of selective serotonin reuptake inhibitors and lifestyle among women of childbearing age: a Danish cross-sectional survey
AUTHORS	Laugesen, Kristina; Telén Andersen, Ane Birgitte; Nørgaard, Mette; Beck Nielsen, Rikke; Wernich Thomsen, Reimar; Breinholt Larsen, Finn; Toft Sørensen, Henrik

VERSION 1 - REVIEW

REVIEWER	Dr. Helga Zoëga, assistant professor of public health, Centre of Public Health Sciences, Faculty of Medicine, University of Iceland, Iceland No conflict of interest.
REVIEW RETURNED	07-May-2013

GENERAL COMMENTS	<p>this cross-sectional study of 4,234 Danish women of childbearing age (25-44 years) in 2006, the authors demonstrate associations between several unhealthy lifestyle factors and use of SSRI drugs. The overall results suggest that, compared with women with a healthier lifestyles, those with unhealthier lifestyles are in general about 50% more likely to use, or have recently used, SSRIs.</p> <p>The findings add to the existing literature on depression, treatment and lifestyle factors. More importantly the study results are likely to contribute the evaluation of lifestyle factors in future studies on the effects of SSRI drugs among women of childbearing age; i.e. to which extent such lifestyle factors, often un-controlled for in studies, may effect associations between SSRI use and outcomes. This is especially relevant for emerging research based on the Nordic registries on prescribed drugs and health outcomes, where information on such potential confounding lifestyle factors (incl. smoking, alcohol use, diet and exercise) is very limited.</p> <p>The study is clear and well written, with a focused objective, clear results and message. References to existing literature seem appropriate, although the discussion related to previous results is not very extensive. The methodology is simple and seems adequate.</p> <p>But as the study is based on data on prescribed drugs and self-reported answers from volunteers of a health survey conducted within a confined geographical area in Denmark, it is crucial to consider the external validity/generalizability of the study and its results.</p> <p>- The study sample for the health survey in question is derived from the Danish Civil Registration System in Denmark, increasing the external validity (at least for generalizations within Denmark.) The authors might consider mentioning whether this was a random selection or not (please refer to page 6)</p>
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- The authors focus on the importance of the results for pregnancy studies of SSRI use, although the women under study are not pregnant, but of childbearing age. The authors might consider downplaying the generalizability of the results to pregnant women, or at least mention, that women often alter their lifestyle in terms of smoking, diet, alcohol use before or during pregnancy.

The authors adequately discuss the study's limitation in terms of women who participated of the health survey (71.5% participation) being more likely to be health conscious than non-participants. Is anything known about SSRI use among non-responders, i.e. whether its prevalence is similar to that of the responders?

The authors might consider adding a short discussion on whether women who are depressed/taking SSRIs are likely to self-report lifestyle information differently than those not taking SSRIs. Might such differential self-reporting affect the study results – how?

Data on SSRI prescriptions are obtained from the so-called Aarhus University Prescription Database, which is based on computerized reimbursement information derived from all pharmacies in the Central Denmark Region. The ascertainment of SSRI use is sound and a major strength of the study.

- Related to the likelihood potential misclassification of SSRI use (or classification thereof), it might be informative to add information on how long each SSRI prescription generally last in Denmark?

- Please elaborate on the sentence on p. 11 line 2: "his database is complete regarding SSRIs". It is not quite clear to the reader what the word complete refers to here.

The measurement and ascertainment of lifestyle factors is among the most severe limitations of the study:

- The original information and then dichotomization of the diet variable is bit unclear. Does the survey include a validated food frequency questionnaire? How exactly did the authors derive the values "healthy diet" and "unhealthy diet" from the survey?

- The measurement of physical activity seems a bit vague. Was this information derived from a single survey question "participation in leisure sports or other regular activity"? The authors might consider the validity of this measurement for physical activity. Does the question incorporate physical activity exerted during work hours or transportation to/from work? The authors might consider downplaying the interpretations drawn from the results based on physical activity. At least use consistent terminology for this measure (e.g. not all terms: physical activity, engaging in regular exercise, amount of regular exercise, participation in leisure sports).

- The reviewer wonders how much information is lost by the dichotomization of all life style factors. Their dichotomization does, however, facilitate the presentation of the results and the interpretations of the study

Is there any additional information on the age distribution of the study participants? It might be helpful to either provide such information to better describe the study population, or better inform the reader with results stratified by age groups (e.g. 25-34, 35-44 years).

