

Correspondence and Reply

Can left truncation of the data explain the observed null associations?



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To the Editor:

The article “Safety of Fluticasone Propionate Prescribed for Asthma during Pregnancy: A UK Population-Based Cohort Study”¹ sought to address a relevant topic regarding drug exposures during pregnancy. The methodological definitions for exposure are novel and are especially useful for the conduct of pregnancy studies using administrative data and to clinical practice. Unfortunately, a study design flaw may have confounded or biased the risk estimates toward the null.

Left truncation in pregnancy studies occurs whenever time zero (conception) is not observed during the study timeline (gestational period).² This poses significant threat to study validity in scenarios in which the degree of truncation varies by exposures of interest or by other underlying risk factors associated with the outcome of interest. Differential left truncation has been found to explain paradoxical associations between smoking during pregnancy and preeclampsia³ and trihalomethane exposure and spontaneous abortions.²

In the study by Charlton et al,¹ the study entry date for defining the asthma pregnancy cohort was set to the earliest date of the second asthma treatment prescription after an asthma diagnosis or the date of the sixth asthma treatment prescription in the 6 months before or during the first trimester. A final requirement of at least 1 prescription during the 6 months before the start date of pregnancy or during the first trimester was applied. This study entry criterion suggests that patients had to enter the study cohort via either of these definitions. Study entry criterion set up this way will likely left truncate the data for patients with more severe asthma because we expect these patients to accrue more prescriptions rather than with the former entry definition. Conversely, patients with milder asthma severity or patients with new-onset asthma will likely enter the cohort sooner than those with more severe asthma. Because patients with relatively severe asthma will need to accrue 6 prescriptions, they will have a longer waiting period to study entry compared with patients with mild-moderate asthma. Given the higher risk for early pregnancy loss among women with more severe asthma, the left truncation of data would result in excluding early pregnancy losses associated with this cohort of women, thus increasing the probability of a live birth with a diminished risk of major congenital malformations (MCMs). The result is an underestimation of the risk for pregnancy loss and an ensuing decreased risk for MCMs by asthma severity. This hypothesis is supported in the data presented in Tables II and E2, which suggest a similar or increased risk of MCMs with decreasing asthma severity (Table II), whereas previous studies indicate that women with moderate to severe asthma exacerbations are at an increased risk for congenital malformations.^{4,5} Because patients with more severe disease were also more likely to receive fluticasone inhaled corticosteroids, this issue of left truncation of the data may also explain the nonsignificant risk observed in this study. Would the observed association remain null if either entry criterion for asthma definition was applied?

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Reply



To the Editor:

Thank you for the opportunity to respond to the correspondence¹ received in relation to our article “Safety of Fluticasone Propionate Prescribed for Asthma During Pregnancy: A UK Population-Based Cohort Study.”² The correspondence addresses the issue of left truncation and subsequent confounding or bias of the risk estimates toward the null. This, however, appears to stem from a misunderstanding of how the cohort for our study was selected and how the inclusion criteria were applied. Below we address the issue raised and provide further clarification on how the study cohort was selected.

In the correspondence letter, the author states that “left truncation on pregnancy studies occurs whenever time zero (conception) is not observed during the study timeline (gestational period).”¹ In our study, however, pregnancies were included in the study only if the woman had been followed in the database for the 6 months before pregnancy, throughout the entire pregnancy (from the estimated date of the first day of the last menstrual period through to the end of pregnancy), and the 3 months postpregnancy. As a result, the left truncation referred to within the correspondence did not occur in our study because all pregnancies were followed for their entirety.

The concern about left truncation and the possible impact of this appears to have come from a misunderstanding of how our study cohort was selected, which perhaps we should have made clearer in the article. The letter states that “In the study by Charlton et al, the study entry date for defining the asthma

pregnancy cohort was set to the earliest date of the second asthma treatment prescription after an asthma diagnosis or the date of the sixth asthma treatment prescription in the 6 months before or during the first trimester.” This, however, was not the case. In our study, most women with asthma (>85%) were identified as having asthma and were eligible for the study based on a Read code diagnosis of asthma and supporting evidence of 2 or more asthma treatment prescriptions. In addition to these, there was a relatively small number of women who did not have an asthma diagnosis code but did have a large number of prescriptions for asthma treatment. A minimum of 6 prescriptions was required for these individuals to be eligible to enter the cohort to increase the likelihood that they did truly have asthma, given the lack of confirmation from an asthma diagnosis code. These were 2 totally separate entry criteria that were applied solely on the basis of whether the woman had an asthma diagnosis code within her medical record and not on the basis of the number of prescriptions a woman had received and would not have been significantly impacted by asthma severity. In addition, the 2 or 6 prescriptions required to make an individual eligible for the asthma cohort could have been prescribed at any time within the study period (January 1, 2000, to December 31, 2010) and did not have to have been prescribed in the 6 months before or during pregnancy as suggested in the letter of correspondence.

The entry inclusion criteria used as part of our study, combined with the fact that all pregnancies were followed for their entirety, means that it is unlikely that differential left truncation will explain the observed null association within our study. We do,

however, accept that the lack of an asthma diagnosis code for those individuals who became eligible based on 6 prescriptions should have been clearly stated in the article.

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