Analyzing Missing Data in Perinatal Pharmacoepidemiology Research: Methodological Considerations to Limit the Risk of Bias

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ABSTRACT

Pharmacoepidemiological studies on the safety of medication during pregnancy are all susceptible to missing data (ie, data that should have been recorded but for some reason were not). Missing data are ubiquitous, irrespective of the data source used. Bias can arise when incomplete data on confounders, outcome measures, pregnancy duration, or even cohort selection criteria are used to estimate prenatal exposure effects that would be obtained from the fully observed data, if these were available for each mother–child dyad. This commentary describes general missing data mechanisms and methods, and illustrates how missing data were handled in recent medication in pregnancy research, according to the utilized data source. We further present one applied example on missing data analysis within MoBa (the Norwegian Mother, Father and Child Cohort Study), and finally illustrate how the causal diagram framework can be helpful in assessing risk of bias due to missing data in perinatal pharmacoepidemiology research. We recommend that applied researchers limit missing data during data collection, carefully diagnose missingness, apply strategies for missing data mitigation under different assumptions, and finally include evaluations of robustness results under these assumptions. Following this set of recommendations can aid future perinatal pharmacoepidemiology research in avoiding the problems that result from failure to consider this important source of bias. (*Clin Ther*. 2019;41:2477–2487) © 2019 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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INTRODUCTION

Missing data is a global problem in research involving human subjects and a serious threat to both validity and efficiency in effect estimation. The CONSORT 2010 Statement[1] advocates transparent reporting of the extent of missing data and how this issue was dealt with in the analysis, as this factor is crucial for readers to critically evaluate the study findings and potential biases. Recognition of the threat from these biases has resulted in calls for increased use of methods for dealing with missing data.[2] However, barriers exist that prevent applied pharmacoepidemiology researchers from assessing the potential gains to their own work, including understanding scenarios when simpler methods might be sufficient, or when complex approaches are needed. These barriers include a lack of resources that integrate missing data terminology and approaches with epidemiologic concepts, and a discussion of the strengths and weaknesses of the most common approaches.

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The present article reviews the critical concepts for missing data problems, with the aim of integrating more traditional statistical language on missingness mechanisms with epidemiologic methods based on causal diagrams.[3] We have framed this commentary by using examples from perinatal pharmacoepidemiology, including an applied example from MoBa (the Norwegian Mother, Father and Child Cohort Study); that is, evaluating the effect of prenatal use of selective serotonin reuptake inhibitor (SSRI) antidepressants on preeclampsia in the scenario of missing data on relevant confounders such as smoking status in gestation.

Missing data methods and mechanisms

Missing data are generally classified as missing completely at random (MCAR), missing at random (MAR), or missing not at random (MNAR)[2,4,5] as briefly described here.

Missing completely at random

Under the MCAR scenario, there are no systematic differences between the missing and the observed values.[2,5] For example, if unexperienced health care personnel forget to ask about smoking during pregnancy, information about smoking will be missing at random in the pregnant woman's medical chart. The same occurs when study participants randomly forget to fill in or skip responses. There is no risk of bias with MCAR data, but there will be loss of precision.

Missing at random

MAR is classified as any systematic difference between the missing values and the observed values, which can be explained by the observed data.[2,5] For instance, pregnant women with depression may be less likely to report smoking than nondepressed pregnant women.

Missing not at random

MNAR occurs in situations when systematic differences remain between the missing values and the observed values, even after the observed data are taken into account; missingness is thus related to unmeasured variables. For example, women who smoke during pregnancy may be less likely to report their smoking status. When missingness in a variable depends on the missing value itself, the unbiased estimate is not recoverable in observed data.

Exploring extent and patterns of missingness

Although Little's test may help researchers to identify missingness that is MCAR versus MAR, this test is not conclusive. In addition, no numerical diagnostics can differentiate MAR from MNAR. Thus, we are left with logical reasoning to inform us on the mechanism behind data missingness. Exploring the extent and pattern of missing data in one's own data sample (eg, by cross-tabulating variables with missing data against exposure and outcome), as well as using findings from previous studies and normative data (eg, score distribution in a reference population), can give a hint of the underlying mechanism of missingness. This is important to appraise as it will guide decision-making of missing data handling: the various approaches to missing data analysis require different assumptions about the underlying mechanisms.

METHODS TO HANDLE MISSING DATA

Multiple methods for handling missing data are used in perinatal pharmacoepidemiology research. These methods fall into 2 broad categories: analyze the observed data (complete case analysis) or use some principled method for filling in the missing data (imputation). In complete case analysis, observations with missing data on relevant variables are dropped from the analysis. This approach will always produce unbiased results under the MCAR assumption and may produce unbiased results under MAR or MNAR. Complete case analysis is commonly used in perinatal pharmacoepidemiology due to its simplicity (Table I). In database linkage studies in which the study size is large, the loss of data has less impact on precision than in smaller sized or different design studies.[6–10]

Single imputation comprises a set of techniques in which the missing values are replaced by a value from the observed data; for instance, the mean or mode. The imputed values are assumed to be equal to the values that would have been observed if the data had been complete. This method, however, underestimates uncertainty about the missing values

Table I. Examples of functional approaches to missing data in recent pregnancy medication safety research according to type of data source.