Which method was used to estimate the 95% confidence intervals for prevalence ratios?

REVIEWER	Espen Jimenez-Solem M.D. Laboratory of Clinical Pharmacology I have no competing interests to declare
REVIEW RETURNED	13-May-2013

THE STUDY	<p>In this study, the authors perform a cross-sectional study describing the prevalence of SSRI redemptions among a cohort of women of childbearing age according to lifestyle factors. The paper is very welcomed since identification of possible confounding factors when analyzing use of SSRIs during pregnancy is needed. The manuscript is well written and clearly formulated. I have however encountered some important issues that, in my opinion, need to be addressed.</p> <p>1. Is the overall study design appropriate and adequate to answer the research question? No</p> <p>I understand that the research question is identification of confounding factors to aid in epidemiological research regarding use of SSRIs during pregnancy. I believe that the cohort included in the present study is not representative of a cohort of pregnant women, and the results can therefore not be directly extrapolated to a cohort of pregnant women. This limitation needs to be discussed in the manuscript. Furthermore, I have these general comments:</p> <p>a) My main concern is the presentation of the results. The authors analyze an association between lifestyle factors and redeeming a prescription for an SSRI. The authors need to underline that this is an association and not a causal relation.</p> <p>b) The prevalence of current users of SSRIs is considerably higher (3.8%) than among pregnant women. A recent study by Jimenez-Solem et al. described a prevalence of approx. 1.5% in 2006 increasing to approx. 2.8% in 2010 in Denmark (Prevalence of Antidepressant Use during Pregnancy in Denmark, a Nation-Wide Cohort Study. PLoS ONE 8(4): e63034. doi:10.1371/journal.pone.0063034). The discrepancy between these numbers and the present study could be explained by the fact that women redeeming a prescription for an SSRI might have a lower rate of pregnancies. The reason for this lower rate could be the lifestyle factors analyzed in the present study. Do the authors have information on the number of pregnant women in the cohort? Does the rate differ between the groups (adjusted for age)?</p> <p>c) It would be interesting to have information on the reason for SSRI discontinuation in the "recent" and "former" users group. It is well known that many women discontinue use of antidepressants upon recognition of pregnancy. Were these women cured from their symptoms (depression, anxiety, etc.)?</p> <p>d) One could hypothesize that pregnancy is a lifestyle changing event. At the time of pregnancy planning or recognition one would expect women to take more care of themselves by smoking and drinking less (teratogens that are well known in the general population), exercising more and eating a more healthy diet. Would it be possible that the results presented by the authors are not applicable to pregnant women due to changes in behavior associated with pregnancy?</p> <p>e) Approx. 17% percent of potentially pregnant women are not represented in the cohort (women aged <25 years). Prevalence of SSRI use increases with age, which could contribute to the higher prevalences found in the present study. I would suggest the authors</p>
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present the age distribution (or mean) among the different exposure groups, and , if possible, include data on women aged 17-25 included in the survey “Hvordan har du det?:unge”/“How are you?:young”.

f) Were questionnaires (or responders) evenly distributed between 2006 and 2010? Use of SSRIs has increased in this period. An uneven distribution could skew the results.

g) I would suggest including information on other antidepressants (TCAs (ATC N06AA) and “other antidepressants” (ATC N06AX)). Some women may have switched treatment from an SSRI to another antidepressant. It would be interesting for the reader to know whether former/recent users switch to a different antidepressant?

h) Did exposed women take any other medication that is associated with unhealthy lifestyle (eg. Antipsychotics, antidiabetics, antiepileptics or anxiolytics)? Women redeeming prescriptions for antidepressants have a higher prevalence of exposure to other drugs, which could confound the results.

i) I suggest adding the age distribution in the different groups to table 1. I would expect SSRI users to be older than the background population.

j) I would expect that there is an association between BMI, smoking, drinking and diet. Have the authors performed any interaction analyses?

k) Do the authors have access to information on over the counter drugs? This information is not included in the register, but was it included in the questionnaires? It would be interesting to know how many women switched to “alternative” drugs (eg. St Johns Wort).

I believe these issues need to be addressed in the manuscript.

