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# Drug exposure: inclusion of dispensed drugs before pregnancy may lead to underestimation of risk associations

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## Abstract

**Objectives:** To assess the impact of exposure misclassification on risk associations when using prescription databases as the source for drug exposure in pregnancy by applying results from a validation analysis of exposure classification.

**Study Design and Setting:** Linkage of data on 27,656 participants in the Norwegian Mother and Child Cohort Study (MoBa) with the Norwegian Prescription Database (NorPD). Exposure to selective serotonin reuptake inhibitors (SSRIs) was defined by dispensed drugs during pregnancy including different time windows before pregnancy. The validity of NorPD data was estimated using self-reported use in MoBa as the reference standard. We applied the results from the validation analysis on data from a Nordic study on SSRI use in pregnancy and risk of persistent pulmonary hypertension in the newborn.

**Results:** Sensitivity increased and specificity decreased when the time window in NorPD was expanded before pregnancy. Using the same time window as in the Nordic study (+90 days before pregnancy), for use in early pregnancy, the odds ratio (OR) corrected for misclassification was 2.6 compared with the OR of 1.6 in the Nordic study.

**Conclusion:** Expansion of the time window to include intervals before pregnancy can lead to lower specificity and underestimation of risk associations. 

*Keywords:* SSRI exposure; Prescription databases; Pregnancy; Validity; Misclassification; MoBa

## 1. Introduction

Drug safety studies in pregnancy require very large study populations because the outcomes and exposures tend to be rare. Linkage of population-based registries (i.e., nationwide medical birth registries and prescription databases) in the Nordic countries enables the use of large study populations to assess effects of drug use in pregnancy.

Depression during pregnancy is common [1]. Untreated maternal depression is associated with serious risks for the mother and may result in poorer pregnancy outcomes [2]. However, treatment with antidepressants during pregnancy is also challenging. Selective serotonin reuptake inhibitors (SSRIs) are the most prescribed drugs for depression during pregnancy [3]. Both early and late fetal exposure to SSRIs may be a risk factor for adverse neonatal outcomes [4,5], but studies report inconsistent findings, ranging from no association to increased risk of adverse outcomes, but most studies lack statistical power [4,5].

Recently, the first Nordic study on SSRI use in pregnancy was published [6]. This study was based on linkage of population-based prescription databases and birth registries in the five Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden). In total, more than 1.6 million singleton births were included in this study, and of them, 1.1% and 0.7% women were dispensed an SSRI during early and late pregnancy, respectively. The outcome studied was persistent pulmonary hypertension in the newborn (PPHN), and exposure to SSRIs was shown to increase the risk of PPHN [6]. The risk of PPHN was slightly increased after exposure to SSRIs in early pregnancy

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**What is new?**

- Linkage of nationwide prescription databases enables the use of very large study sizes that are required to study rare outcomes and exposure to assess effects of drug use in pregnancy. Noncompliance in the use of prescribed drugs may result in misclassification of exposure and bias the risk estimates. The specificity is more important than the sensitivity for the estimated risk associations when the prevalence of exposure is low. Thus, it is important to minimize the number of truly unexposed patients in the exposed group.
- When using prescription databases as the source for exposure, expansion of the time window to include intervals before pregnancy leads to lower specificity and higher degree of underestimation of risk estimates.
- When using prescription databases in measurements of exposure without expansion of the period before the pregnancy, the underestimation of measured risk associations was low for use of selective serotonin reuptake inhibitor and persistent pulmonary hypertension in the newborn.

[unadjusted odds ratio (OR), 1.6; adjusted OR, 1.4). In late pregnancy, the risk of PPHN after exposure to SSRIs was more than doubled (unadjusted OR, 2.5; adjusted OR, 2.1). Timing of exposure was based on the date SSRIs were dispensed at the pharmacy. Use in early pregnancy was defined as an SSRI dispensed at least once from 90 days before the start of pregnancy until the eight gestational week of pregnancy. Use in late pregnancy was defined as an SSRI dispensed after gestational week 20 until birth.

Data from prescription databases have its weaknesses, and it has been pointed out that a major challenge in prescription database studies is to validate exposure [7]. Medicines can be obtained at pharmacies but do not have to be used. Noncompliance may result in misclassification of exposure and bias the risk estimates. Other data sources as self-reports and interviews may be used in drug safety studies in pregnancy, but no data source is without weaknesses. Self-reported data can be influenced by the fact that women do not remember or do not want to report drug use. Thus, it is possible in both prescription database studies and surveys to question the validity of the data on drug exposure.

In Norway, a large population-based pregnancy cohort, the Norwegian Mother and Child Cohort Study (MoBa) has been established [8]. Women who agreed to participate in MoBa received self-administered questionnaires by mail during pregnancy, in which self-reported drug use is collected as pregnancy progresses. Pregnant women are generally cautious when it comes to using medicines and drug used daily are more easily remembered [9]. Participants in MoBa were motivated to participate, and this might be even truer for women who answered all the relevant questionnaires and who are eligible in drug safety studies. Recall bias are also minimized because the women mainly reported on drug use before the outcome was known. In addition, the recall time on drug use was short in MoBa. Data on self-reported drug use in MoBa are therefore suitable as the reference standard in the validity analyses.

The Norwegian Prescription Database (NorPD) is one of the nationwide databases that the Nordic SSRI study was based on. The self-reported data on drug use from the MoBa pregnancy cohort give the opportunity to assess the comparability of data from prescription databases and self-reported data on SSRI use in the same pregnant women [8,10].

A recent review article emphasized the need for further research exploring differences in exposure classification and the effects on calculated risk estimates [11]. Thus, the main aim of our study was to assess the impact of misclassification of drug exposure on risk estimates by using data from the first large published Nordic study that have used prescription databases as the source for exposure information. To do this, we first estimated the sensitivity, specificity, and positive and negative predictive values of SSRI exposure recorded in NorPD by using self-reported drug use in MoBa as reference. Then, we applied the results data from the Nordic study on SSRI use in pregnancy and risk of PPHN [6]. The Nordic study included a period before pregnancy in the definition of exposure early in pregnancy because some women may fill a prescription before pregnancy and use the drug after becoming pregnant. Finally, we therefore assessed how inclusion of SSRIs dispensed in different periods before pregnancy influenced misclassification of exposure and estimated risk associations.

## 2. Materials and methods

We obtained data from the NorPD, MoBa, and Medical Birth Registry of Norway (MBRN). The three data sources were linked using the unique personal identity number assigned to all individuals living in Norway, and the linkage was 100% complete between all the three data sources. If information were available from several data sources, data from nationwide health registries (MBRN and NorPD) were preferred because of completeness.

Data on dispensed drugs recorded in NorPD were compared with data on self-reported drug use by pregnant women participating in MoBa. The estimated sensitivity and specificity of drug exposure recorded in the NorPD were used to assess the impact of misclassification on the risk estimate in the Nordic study on SSRI use in pregnancy [6].