PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Medication use in pregnancy: a cross-sectional, multinational web-based study
AUTHORS	Lupattelli, Angela; Spigset, Olav; Twigg, Michael; Zagorodnikova, Ksenia; Mårdby, Ann-Charlotte; Moretti, Myla; Drozd, Mariola; Panchaud, Alice; Hämeen-Anttila, Katri; Rieutord, Andre; Gjergja Juraski, Romana; Odalovic, Marina; Kennedy, Debra; Rudolf, Gorazd; Juch, Herbert; Passier, Anneke; Björnsdóttir, Ingunn; Nordeng, Hedvig

VERSION 1 - REVIEW

REVIEWER	Anton Pottegård University of Southern Denmark Clinical Pharmacology, Institute of Public Health Denmark.
REVIEW RETURNED	29-Nov-2013

GENERAL COMMENTS	Overall The authors have conducted an internet-based survey on drug use during pregnancy in 18 countries. The study seems well planned and executed, the analysis seems sound and the presentation and interpretation of the findings seems valid. The comprehensive nature of the paper implies that many things can be discussed. However, I hope that this does not deny the fact that I generally find this well-written paper to be of very high quality. Major comments Figure 2: This figure can easily be improved quite a bit. Firstly, I am not interested in the rate 'including vitamins etc.', as vitamins/iron is clearly underreported. This is no surprise as it was not what participants were asked about. In case it was not underreported, the difference between the two proportions (including vs. excluding) would have been much larger. Secondly, I am very interested in assessing the proportion of respondents (by country) that used prescription drugs, preferably even specified by acute vs. chronic. I cannot see these figures from the current figure (as the total minus the OTC is not the proportion using prescription drugs). I suggest reporting four proportions for each country: Any drug; OTC; chronic prescription; acute prescription. I might argue that these four proportions is actually a main finding of the study, perhaps even THE main finding. The study sample comprises two groups: Those currently pregnant and those already having given birth (roughly 50/50). I am not sure how this was handled in the analyses. More importantly, it seems that the authors have not looked into potential differences between the two groups.

	In ‘Strengths and limitations’, the authors state that ‘Inclusion of pregnant women at any gestational week might have inflated the prevalence of non-users of medications during pregnancy’. Does this mean that women, e.g. only 14 weeks pregnant, could enter the study and be registered as a non-user and then handled completely equivalent to someone having completed the entire pregnancy and not having used any drugs? Did the authors record gestational age at participation? As the groups are equally sized, the authors should at least look at the two halves separately (as a supplementary analysis) to evaluate whether the inclusion of ‘women at any gestational week’ actually biased the overall result. Simply stating that they ‘might have’ is not enough – particularly when it would be so easy to evaluate. Minor comments Could the actual survey or a schematic representation of this be included as an appendix? Abstract, conclusion: Three points are mentioned. The first (substantial variation) is supported by the data reported in the abstract/study. However, the second (certain sub-groups needs specific information) and third point (a need for future research) are not directly related to the results of this study, as they refer to more speculative parts of the discussion section. E.g. the second point actually mainly refers to reference 33 and not the findings of the paper itself. I suggest removing these two latter points from the abstract. Strength and limitation bullets: The third bullet (Lack of validity…) seems like a text ‘fragment’. I would suggest to consider adding ‘is a potential limitation’. Introduction, “The objectives of…”: The last objective is ‘to identify maternal background factors potentially associated with the use of specific types of medication during pregnancy’. However, comparing this to the methods section (‘Statistical analysis’), it seems that this is only done at an aggregate level, i.e. that ‘specific types’ only refers to acute vs. chronic vs. OTC drugs. From the wording, I had anticipated something more ‘specific’ (i.e. single substances). I suggest re-wording this objective accordingly. Appendix 1: The layout should be checked/streamlined. E.g. the main regions are split into separate tables, although ‘North America’ has its own, under which lies ‘South America’? Why not just having one large table? Even though Central America has been excluded, it could/should still be included here (as this is the only place where we might actually assess why the data catchment was so poor for this particular region). Method, outcome variables, first paragraph: “Timing of exposure (…) could be reported for…”. Does this ‘could’ mean that this was optional? If so, it should be stated explicitly. Reference 16: Should be stated as “WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATC classification and DDD assignment 2013. Oslo, 2012.” (according to the reference itself). Table 2: Educational level should be ordered Less than, High school, More than, others instead of High school; Less, Higher. Even

	though this will cause the reference group not to be on top, it will increase readability. Discussion, initial statement: I do not quite follow why the discussion of the potential limited generalizability for some specific countries is mentioned 'up front' like this. This should of course be discussed (under the sub-header 'Strengths and limitations'), but not as part of the 'principal finding'. 'Strengths and limitations': The authors have identified a potential bias in that the participants are generally better educated than the background population. This could potentially be a major bias. Their own results suggest that this might bias the results downwards (see table 2). This should be discussed more thoroughly, preferably with other references from the literature on the influence of educational level on drug use during pregnancy.