2. Are the participants adequately described, their conditions defined, and the inclusion and exclusion criteria described? No

a) It would be interesting to have a more detailed description of healthy/unhealthy diet since it differs between current and former users. What is the definition of healthy and unhealthy diet?

b) Alcohol intake is divided into more/less than 14 drinks weekly. Is this definition solely based on the Danish Health and Medicine Authority's recommendations or is there a scientific basis for the definition?

3. Are the patients representative of actual patients the evidence might affect? No (please see comments under #1)

4. Are the references up to date and relevant? (If not, please provide details of significant omissions below.) No

a) Page 11, line 9. Reference #30. The cited reference does not include information on completeness of the database regarding SSRIs. Please correct this.

b) The authors might find a paper by Jimenez-Solem interesting (Jimenez-Solem E, Andersen JT, Petersen M, et al. Exposure to selective serotonin reuptake inhibitors and the risk of congenital malformations: a nationwide cohort study. *BMJ Open* 2012;2:e001148. doi:10.1136). In this paper the authors' conclusion is that the apparent increased risk of congenital malformations associated with use of SSRIs during pregnancy is due to confounding by indication. This paper supports the need of the present study since the unaccounted confounder in the study by Jimenez-Solem et al could be lifestyle factors.

	<p>5. Do any supplemental documents e.g. a CONSORT checklist, contain information that should be better reported in the manuscript, or raise questions about the work? No. a) The authors do not explain how missing data were addressed. (STROBE, #12(c))</p>
RESULTS & CONCLUSIONS	<p>1. Are they well presented? No a) Table 1. As mentioned earlier, I suggest including the women’s age in this table. b) Table 2. The confidence intervals of some of the results include the value 1.0. I suggest including a p-value to fully determine the statistical significance.</p> <p>2. Are the interpretation and conclusions warranted by and sufficiently derived from/focused on the data? No (please see comment #1 under “The Study”)</p> <p>3. Is the message clear? No a) Please refer to my earlier comment regarding association and causality (THE STUDY, 1a). Furthermore, the possibility of extrapolating to a cohort of pregnant women needs to be further discussed in the manuscript before it can be included in the conclusion. Another limitation that could be mentioned in the discussion, is the possibility of recall bias when conducting a study including questionnaires.</p>

VERSION 1 – AUTHOR RESPONSE

Reviewer Dr. Helga Zoëga comments and our responses:

In this cross-sectional study of 4,234 Danish women of childbearing age (25-44 years) in 2006, the authors demonstrate associations between several unhealthy lifestyle factors and use of SSRI drugs. The overall results suggest that, compared with women with a healthier lifestyles, those with unhealthier lifestyles are in general about 50% more likely to use, or have recently used, SSRIs.

The findings add to the existing literature on depression, treatment and lifestyle factors. More importantly the study results are likely to contribute the evaluation of lifestyle factors in future studies on the effects of SSRI drugs among women of childbearing age; i.e. to which extent such lifestyle factors, often un-controlled for in studies, may effect associations between SSRI use and outcomes. This is especially relevant for emerging research based on the Nordic registries on prescribed drugs and health outcomes, where information on such potential confounding lifestyle factors (incl. smoking, alcohol use, diet and exercise) is very limited.

The study is clear and well written, with a focused objective, clear results and message. References to existing literature seem appropriate, although the discussion related to previous results is not very extensive. The methodology is simple and seems adequate. But as the study is based on data on prescribed drugs and self-reported answers from volunteers of a health survey conducted within a confined geographical area in Denmark, it is crucial to consider the external validity/generalizability of the study and its results.

1.- The study sample for the health survey in question is derived from the Danish Civil Registration System in Denmark, increasing the external validity (at least for generalizations within Denmark.) The authors might consider mentioning whether this was a random selection or not (please refer to page 6)

Response to comment 1:

The people invited to participate in the health survey are randomly selected by means of the Danish Civil Registration System. This information has been added in the manuscript on page 6, line 19.

-2 The authors focus on the importance of the results for pregnancy studies of SSRI use, although the women under study are not pregnant, but of childbearing age. The authors might consider downplaying the generalizability of the results to pregnant women, or at least mention, that women often alter their lifestyle in terms of smoking, diet, alcohol use before or during pregnancy.