Study	Medication, Outcome	Diagnosing Missing Data		Handling and Analyzing Missing Data*				
		Mechanism Assumption	Amount, Variable Type	Complete Case	Single Imputation	Multiple Imputation	Indicator Variable	Others
Birth cohorts								
Magnus et al[19]	Paracetamol, child asthma	Unspecified	10%–15% multiple confounders	SA		MA		
Radojcic et al[20]	Anxiolytics/hypnotics, child development	Unspecified	<1%–18% multiple confounders			MA		
Ernst et al[10]	Paracetamol, child puberty	Unspecified	<5% multiple confounders	MA†				
Caniglia et al[7]	Atazanavir, child development	Unspecified	40% outcome 1%–40% multiple confounders	MA		SA		
Brandlistuen et al[30]	Paracetamol, child development	Unspecified	<1%–4% multiple outcomes					MA‡
			<1%–18% multiple confounders				MA	
Case–control studies (birth defects surveillance)								
Tinker et al[31]	Anxiolytics, congenital anomaly	Unspecified	<10% multiple confounders§	MA†				
Health registries and administrative claims								
Pasternak et al[12]	Ondansetron, adverse fetal outcomes	Unspecified	<1%–7% multiple confounders		MA			
Beau et al[17]	Atropinic drugs, child development	MAR	5%–19% multiple confounders			MA		
Bateman et al[6]	B-blocker, congenital anomaly	Unspecified	1% parity	MA				
Elkjaer et al[9]	Valproate, child cognition	Unspecified	<1% multiple confounders	MA				

(continued on next page)

Table I. (*Continued*)

Study	Medication, Outcome	Diagnosing Missing Data		Handling and Analyzing Missing Data*				
		Mechanism Assumption	Amount, Variable Type	Complete Case	Single Imputation	Multiple Imputation	Indicator Variable	Others
General practice research databases								
McGrogan et al[32]	Statins, pregnancy loss	Unspecified	5%–16% multiple confounders				MA	
Dhalwani et al[8]	Nicotine replacement, stillbirth	Unspecified	8%–30%	MA†			MA†	
Teratology information services–based studies								
Panchaud et al[11]	Metformin, adverse pregnancy outcomes	Unspecified	6% gestational age 57% body mass index		MA		MA	
Scherneck et al[21]	Metformin, congenital anomaly and spontaneous abortion	MAR	<1%–43% multiple confounders§			MA		
Pregnancy registries								
Cohen et al[33]	Quetiapine, congenital anomaly	Unspecified	Unspecified	MA				
Randomized clinical trials								
Coomarasamy et al[18]	Progesterone, live-birth and other neonatal outcomes	Unspecified	3% outcome	MA		SA		

MA = main analysis; MAR = missing at random; SA = sensitivity analysis.
* Inverse probability weighting method not presented because we found no study using it.
† Unspecified in the article was how missing data were handled; we assume it was a complete case approach or indicator variable use.
‡ Other method used: expectation maximization.
§ The extent of missing data was unspecified in the original study; we computed that by using data reported in the baseline factor table or in the text.

and will therefore result in SEs that are too small.[2,5] In the study by Panchaud et al,[11] gestational age was conditionally imputed for 6% of the pregnancies based on the sample mean. In the study by Pasternak et al,[12] missing information on several baseline maternal characteristics was replaced using the mode. In longitudinal studies with repeated variable measurement (eg, using questionnaires at several time points in pregnancy), the "last-value-carried-forward" technique can be used to replace missing values with the last measured value of the individual, as done by Norby et al.[13] This method assumes that the observation of the individual remains the same since the last measured observation. Due to well-established shortcomings,[2,5] single imputation techniques are less used in perinatal pharmacoepidemiology.

Advanced model—based methods for handling missing data have become more accessible to researchers in recent years through packages in standard statistical software. The 2 most common model-based methods are maximum likelihood using the expectation maximization algorithm and multiple imputation.'[14,15] These are considered model-based methods because the researcher must make assumptions about the joint distribution of all variables in the model (including both outcomes and predictors).