REVIEWER	Lyn Colvin Telethon Institute for Child Health Research, The University of Western Australia
REVIEW RETURNED	11-Dec-2013

GENERAL COMMENTS	2. Is the abstract accurate, balanced and complete? No Primary and secondary outcome measures: Prevalence and determinants of medication use for acute illnesses, chronic disorders and over-the-counter (OTC) medication use. >The study could not measure determinants. The prevalence measures are not shown to be representative. 3. Is the study design appropriate to answer the research question? No > The sample sizes are too small to determine outcomes at a national level. 4. Are the methods described sufficiently to allow the study to be repeated? No > A copy of the internet survey would be useful in the supplementary material provided. > The participants are self-selected and their reasons for seeking advice regarding their pregnancy via a website cannot be shown to be representative of pregnant women in their country as a whole. 11. Are the discussion and conclusions justified by the results No > The study sizes for each country are very small. Selection bias is a major issue. 12. Are the study limitations discussed adequately? No > Some of the study limitations are highlighted in the article summary section. The final statement in the conclusion sums up the major selection bias issue in this study. 1. I have serious concerns around how representative the study samples are for each country/region. 2. I do not like the term "housewives" – without seeing the survey question relating to the occupation of the participants, it is difficult to accept this as a scientifically-based description.

	3. The use of HCP as a separate employment may be understandable but it should also be used in relation to “housewives” and the other categories – there may be some pregnant women who are categorised as “housewives” but were actually nurses, clinicians, HCPs before they became pregnant and equally would be “possibly reflecting higher confidence in self-treatment and use of medications in general” (p 21). Even medical students could be in this definition. 4. A copy of the internet survey as an appendix may have been useful. 5. What does this mean in final paragraph: "Inclusion of pregnant women at any gestational week might have inflated the prevalence of non-users of medications during pregnancy."?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:
The authors have conducted an internet-based survey on drug use during pregnancy in 18 countries. The study seems well planned and executed, the analysis seems sound and the presentation and interpretation of the findings seems valid. The comprehensive nature of the paper implies that many things can be discussed. However, I hope that this does not deny the fact that I generally find this well-written paper to be of very high quality.

Major comments
Comment 1:
Figure 2: This figure can easily be improved quite a bit.
Firstly, I am not interested in the rate ‘including vitamins etc.’, as vitamins/iron is clearly underreported. This is no surprise as it was not what participants were asked about. In case it was not underreported, the difference between the two proportions (including vs. excluding) would have been much larger.
Secondly, I am very interested in assessing the proportion of respondents (by country) that used prescription drugs, preferably even specified by acute vs. chronic. I cannot see these figures from the current figure (as the total minus the OTC is not the proportion using prescription drugs). I suggest reporting four proportions for each country: Any drug; OTC; chronic prescription; acute prescription.
I might argue that these four proportions is actually a main finding of the study, perhaps even THE main finding.

Reply 1:
Thank you for the comment about Figure 2. We have improved Figure 2 as advised and removed medication estimates “including vitamins, supplements, etc”. The revised Figure 2 now presents the proportions of respondents reporting use of any medication during pregnancy, OTC medications, medication for acute/short-term illnesses, and medication for chronic/long-term disorders according to individual country and region. In the survey questionnaire participants were not specifically asked whether the medications they took for treatment of acute illnesses and/or chronic disorders were prescribed or not. Hence, we cannot infer that such medications were all prescribed. On the other hand, study participants were specifically asked about use of OTC medications during pregnancy. Hence in Figure 2 we have named and specified the following proportions of medication use: Any medication; OTC medication; medication for acute/short-term illnesses; medication for chronic/long-term disorders. For readability reasons, we have not used the track changes mode for Figure 2. The title of Figure 2 has also been rephrased accordingly. A footnote to Figure 2 has been added.
In the Results section of the manuscript we have now specified that Figure 2 outlines the proportions of any medication use, OTC medication use, medication use for acute/short-term illnesses and medication use for chronic/long-term disorders according to country of residency. The Results part of the Abstract has also been implemented with overall rates of medication use for acute/short-term illnesses and chronic/long-term disorders.

Comment 2:
The study sample comprises two groups: Those currently pregnant and those already having given birth (roughly 50/50). I am not sure how this was handled in the analyses. More importantly, it seems that the authors have not looked into potential differences between the two groups.
In 'Strengths and limitations', the authors state that 'Inclusion of pregnant women at any gestational week might have inflated the prevalence of non-users of medications during pregnancy'. Does this mean that women, e.g. only 14 weeks pregnant, could enter the study and be registered as a non-user and then handled completely equivalent to someone having completed the entire pregnancy and not having used any drugs?