Response to comment 2:

We agree with the reviewer and accordingly we have mentioned in the discussion that the study does not concern pregnant women as such, but women of childbearing age, and that women might alter their lifestyle in terms of alcohol use, smoking and diet before or during pregnancy. Please see page 13, lines 1-6.

- 3 The authors adequately discuss the study's limitation in terms of women who participated of the health survey (71.5% participation) being more likely to be health conscious than non-participants. Is anything known about SSRI use among non-responders, i.e. whether its prevalence is similar to that of the responders?

Response to comment 3:

We recognize this issue but unfortunately we are not able to identify the non-responders in the health survey.

- 4 The authors might consider adding a short discussion on whether women who are depressed/taking SSRIs are likely to self-report life-style information differently than those not taking SSRIs. Might such differential self-reporting affect the study results – how?

Response to comment 4:

It is possible that women who are depressed/taking SSRI may report lifestyle factors differently than other women. However, we may only speculate whether they report more or less accurately and we therefore do not know how such potential misclassification may affect our results. This is added to the discussion on page 12, lines 14-17.

Data on SSRI prescriptions are obtained from the so-called Aarhus University Prescription Database, which is based on computerized reimbursement information derived from all pharmacies in the Central Denmark Region. The ascertainment of SSRI use is sound and a major strength of the study.

- 5 Related to the likelihood potential misclassification of SSRI use (or classification thereof), it might be informative to add information on how long each SSRI prescription generally last in Denmark?

Response to comment 5:

We agree that this is relevant. Based on packsizes available in Denmark, we have now added lengths of SSRI prescriptions, given that the 1 DDD is taken daily, to the manuscript on page 8, line 17.

- 6 Please elaborate on the sentence on p. 11 line 2: "his database is complete regarding SSRIs". It is not quite clear to the reader what the word complete refers to here.

Response to comment 6:

We apologize for not having explained this more clearly. In Denmark, SSRIs are sold by prescription only and not available over the counter. This information has been added to the discussion on page 12, lines 2-3.

7 The measurement and ascertainment of lifestyle factors is among the most severe limitations of the study:

- The original information and then dichotomization of the diet variable is bit unclear. Does the survey include a validated food frequency questionnaire? How exactly did the authors derive the values “healthy diet” and “unhealthy diet” from the survey?

Response to comment 7:

To assess diet, the health survey used a score system developed by the Research Centre for Prevention and Health, the Capital Region of Denmark (Toft U, Kristoffersen LH, Lau C, et al. The Dietary Quality Score: validation and association with cardiovascular risk factors: the Inter99 study. *Eur J Clin Nutr* 2007;61:270-278). This included 30 different questions regarding intake of fruit, vegetables, fish and fat. By the score system, the responses were summarized into categories of healthy (high amount of fruit, vegetables, fish and low amount of saturated fat), reasonably healthy (median high intake of fruit, vegetables, fish and saturated fat), or unhealthy diet (low amount of fruit, vegetables, fish and high amount of saturated fat). We inserted this information in the methods section, please see page 7.

-8 The measurement of physical activity seems a bit vague. Was this information derived from a single survey question “participation in leisure sports or other regular activity”? The authors might consider the validity of this measurement for physical activity. Does the question incorporate physical activity exerted during work hours or transportation to/from work? The authors might consider downplaying the interpretations drawn from the results based on physical activity. At least use consistent terminology for this measure (e.g. not all terms: physical activity, engaging in regular exercise, amount of regular exercise, participation in leisure sports).

Response to comment 8:

We acknowledge that we may not have been entirely consistent in our terminology regarding physical activity. Seven questions were asked regarding amount of daily activity (work, gardening, cleaning and so on). In our study we assessed physical activity based only on the answers to the question: Do you participate in leisure sport or other regular activity? (Yes/no). The terminology has been altered and we apologize for the inconsistency.

-9 The reviewer wonders how much information is lost by the dichotomization of all life style factors. Their dichotomization does, however, facilitate the presentation of the results and the interpretations of the study

Response to comment 9:

We did not dichotomize all life style factors. BMI was calculated and categorized into four categories based on WHO criteria and these categories are presented in Table 1. However, when we computed the prevalence ratios (PR) we compared the prevalence of obesity with that of non-obese and collapsed underweight, normal weight and overweight into the non-obese group. As a consequence of the reviewer’s comment, we have additionally computed the PR comparing obese/overweight vs. normal weight/underweight, obese vs. normal weight/underweight and overweight vs. normal weight/underweight. The PRs did (please see below), however, not change much in the different analyses and we have therefore kept the initial analyses. We are of course willing to include this information in the paper if requested.

