Response to Editors and Reviewers Comments
"Maternal use of oral contraceptives and risk of birth defects: nationwide cohort study in Denmark" [manuscript ID BMJ.2015.028891]

Reviewer 1, Comment #1, Reviewer 2, Comment #1, and Editors, Comment #5 We appreciate the reviewers' positive remarks about this paper being "clearly executed" and "well written" with "modern, sound" methods. We also hope to shed light on "an important area of research" that has "considerable public health importance "using "classic Scandinavian drug safety epidemiology."

Reviewer 1, Comment #2 and Reviewer 2, Comment #8: Reviewer 1 suggests clarifying the amount of missing covariate data in Table 1. Given the size and detail of Table 1, we have taken Reviewer 2's suggestion and added a footnote about the amount of missing and referred the reader to Table S2, which provides even more information about each covariate including the frequency and percentage of missingness. We also added new text to page 6, paragraph 1 to clarify our missing data approach.

Reviewer 1, Comment #3: The reviewer asked us to provide more information about our exposure classification. We have added two sentences to page 4, paragraph 4 outlining the type of oral contraceptives (OCs) that were included with our anatomical therapeutic chemical code as well as how we handled other hormonal contraceptive use.

Reviewer 1, Comment #4: The reviewer asked about our definition of "calendar year" so we have added text to page 5, paragraph 4 to clarify this is the calendar year of the pregnancy onset.

Reviewer 1, Comment #5: We appreciate the reviewer, Dr. Waller, making suggestions for how we can further contextualize our findings in relation to her 2010 case-control study. As she suggested, we have noted on page 8, paragraph 2 that both studies found an elevated risk for hypoplastic left heart syndrome and our finding may have not reached statistical significance due to limited statistical power. We also added new text to page 9, paragraph 1 that contextualizes these results as well.

Reviewer 1, Comment #6: We appreciate the reviewer's careful editing and have corrected the misspelling of gastroschisis in Table 3.

Reviewer 1, Comment #7, Reviewer 2, Comment #7, and Editors, Comment #1 and #6: Reviewer 1 commented on our unique exposure assessment as compared to previous studies which have used maternal interview so we have highlighted this issue on page 9, paragraph 3. This should complement the other novel aspects of our paper as outlined in our strengths section. In response to the point raised by Reviewer 2 about not knowing if participants took the OCs listed in the prescription registry, and wondering how this compares to other self-reported assessments, we have noted this in our limitations section and would note here that the Editors highlighted in Comment #6 that registry data "is as good as you can get." The Editors wanted to see the unique aspects of our paper in

comparison to other studies in Comment #1 so the above changes along with the entire second paragraph of page 10, which also includes new text.

Reviewer 2, Comment #1: As suggested, we have spelled out oral contraceptives at the first use in the abstract.

Reviewer 2, Comments #2, #4, and #9: We have now clarified in all of the relevant table footnotes about our definition of "never users" by noting that the National Prescription Register contains information since 1995 and our follow-up for pregnancies began in 1997. Therefore, never users are individuals who have never once filled an OC prescription since the National Prescription Register began in 1995.

Reviewer 2, Comment #3: The reviewer suggested adding a percentage to the birth defect prevalence in the first sentence of the results so that can now be found on page 6, paragraph 4.

Reviewer 2, Comment #5: We appreciate the reviewer's careful editing and have corrected the typographical error of "than" in the fifth paragraph of the results section.

Reviewer 2, Comment #6: The reviewer highlighted the possibility for exposure misclassification in the "never users" group so we have emphasized this not only in our study limitations but also now elsewhere in the discussion on page 9, paragraph 1.

Reviewer 2, Comment #10: The reviewer inquired about the Table 4 sensitivity analyses. Our objective was to test the sensitivity of our main hypothesis (all major defects). This decision was also driven by the statistical power.

Editors, Comment #2: We agree with the editors that many different formulations are included in any OC assessment. We discussed this weakness in our limitation section with the following text: "Data on filled prescriptions was available from 1995, which limited our ability to examine different aspects of OC exposure that were not available in the registry, such as different OC formulations. Other health outcomes, such as breast cancer, have varied by formulation—with triphasic levonorgestrel formulations driving the increased breast cancer risk. However, there is no literature demonstrating any heterogeneity in the risk of birth defects by OC formulations; this may be worth exploring in future research since prescribing practices could be easily altered if any one formulation were associated with defects."

Editors, Comment #3: The editors asked about confounder adjustment including comorbidities. One of our study's strengths was the large number of potential confounders we could consider. Potential confounders included detailed demographic information and medical information including previous birth defects and various measures of health care utilization (prescription drugs, hospital admissions, and outpatient hospital contacts). We discuss the above as well as the possibility for residual confounding in our limitation section with the following text: "Residual confounding was

possible but we addressed this by conducting propensity score matched sensitivity analysis, which provides more extended control for potential confounders."

Editors, Comment #4: We agree with the editors that folate may influence this association. We discussed this in our limitation section with the following text: "We also lacked information on folate, one of our proposed mechanisms, so we could not examine this further. If there is a causal link between OC use and birth defects, it's possible that differential folate exposure could explain our null finding. However, our null findings were consistent across birth defects that are folate-dependent (e.g. orofacial clefts) as well as those that are not."

Editors, Comment #7: The editors thought we could use more clarity in comparing our findings to the Waller et al. case-control study so we hope the new text on page 8, paragraph 2 does that. Dr. Waller's review also helped to clarify a few places where we could improve this as well including on page 9, paragraph 3. Our statement regarding our study not corroborating previous finding immediately follows and specifically refers to our discussion of the four categories of birth defects for which significant associations with OC exposure have been reported. On page 9, paragraph 1, we have revised to clarify how our study compares to these previously reported associations and hope that our discussion provides a balanced view. Please also note that this paragraph starts with a sentence that underlines that our study confirms the bulk of previous work that did not document any increase in risk.

Editors, Comment #8: As the editors highlight, the Waller et al. study did have greater statistical power than our cohort but that our study is possibly less prone to bias. We have more clearly highlighted this on page 8, paragraph 2 as well as commented on the strengths of our cohort on page 9, paragraph 3.