Reply 2:
In the data analysis, pregnant women were treated equally to women who had given birth with respect to the estimation of medication use rates. Participants reporting use of any medication during pregnancy were handled as "medication users", whereas those reporting no medications were treated as "non-users", independently of their pregnancy status. While new mothers answered all questions about medication use retrospectively and thus covering the entire length of the pregnancy, pregnant women could only report any medication use that occurred until the gestational week when the questionnaire was completed. This means that pregnant women in early gestation might not have experienced yet illnesses or bothers such as pain, sleeping problems, constipation, and heartburn usually occurring in mid or late pregnancy and possibly requiring pharmacotherapy. Thus, this latter group of women might not have had the opportunity to report any medication simply because they were in an early stage of their pregnancies. Moreover, women in early gestation may avoid taking medications during the first trimester of pregnancy because this is the most sensitive period for teratogenesis; however they might use medications later in pregnancy, i.e. during the second or third trimester. The sentence "Inclusion of pregnant women at any gestational week might have inflated the prevalence of non-users of medications during pregnancy" in "Strengths and Limitations" reflected this potential bias.
We have now carried out corollary analyses according to pregnancy status as advised by the reviewer. We performed a chi-square test and compared the proportions of medication use at any time during pregnancy as well as by trimester among pregnant women versus women who had delivered. The trimester of pregnancy was calculated as follows: gestational weeks 0-12 (1st trimester), 13-24 (2nd trimester) and 25-delivery (3rd trimester). We found that medication use rates were significantly higher among new mothers than among pregnant women, specifically:

• Rates of Any medication use during pregnancy were 78.8% (pregnant women) vs. 84.0% (new mother), p-value=<0.001;
• Rates of Any medication use during 1. trimester were 53.0% (pregnant women) vs. 46.1% (new mother), p-value=<0.001;
• Rates of Any medication use during 2. trimester were 53.5% (pregnant women) vs. 64.4% (new mother), p-value=<0.001;
• Rates of Any medication use during 3. trimester were 32.3% (pregnant women) vs. 69.0% (new mother), p-value=<0.001;

• Rates of OTC medication use during pregnancy were 63.0% (pregnant women) vs. 71.5% (new mother), p-value=<0.001;
• Rates of OTC medication use during 1. trimester were 44.4% (pregnant women) vs. 41.1% (new mother), p-value=<0.001;
• Rates of OTC medication use during 2. trimester were 45.4% (pregnant women) vs. 57.1% (new mother), p-value=<0.001;
• Rates of OTC medication use during 3. trimester were 28.4% (pregnant women) vs. 61.7% (new mother), p-value=<0.001;

• Rates of Medication use for acute/short-term illnesses during pregnancy were 66.2% (pregnant women) vs. 70.9% (new mother), p-value=<0.001;
• Rates of Medication use for acute/short-term illnesses during 1. trimester were 46.5% (pregnant women) vs. 41.4% (new mother), p-value=<0.001;
• Rates of Medication use for acute/short-term illnesses during 2. trimester were 48.0% (pregnant women) vs. 57.1% (new mother), p-value=<0.001;
• Rates of Medication use for acute/short-term illnesses during 3. trimester were 29.3% (pregnant women) vs. 60.8% (new mother), p-value=<0.001;

• Rates of Medication use for chronic/long-term disorders during pregnancy were 17.4% (pregnant women) vs. 16.5% (new mother), p-value=0.271.
• Rates of Medication use for chronic/long-term disorders during 1. trimester were 12.2% (pregnant women) vs. 9.9% (new mother), p-value=<0.001;
• Rates of Medication use for chronic/long-term disorders during 2. trimester were 11.7% (pregnant women) vs. 13.3% (new mother), p-value=0.02;
• Rates of Medication use for chronic/long-term disorders during 3. trimester were 7.1% (pregnant women) vs. 13.3% (new mother), p-value=<0.001;

Pregnant women reported in a significant lesser degree than new mothers all medication groups at any time during pregnancy. This was also the case for medication use during the second and third trimester. Use of medication during the first trimester was instead higher among pregnant women than among new mothers (probably due to a recall bias among new mothers). Since the mean gestational week of pregnant women at the time of questionnaire completion was 22.4 weeks (standard deviation: 10.3), it can be substantiated that inclusion in the data analysis of pregnant women at any gestational week has inflated the rate of non-users of medication.
An additional sub-analysis restricted to new mothers (n=4370) and pregnant women in the third trimester of pregnancy (n=2291) showed that the proportions of medication use were not significantly different between the two groups, specifically:

• Rates of Any medication use during pregnancy were 84.8% (pregnant women 3. trimester) vs. 84.0% (new mother), p-value=0.390;
• Rates of OTC medication use during pregnancy were 70.3% (pregnant women 3. trimester) vs. 71.5% (new mother), p-value=0.299;
• Rates of Medication use for acute/short-term illnesses during pregnancy were 73.0% (pregnant women 3. trimester) vs. 70.9% (new mother), p-value=0.079;
• Rates of Medication use for chronic/long-term disorders during pregnancy were 17.4% (pregnant women 3. trimester) vs. 16.5% (new mother), p-value=0365.

A brief description of these results has been provided in the Results section, specifically the following text has been added: “A corollary analysis according to pregnancy status showed that pregnant women reported in a significantly lower degree than new mothers any medication use during pregnancy (78.8% vs. 84.0%, p-value<0.001), as well as OTC medication use (63.0% vs. 71.5%, p-value<0.001) and medication use for acute/short-term illnesses (66.2% vs. 70.9%, p-value<0.001). In contrast, the difference in medication use for chronic/long-term diseases was not significant (17.4% vs. 16.5%, p-value=0.271). None of the rates differed significantly when women in the third trimester of pregnancy were compared to new mothers”.
We rephrased the sentence “Inclusion of pregnant women at any gestational week might have inflated the prevalence of non-users of medications during pregnancy” in the section “Strengths and Limitations” into “Since many ailments requiring pharmacotherapy occur in mid or late pregnancy, inclusion of pregnant women at early gestation in the total material has somewhat inflated the prevalence of non-users of medications during pregnancy”.

Comment 3:
Did the authors record gestational age at participation?

Reply 3:
Respondents who were pregnant at the time of completion of the questionnaire were asked about their current gestational week. Respondents who had already given birth were instead asked about the age (in weeks) of their newborn babies. In the Results section of the manuscript we have now added this information as follows: “A total of 5,089 women (53.8%) were pregnant at the time of completion of the questionnaire, whereas 4,370 women (46.2%) had delivered their babies within the previous year. Of the former group, 1,095 (21.5%), 1,702 (33.4%) and 2,291 (45.0%) women were in their first, second and third trimester of pregnancy, respectively. Of the latter group, 1,320 (30.2%), 947 (21.7%) and 2,102 (48.1%) had a baby of age ≤ 16 weeks, 17-28 weeks, and ≥ 29 weeks, respectively. For two women the time of gestation/baby´s age was unknown”.

Comment 4:
As the groups are equally sized, the authors should at least look at the two halves separately (as a supplementary analysis) to evaluate whether the inclusion of 'women at any gestational week' actually biased the overall result. Simply stating that they 'might have' is not enough – particularly when it would be so easy to evaluate.

Reply 4:
We have carried out supplementary analysis according to pregnancy status as advised (please see reply to comment no. 2 above). According to the results obtained, we can substantiate that inclusion of pregnant women in early gestation has inflated the rate of non-use of medication during pregnancy. Hence, in the section "Strengths and Limitations" the sentence "Inclusion of pregnant women at any gestational week might have inflated the prevalence of non-users of medications during pregnancy" has been rephrased into "Since many ailments requiring pharmacotherapy occur in mid or late pregnancy, inclusion of pregnant women at early gestation in the total material has somewhat inflated the prevalence of non-users of medications during pregnancy".

Minor comments
Comment 5:
Could the actual survey or a schematic representation of this be included as an appendix?

Reply 5:
The questionnaire is now included as Appendix 1. The following sentence has been added to the Methods section, under Study Design and data collection: "The complete questionnaire is presented in Appendix 1". The psychometric instruments utilized in the survey questionnaire (i.e. Beliefs about Medicine Questionnaire (General and Specific), the Morisky Medication Adherence Questionnaire, the Edinburgh Postnatal Depression Scale and the Big Five Inventory) are copyrighted and cannot be fully published; therefore we have indicated in Appendix 1 at which stage of the questionnaire such scales were presented, along with relevant references of the psychometric instruments.

Comment 6:
Abstract, conclusion: Three points are mentioned. The first (substantial variation) is supported by the data reported in the abstract/study. However, the second (certain sub-groups needs specific information) and third point (a need for future research) are not directly related to the results of this study, as they refer to more speculative parts of the discussion section. E.g. the second point actually mainly refers to reference 33 and not the findings of the paper itself. I suggest removing these two latter points from the abstract.

Reply 6:
The two last points have been removed from the abstract. The Conclusion of the abstract has been rephrased as follows: "In this study, the majority of women in Europe, North America, South America and Australia used at least one medication during pregnancy. There was a substantial inter-region variability in the types of medication used". The Conclusions section in the main text was also revised accordingly.