PRs comparing obese/overweight vs. normal weight/underweight: For current use, PR= 1.7, 95% CI (1.3 to 2.3) and for former use PR = 1.1, 95% CI (0.8 to 1.4).

PRs comparing obese vs. normal weight/underweight: For current use, PR= 1.8, 95% CI (1.2 to 2.7) and for former use PR = 1.4, 95% CI (1.0 to 1.9).

PRs comparing overweight vs. normal weight/underweight: For current use, PR= 1.6, 95% CI (1.2 to 2.3) and for former use PR = 0.9, 95% CI (0.7 to 1.3).

Regarding use of alcohol, we have unfortunately discovered a mistake in our manuscript. The analyses are conducted based on an intake above seven standard drinks per week and not as written in the paper on an intake above 14 drinks per week. We have reanalyzed data using 14 drinks per week as level for overuse and this increased the PRs. We are now presenting both measurements in the paper. Please see Table 1 and Table 2.

For smoking and diet, we used the categories from the questionnaire as explained above.

- 10 Is there any additional information on the age distribution of the study participants? It might be helpful to either provide such information to better describe the study population, or better inform the reader with results stratified by age groups (e.g. 25-34, 35-44 years).

Response to comment 10:

We agree with the reviewer. In Table 1 we have added information on median age and range of age according to use of SSRIs. Furthermore, we have stratified on age (25-34 and 35-44 years of age). These stratification analyses are uploaded as supplementary files.

- 11 Which method was used to estimate the 95% confidence intervals for prevalence ratios?

Response to comment 11:

We used the Clopper-Pearson exact method, which is now mentioned in the manuscript on page 9, line 10.

Reviewer Espen Jimenez-Solem comments and our responses:

In this study, the authors perform a cross-sectional study describing the prevalence of SSRI redemptions among a cohort of women of childbearing age according to lifestyle factors. The paper is very welcomed since identification of possible confounding factors when analyzing use of SSRIs during pregnancy is needed. The manuscript is well written and clearly formulated. I have however encountered some important issues that, in my opinion, need to be addressed.

1. Is the overall study design appropriate and adequate to answer the research question? No
I understand that the research question is identification of confounding factors to aid in epidemiological research regarding use of SSRIs during pregnancy. I believe that the cohort included in the present study is not representative of a cohort of pregnant women, and the results can therefore not be directly extrapolated to a cohort of pregnant women. This limitation needs to be discussed in the manuscript.

Response to comment 1:

This is a random sample of the general population describing use of SSRIs among women of childbearing age representing the distribution of SSRI use in the population, from which pregnancies arise. We are aware that women who become pregnant may somehow be selected and that they may alter their lifestyle factors once they realize that they are pregnant. However, we still find it of interest that we find important large differences between SSRI users and non-users in a representative sample of Danish women of childbearing age. In the discussion on page 13, lines 1-6 that women might alter their lifestyle when they become pregnant.

a) My main concern is the presentation of the results. The authors analyze an association between lifestyle factors and redeeming a prescription for an SSRI. The authors need to underline that this is an association and not a causal relation.

Response to comment 1a:

In our manuscript we do not use the term association as a synonym for causal association. In this cross sectional study we have no information on the causal directions and we simply measures the association between use of SSRI and prevalence of different life style factors.

b) The prevalence of current users of SSRIs is considerably higher (3.8%) than among pregnant women. A recent study by Jimenez-Solem et al. described a prevalence of approx. 1.5% in 2006 increasing to approx. 2.8% in 2010 in Denmark (Prevalence of Antidepressant Use during Pregnancy in Denmark, a Nation-Wide Cohort Study. PLoS ONE 8(4): e63034. doi:10.1371/journal.pone.0063034). The discrepancy between these numbers and the present study could be explained by the fact that women redeeming a prescription for an SSRI might have a lower rate of pregnancies. The reason for this lower rate could be the lifestyle factors analyzed in the present study. Do the authors have information on the number of pregnant women in the cohort? Does the rate differ between the groups (adjusted for age)?