Comment 7:
Strength and limitation bullets: The third bullet (Lack of validity…) seems like a text 'fragment'. I would suggest to consider adding 'is a potential limitation'.

Reply 7:
The text of the third bullet point has been amended as follows: "Lack of validity of the self-reported diagnoses is a limitation since all disorders and related medication use were self-reported by the study participants".

Comment 8:
Introduction, "The objectives of…": The last objective is 'to identify maternal background factors potentially associated with the use of specific types of medication during pregnancy'. However, comparing this to the methods section ('Statistical analysis'), it seems that this is only done at an

aggregate level, i.e. that ‘specific types’ only refers to acute vs. chronic vs. OTC drugs. From the wording, I had anticipated something more ‘specific’ (i.e. single substances). I suggest re-wording this objective accordingly.

Reply 8:
We have rephrased the concerned objective in a more unambiguous way. The wording “to identify maternal background factors potentially associated with the use of specific types of medication during pregnancy” has been rephrased into “to identify maternal background factors potentially associated with medication use for acute/short-term illnesses, chronic/long-term disorders and OTC medication use during pregnancy”.

Comment 9:
Appendix 1: The layout should be checked/streamlined. E.g. the main regions are split into separate tables, although ‘North America’ has its own, under which lies ‘South America’? Why not just having one large table? Even though Central America has been excluded, it could/should still be included here (as this is the only place where we might actually assess why the data catchment was so poor for this particular region).

Reply 9:
The layout of Appendix 2 (Appendix 1 in the original version of the manuscript) has been improved as advised. We have now created one large table with relevant subsections, i.e. Europe (Western, Northern and Eastern), Americas (North, South, Central) and Australia. The internet penetration rates for Central American countries where data were collected have also been added, along with specification of the countries where the few study responses originated. We have also specified the individual internet penetration rates for the South American countries where data were collected. The order in which the various countries were listed has also been modified; country names are now sorted alphabetically within each region.

Comment 10:
Method, outcome variables, first paragraph: “Timing of exposure (…) could be reported for…”. Does this ‘could’ mean that this was optional? If so, it should be stated explicitly.

Reply 10:
The question about timing of exposure to medication was not compulsory. We have now rephrased the concerned text as follows: “It was optional to report timing of exposure for each of the medication use questions (the alternatives were gestational weeks 0-12 (1st trimester), 13-24 (2nd trimester) and 25-delivery (3rd trimester))”.

Comment 11:
Reference 16: Should be stated as “WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATC classification and DDD assignment 2013. Oslo, 2012.” (according to the reference itself).

Reply 11:
The reference has been corrected.

Comment 12:
Table 2: Educational level should be ordered Less than, High school, More than, others instead of High school; Less, Higher. Even though this will cause the reference group not to be on top, it will increase readability.

Reply 12:
Table 2 has been amended as advised.

Comment 13:

Discussion, initial statement: I do not quite follow why the discussion of the potential limited generalizability for some specific countries is mentioned 'up front' like this. This should of course be discussed (under the sub-header 'Strengths and limitations'), but not as part of the 'principal finding'.

Reply 13:
We have now moved the concerned text under the sub-section 'Strengths and limitations'.

Comment 14:
'Strengths and limitations': The authors have identified a potential bias in that the participants are generally better educated than the background population. This could potentially be a major bias. Their own results suggest that this might bias the results downwards (see table 2). This should be discussed more thoroughly, preferably with other references from the literature on the influence of educational level on drug use during pregnancy.

Reply 14:
The observed association between educational level and medication use during pregnancy is now discussed more thoroughly in the Discussion section where the following text has been added: "Contrary to previous studies indicating an association between higher maternal education and more prevalent use of medication during pregnancy [14,17,23], we found that lower education was associated with a higher use of OTC medications as well as medication for chronic/long-term disorders (30-50% increased risk). Results of similar magnitude (30% increased risk) were also observed by Olesen et al.[34], whereas Stokholm et al.[35] identified a stronger association (2.3-fold increased risk) between low maternal education and use of antibiotic for respiratory tract infections during pregnancy". The section 'Strengths and limitations' has been amended as follows: "The sample in each country had a somewhat higher educational level than the general birthing populations. Such a limitation might have led to biased estimates of the association between maternal education and medication use during pregnancy".

Reviewer 2:

Comment 15:
2. Is the abstract accurate, balanced and complete? No
Primary and secondary outcome measures: Prevalence and determinants of medication use for acute illnesses, chronic disorders and over-the-counter (OTC) medication use.
The study could not measure determinants. The prevalence measures are not shown to be representative.