Response to comment 1b:

We investigated the number of pregnant women in our study population as the number of women who gave birth up to nine month after filling in the questionnaire. In total, we identified 232 pregnant women in our study population. Among these, 3 (1.3%) were current users, 3 (1.3%) were recent users, and 11(4.7%) were former users. This prevalence is in accordance with the findings by Jimenez-Solem et al and others. We have added this information to the results section, page 10, lines 6-9. However, these small numbers did not allow us to examine associations between use of SSRI and lifestyle factors among pregnant women.

c) It would be interesting to have information on the reason for SSRI discontinuation in the “recent” and “former” users group. It is well known that many women discontinue use of antidepressants upon recognition of pregnancy. Were these women cured from their symptoms (depression, anxiety, etc.)?

Response to comment 1c:

We agree that this would be interesting but unfortunately we are not able to provide such information.

d) One could hypothesize that pregnancy is a lifestyle changing event. At the time of pregnancy planning or recognition one would expect women to take more care of themselves by smoking and drinking less (teratogens that are well known in the general population), exercising more and eating a more healthy diet. Would it be possible that the results presented by the authors are not applicable to pregnant women due to changes in behavior associated with pregnancy?

Response to comment 1d:

Please see our response to reviewer 1, comment 2.

e) Approx. 17% percent of potentially pregnant women are not represented in the cohort (women aged <25 years). Prevalence of SSRI use increases with age, which could contribute to the higher prevalences found in the present study. I would suggest the authors present the age distribution (or mean) among the different exposure groups, and , if possible, include data on women aged 17-25 included in the survey “Hvordan har du det?:unge”/“How are you?:young”.

Response to comment 1e:

We have included median age and range of age by use of SSRI in Table 1. People under 25 years of age are not invited to participate in the survey and thus we do not have data to perform analyses on this young age group.

f) Were questionnaires (or responders) evenly distributed between 2006 and 2010? Use of SSRIs has increased in this period. An uneven distribution could skew the results.

Response to comment 1f)

Questionnaires were sent out to 31,500 persons in 2006, including 4234 women of childbearing age. We do not have access to data from the 2010 survey and we therefore do not quite follow the reviewers suggestion.

g) I would suggest including information on other antidepressants (TCAs (ATC N06AA) and “other antidepressants” (ATC N06AX)). Some women may have switched treatment from an SSRI to another antidepressant. It would be interesting for the reader to know whether former/recent users switch to a different antidepressant?

Response to comment 1g:

We investigated if former and recent users of SSRI redeemed a prescription on TCA (N06AA) or other antidepressants (N06AX) one year before and one year after filling in the questionnaire. Regarding TCA: two of 60 (3.3%) of recent users redeemed a prescription one year before or after filling in the questionnaire. For former users this was 13 of 223 (5.8%). Regarding other antidepressants: 11 of 60 (18.3%) of recent users redeemed a prescription and 34 of 223 (15.2%) of former users. We find that this information is outside the main scope of our paper and have therefore not included this information in the manuscript. We are, however, willing to do so at the editor's request.

h) Did exposed women take any other medication that is associated with unhealthy lifestyle (eg. Antipsychotics, antidiabetics, antiepileptics or anxiolytics)? Women redeeming prescriptions for antidepressants have a higher prevalence of exposure to other drugs, which could confound the results.

Response to 1h:

The reviewer has a good point and we have included data on use of antiepileptica, antidiabetica and antipsychotica by use of SSRI in Table 1.

i) I suggest adding the age distribution in the different groups to table 1. I would expect SSRI users to be older than the background population.

Response to 1i:

We have added median age and range to table 1.

j) I would expect that there is an association between BMI, smoking, drinking and diet. Have the authors performed any interaction analyses?

Response to 1j:

We agree that there might be an association between BMI, smoking, drinking and diet, however, the study does not have statistical precision to stratify further why doing so will not allow for any meaningful estimates.

k) Do the authors have access to information on over the counter drugs? This information is not included in the register, but was it included in the questionnaires? It would be interesting to know have many women switched to “alternative” drugs (eg. St Johns Wort).

Response to 1k:

No, unfortunately we do not have information on over the counter drugs from the questionnaire or prescription database.

I believe these issues need to be addressed in the manuscript.