Reply 15:
Thank you for the comment about the representativeness of the study results in each participating country. In the original version of the manuscript we had addressed the representativeness issue. The extensive information outlined in the now Appendix 3 enabled us to extrapolate to which extent the study participants actually represented the birthing population in each country in terms of age, marital status, educational level, smoking before and during pregnancy, and other socio-demographic characteristics. In the same tables we had also included the ratio (in per cent) between the number of respondents and the number of births in the 2-month period the study took place, for each participating country. This allowed for a critical assessment of the external validity of the study results. However, we do agree with the reviewer that for some countries (i.e. Australia, Canada, France, Russia, and the US) the number of respondents represented a very small proportion of the general birthing population. This important limitation was already addressed in the original version of the manuscript. In order to highlight this limitation even more, we have now sorted in Appendix 3 the countries under each region according to the ratio (in per cent) between the number of respondents and the number of births in the 2-month period (from largest to smallest). Also, the ratio (in per cent) has been moved from the last to the first row of the tables in Appendix 3.
Furthermore, we have added a new Appendix (Appendix 4) showing the required sample sizes for determining various prevalence estimates of medication use (80%, 70%, 60%, 30% and 15%) as shown by previous studies published in the literature. The sample size calculation was determined using a precision of 5% with 95% confidence interval. As shown in Appendix 4, the study sample recruited in most countries was satisfactory to determine the expected prevalence estimates of

medication use. As also specified in Appendix 4, for some countries the study sample was too small for allowing a precision of 5% in the prevalence estimates, however it was satisfactory when a precision with range 6-11% was allowed. In the section “Strengths and Limitations” we have now added a statement reflecting the precision of our prevalence estimates – as permitted by the sample size in each country; the newly added statement is as follows: “In most participating countries the study sample was large enough to warrant calculation of prevalence estimates with a precision of 5%. However, less precise estimates were permitted by the study sample in Austria, Iceland and The Netherlands (precision of 9-11%), as well as in Australia, Canada, Croatia, Serbia, Slovenia, and USA (precision of 6-7%)”. Given this scenario, we consider that the current study did allow for measurement of determinants of medication use during pregnancy. However, since the study was cross-sectional and thus lacking the temporal component, we have substituted the word “determinants” with “factors associated” throughout the manuscript.

Comment 16:
3. Is the study design appropriate to answer the research question? No
The sample sizes are too small to determine outcomes at a national level.

Reply 16:
We have tried to address this issue in the revised manuscript. We have carried out required sample size calculation on individual country level, specifically for the outcomes: any medication use (using a range of 70-80%), medication use for chronic/long-term disorders (using a range of 15-30%) and OTC medication use (using 60% as expected prevalence). The required sample sizes in each country are outlined in Appendix 4. The level of precision in the prevalence estimates has been addressed in the reply to comment 15 above.

Comment 17:
4. Are the methods described sufficiently to allow the study to be repeated? No
A copy of the internet survey would be useful in the supplementary material provided.

Reply 17:
The questionnaire is now included as Appendix 1 (see reply to comment 5 above).

Comment 18:
The participants are self-selected and their reasons for seeking advice regarding their pregnancy via a website cannot be shown to be representative of pregnant women in their country as a whole.

Reply 18:
The representativeness issue has been thoroughly addressed in our replies to previous comments. The current study was a web-based, cross-sectional study performed simultaneously in several countries. Web-based studies are a relatively novel method of data collection in epidemiology. We do agree with the reviewer and acknowledge the fact that this type of study may have pitfalls and limitations, most importantly selective non-response and concerns regarding data reliability. However this study type was not new to the research group at the University of Oslo who initiated the project. Two previous web-based studies from our group have been conducted in Norway (Nordeng et al., Ann Pharmacother. 2010; Nordeng et al., Eur J Clin Pharmacol. 2010). In both studies, a large number of respondents were collected in a population with about 60,000 annual births. Web-based questionnaires have been considered feasible tools to recruit population-based data in countries with high rates of internet coverage. This is especially relevant when the target population comprises women in childbearing age – since younger individuals have a considerably higher rate of internet access than the older counterpart.
Furthermore, internet penetration rates have increased dramatically in recent years, not at least in Europe, Australia, North and South America (Internet World Stats. Usage and Population Statistics. URL: http://www.internetworldstats.com/) Web-based studies can also mirror the role of women in the current society. Women search for information on the internet and they most often consult more than one source. This may be of special relevance during pregnancy, when women have many questions to be answered.
In fact, several studies (e.g. Smith et al., Am J Epidemiol. 2007; West et al., Addiction. 2006) have