2. Are the participants adequately described, their conditions defined, and the inclusion and exclusion criteria described? No

a) It would be interesting to have a more detailed description of healthy/unhealthy diet since it differs between current and former users. What is the definition of healthy and unhealthy diet?

Response to comment 2a:

Please see our response to reviewer 1 comment 7

b) Alcohol intake is divided into more/less than 14 drinks weekly. Is this definition solely based on the Danish Health and Medicine Authority's recommendations or is there a scientific basis for the definition?

Response to 2b

Regarding use of alcohol, we have unfortunately discovered a mistake in our manuscript. The analyses are conducted based on an intake above seven standard drinks per week and not as written in the paper on an intake above 14 drinks per week. We have reanalyzed data using 14 drinks per week as level for overuse and this increased the PRs. We are now presenting both measurements in the paper. Please see Table 1 and Table 2.

3. Are the patients representative of actual patients the evidence might affect? No (please see comments under #1)

Response to 3:

Please see response to comment 1.

4. Are the references up to date and relevant? (If not, please provide details of significant omissions below.) No

a) Page 11, line 9. Reference #30. The cited reference does not include information on completeness of the database regarding SSRIs. Please correct this.

Response to comment 4a:

The database is not validated according to SSRI use/prescriptions. However, since SSRIs are not available over the counter in Denmark and are only available in monopolized community pharmacies which all report to the prescription database (Ehrenstein V, Antonsen S, Pedersen L. Existing data sources for clinical epidemiology: Aarhus University Prescription Database. Clin Epidemiol 2010;2:273-279), we consider the database to be complete in regards to SSRI use. On page 12, lines 4-5 we have outlined that SSRIs are available by prescription only and not sold as over-the-counter drugs.

b) The authors might find a paper by Jimenez-Solem interesting (Jimenez-Solem E, Andersen JT, Petersen M, et al. Exposure to selective serotonin reuptake inhibitors and the risk of congenital malformations: a nationwide cohort study. BMJ Open 2012;2:e001148. doi:10.1136). In this paper the authors' conclusion is that the apparent increased risk of congenital malformations associated with use of SSRIs during pregnancy is due to confounding by indication. This paper supports the need of

the present study since the unaccounted confounder in the study by Jimenez-Solem et al could be lifestyle factors.

Response to 4b:

We have included the paper as suggested.

5. Do any supplemental documents e.g. a CONSORT checklist, contain information that should be better reported in the manuscript, or raise questions about the work? No.

a) The authors do not explain how missing data were addressed. (STROBE, #12(c))

Response to comment 5a:

Women with missing data (BMI: 2.3%, smoking: 0.52%, diet 3.1%, alcohol 7.8%, participation in regular physical activity 1.2%) were excluded from the analyses, this information is added in the manuscript on page 9, line 17.

1. Are the results well presented? No

a) Table 1. As mentioned earlier, I suggest including the women's age in this table.

Response to comment 1a:

We have included median age and range in Table 1.

b) Table 2. The confidence intervals of some of the results include the value 1.0. I suggest including a p-value to fully determine the statistical significance.

Response to comment 1 b:

Based on the STROBE STATEMENT we prefer not to discuss significance in terms of p-values in regards to the descriptive data.

2. Are the interpretation and conclusions warranted by and sufficiently derived from/focused on the data? No (please see comment #1 under "The Study")

Response to comment 2:

Please see the response to comment 1.

3. Is the message clear? No

a) Please refer to my earlier comment regarding association and causality (THE STUDY, 1a)). Furthermore, the possibility of extrapolating to a cohort of pregnant women needs to be further discussed in the manuscript before it can be included in the conclusion. Another limitation that could be mentioned in the discussion, is the possibility of recall bias when conducting a study including questionnaires.

Response to comment 3a:

Please see the response to comments 1 and 1a.

In the discussion we have mentioned issues regarding self-reporting and the possibility of misclassification of lifestyle factors by means of under- or over reporting. We have outlined this further on page 12, lines 13-15.

VERSION 2 – REVIEW

REVIEWER	Espen Jimenez-Solem MD Deptment of Clinical Pharmacology Bispebjerg Hospital Denmark No relevant conflicts of interest to delear
REVIEW RETURNED	27-Jun-2013

GENERAL COMMENTS	I am very pleased with the authors´reply to my comments. They have adressed my main concerns and added highly relevant information to the manuscript.
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