shown that populations recruited via web-based studies is comparable in age, education and health status to populations recruited via paper-based questionnaires. In order to reach the widest segment of the target population, we tried to recruit subjects via banners (study invitation) on pregnancy websites with highest number of daily users. We also utilized social network, pregnancy forum, and email newsletter by pregnancy websites to all subscribed members.
However, since we cannot calculate a conventional response rate, we have addressed the representativeness issue in several points of the manuscript. Moreover, we have attempted to identify which segments of the general pregnant population were captured in the study, thereby allowing for a more critical assessment of the external validity of the study results. We attempted to do so by:
1) Calculating the ratio (in per cent) between the number of respondents and the number of births in the 2-month period the study took place, for each participating country (as described in Appendix 3).
2) Comparing the sociodemographic and lifestyle characteristics of the sample on individual country level with national statistic data in the country.
3) Presenting internet penetration rates in each participating country (as described in Appendix 2).
4) Clearly acknowledging such a study limitation and generalizability of our study findings in the section “Strengths and Limitations”.
5) Adding in the section “Strengths and Limitations” a statement about a potential selection bias, which is as follows: “The questionnaire was only available through internet websites; by using this kind of approach a conventional response rate cannot be calculated and a selection bias of the target population cannot be ruled out”.

Comment 19:
11. Are the discussion and conclusions justified by the results No
The study sizes for each country are very small. Selection bias is a major issue.

Reply 19:
We have carried out sample size calculation for each individual country (see reply to Comments 15 and 16 above). The issue about selection bias has been answered in reply to Comment 18 above.

Comment 20:
12. Are the study limitations discussed adequately? No
Some of the study limitations are highlighted in the article summary section. The final statement in the conclusion sums up the major selection bias issue in this study.

Reply 20:
The section “Strengths and Limitations” now includes a statement about a potential selection bias, which is as follows: “The questionnaire was only available through internet websites; by using this kind of approach a conventional response rate cannot be calculated and a selection bias of the target population cannot be ruled out”.

Comment 21:
1. I have serious concerns around how representative the study samples are for each country/region.

Reply 21:
Please see replies to comments 15, 16 and 18 above.

Comment 22:
2. I do not like the term “housewives” – without seeing the survey question relating to the occupation of the participants, it is difficult to accept this as a scientifically-based description.

Reply 22:
The relevant sections of the survey questionnaire are now available as Appendix 1. In our survey, we aimed to identify women whose working status was “housewife” (i.e. women who managed a household while their husbands earn the family income) when they became pregnant. The question posed to all study participants (cf. question no. 6 in Appendix 1) was the following: “What was your work situation when you became pregnant?” The study participants could tick off only one of the listed

choices: “Student” – “Housewife” – “Health care personnel, i.e., physician, nurse, or pharmacist” – “Employed in another sector” – “Job seeker” – “None of the above”. Multiple choices were not allowed.
We used the term “housewife” rather than “homemaker” because that is a gender specific word, which is of relevance in the current study (since we aimed to recruit only women). Since we used the term “housewife” in the questionnaire, we feel it is not correct to change its wording.

Comment 23:
3. The use of HCP as a separate employment may be understandable but it should also be used in relation to “housewives” and the other categories – there may be some pregnant women who are categorised as “housewives” but were actually nurses, clinicians, HCPs before they became pregnant and equally would be “possibly reflecting higher confidence in self-treatment and use of medications in general” (p 21). Even medical students could be in this definition.

Reply 23:
Thank you for this comment. As described in reply to Comment 22, all study participants were questioned about their work situation when they became pregnant. We feel that this specific wording is unlikely to have generated confusion and/or uncertainty among the respondents in providing the correct answer. This is also supported by the fact that question no. 6 of the questionnaire did not allow for multiple-choice answer – only one answer was allowed. However, in order to avoid confusion in the reader, we have now specified in the Methods section – Exposure variables – that the variable “working status” referred to the time of conception, i.e. when the respondent became pregnant.
Comment 24:
4. A copy of the internet survey as an appendix may have been useful.

Reply 24:
The relevant sections of the questionnaire are now presented as Appendix 1 (see reply to comment 5 above).

Comment 25:
5. What does this mean in final paragraph: "Inclusion of pregnant women at any gestational week might have inflated the prevalence of non-users of medications during pregnancy."?

Reply 25:
Please see reply to comments 2 and 4 above. In the section “Strengths and Limitations” the sentence “Inclusion of pregnant women at any gestational week might have inflated the prevalence of non-users of medications during pregnancy” has been rephrased into “Since many ailments requiring pharmacotherapy occur in mid or late pregnancy, inclusion of pregnant women at early gestation in the total material has somewhat inflated the prevalence of non-users of medications during pregnancy”.

VERSION 2 – REVIEW

REVIEWER	Anton Pottegård University of Southern Denmark, Denmark.
REVIEW RETURNED	15-Jan-2014

GENERAL COMMENTS	This is the second review of this paper. The authors have listened to the points raised during the first round of review, and have offered an impressive and exhaustive list of responses including several major changes/updates to the paper. While the paper was very good to begin with, it is now even better. I have only a few minor comments.

	Title: I think the authors should consider changing the title to include the study design, as suggested in the STROBE-guidelines for cross-sectional analyses. My suggestion would be “Medication use in pregnancy: a multinational internet-based survey”. Abstract, primary and secondary outcome measures: ”Prevalence” should be changed to ”Prevalence of”. Discussion, 5th paragraph: In the previous paragraphs, presence or lack of safety data is discussed. I suggest the authors include a similar comment in paragraph five regarding use of antidepressants, citing the recent publications on the safety profile of SSRIs. Methods, strengths and limitations: Regarding the ‘somewhat higher educational level’ among the respondents compared to the background population, the authors state that “Such a limitation might have led to biased estimates of the association between maternal education and medication use during pregnancy”. This might actually not be the case. However, if educational level is a predictor of medication use (as is the case) this will bias the overall prevalence proportion of use of medicine. Higher education (high school or higher compared to ‘less than highschool’) leads to lower use of medicine (see table 2), and as the sample is more educated than the background population, this will lead to a bias towards lower proportion of use of medicine.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1:

Minor comments
This is the second review of this paper. The authors have listened to the points raised during the first round of review, and have offered an impressive and exhaustive list of responses including several major changes/updates to the paper. While the paper was very good to begin with, it is now even better. I have only a few minor comments.

Comment 1: Title: I think the authors should consider changing the title to include the study design, as suggested in the STROBE-guidelines for cross-sectional analyses. My suggestion would be “Medication use in pregnancy: a multinational internet-based survey”.

Reply 1: Thank you for this comment, we do agree that the design of the study should be reflected in the paper´s title. The study had a cross-sectional design, and utilized a web-based questionnaire to collect population-based data. The word “web-based” was used by van Gelder et al. in the following publication: van Gelder MM, Bretveld RW, Roeleveld N. Web-based questionnaires: the future in epidemiology? Am J Epidemiol 2010;172(11):1292-8. Hence, we would prefer using the word “web-based” rather than “internet-based” in the title. We do propose the following title: “Medication use in pregnancy: a cross-sectional, multinational web-based study”. In order to be consistent, we have replaced the word “internet-based” with “web-based” throughout the manuscript.

Comment 2: Abstract, primary and secondary outcome measures: ”Prevalence” should be changed to ”Prevalence of”.

Reply 2: This has been corrected.

Comment 3: Discussion, 5th paragraph: In the previous paragraphs, presence or lack of safety data is discussed. I suggest the authors include a similar comment in paragraph five regarding use of antidepressants, citing the recent publications on the safety profile of SSRIs.

Reply 3: We have added a comment about safety of SSRIs in pregnancy, with information stemming from the three recent meta-analyses. The comment focuses on specific neonatal outcomes, i.e. cardiac malformations, neonatal adaptation and persistent pulmonary hypertension of the newborn. We have chosen not address any possible long-term effects of SSRIs such as neurodevelopment or autism, or other maternal outcomes such as vaginal bleeding, postpartum haemorrhage or preeclampsia. The added text is as follows: “Selective serotonin reuptake inhibitors (SSRIs) were the most widely used antidepressant class. Recent meta-analyses have shown that antidepressants, including SSRIs, do increase the risk of poor neonatal adaptation syndrome, specific cardiovascular malformations and persistent pulmonary hypertension of the newborn.[33-35] However, the clinical impact of the latter two outcomes, in absolute terms, is small and the risk of pharmacotherapy should always be weighted versus the risk of undertreated depression in pregnancy”.

Comment 4: Methods, strengths and limitations: Regarding the ‘somewhat higher educational level’ among the respondents compared to the background population, the authors state that “Such a limitation might have led to biased estimates of the association between maternal education and medication use during pregnancy”. This might actually not be the case. However, if educational level is a predictor of medication use (as is the case) this will bias the overall prevalence proportion of use of medicine. Higher education (high school or higher compared to ‘less than highschool’) leads to lower use of medicine (see table 2), and as the sample is more educated than the background population, this will lead to a bias towards lower proportion of use of medicine.

Reply 4: Thank for clarifying this comment, which was misunderstood during the first revision. In the revised manuscript, the text “Such a limitation might have led to biased estimates of the association between maternal education and medication use during pregnancy” has been replaced by the following: “Such a limitation might have led to an underestimation of the prevalence of medication during pregnancy”.