Maximum likelihood methods using the expectation maximization algorithm use each observation's available data to compute maximum likelihood estimates, rather than filling in the missing values. It runs until the algorithm converges to the "best fit" model for a set of data. The multiple imputation method fills in missing values by averaging from the distribution of the missing data given the observed data in a way that accounts for the uncertainty associated with the missing values. In multiple imputation by chained equations, a series of regression models are run whereby each variable with missing data is modeled conditional upon the other variables in the data.[14] At the end of one cycle, all missing values have been replaced with predicted values (imputations). The process is repeated for a number of cycles, with the imputations being updated at each cycle, finally resulting in one imputed dataset. The number of imputed datasets is generally between 5 and 20. SEs are calculated by using Rubin's rules.[15,16] The multiple imputation approach produces valid estimates under the MAR assumption. This is a weaker assumption than MCAR and more likely to hold in observational studies.

Multiple imputation is a computationally intensive method that is increasingly used in perinatal pharmacoepidemiology research (Table I).[7,17–21] However, this method needs to be applied after careful reflection about the missing data to avoid misleading conclusions. We recommend the articles by Sterne et al[5] and Perkins et al[2] for comprehensive review of multiple imputation for missing data in epidemiological studies. Recent research has also shown that the proportion of missing data should not be the major driver for the decision on how to handle missing data.[22] In fact, even when the extent of missing data is large, results can still be unbiased provided that the MAR assumption is met and methods to handle missing data have been adequately applied.

Missing data approaches in recent medication in pregnancy literature

Table I summarizes the reporting and handling of missing data in recent perinatal pharmacoepidemiology studies according to type of data source utilized. Of note, this study overview serves as common ground for appraising current methodological gaps, and it is not a comprehensive, systematic extract of the literature. Transparent reporting of the extent and handling of missing data, and the uptake of multiple imputation methods, remain limited. For instance, in multiple cases, we computed the extent of missing data in a study by using baseline characteristic data of the study sample based on numbers reported in each article; in some studies, it was unclear what missing data approach was used. The majority of studies reported missing data on confounding variables, to different extents (from <1% to 65%) depending on the data source utilized.

On the basis of the missing data definition used by study authors, and the information reported, missing data do not seem to be a major problem in health registries, administrative claims, or pregnancy registries. This contrasts with studies set in birth cohorts, teratology information services, or general practice databases, which often have to contend with much higher levels of missingness and with patterns that are likely to be informative. The substantial problem of missing data in these study types has promoted important methodological research on the topic,[23,24] as well as a greater uptake of multiple imputation methods by researchers using this type of data (Table I). Simpler approaches to handle missing data such as indicator variables were often not reported in the articles we evaluated, which is encouraging given the well-established shortcomings of the method. Study authors rarely stated any assumptions they made about the underlying mechanism of missingness in the literature we reviewed.

Directed acyclic graph framework with missing data

Directed acyclic graphs can provide helpful insights into potential biases from assuming various missingness mechanisms. The figure introduces a simplified causal model for the effect of prenatal SSRI exposure on preeclampsia. In this model, we assume a causal effect of depression severity on SSRI use and on smoking, and that smoking has an effect on preeclampsia risk. If these assumptions hold, we could estimate the effect of SSRI use on preeclampsia by conditioning on smoking and depression severity. If some fraction of the study sample lacks data on smoking, assumptions about the mechanism that explains the missingness will point to different strategies for analyzing our data. In Fig. 1A, smoking is MCAR, and we can fit a model for the effect of SSRI use on preeclampsia risk, adjusting for depression severity and smoking, in the complete case sample only, without risk of bias. Fig. 1B shows that if missingness in smoking status is explained by depression severity, we can also estimate unbiased effects in the complete case sample, as the covariates required for confounding control also block bias paths from missingness to the outcome. For missing data mechanisms in which the missingness is predicted by the missing values, as in Fig. 1C, or when the probability of being a complete case depends on the outcome, as in Fig. 1D and E, complete case analysis will result in a biased estimate. Finally, the presence of an auxiliary variable (ie, a variable that predicts missingness but is unrelated to the causal mechanism being considered) (Fig. 1F) allows for unbiased and efficient effect estimation via multiple imputation.

Applied example: prenatal antidepressant use and risk of preeclampsia

As a motivating example, we present recent work on the association between use of SSRI antidepressants during gestation and risk of late-onset preeclampsia using data from the MoBa cohort study.[25] MoBa is a nationwide, population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health, with recruitment occurring between 1999 and 2008. Pregnant women were recruited from all over Norway at the time of their routine ultrasound at 17–18 weeks of gestation. Data were gathered prospectively by using self-administered questionnaires. The cohort now includes 114,500 children, 95,200 mothers, and 77,300 fathers, all of whom are followed up as long as they continue to participate in the study. MoBa has a license from the Norwegian Data Inspectorate and approval from the Regional Committee for Medical Research Ethics. All participants provided written informed consent before participation.[25]

In the present study, we first explored patterns of missing data on important confounders according to exposure and outcome strata. Missing values on these confounders ranged from 1% to 3% for maternal smoking and body mass index, to 7%–8% for education and weight gain. Missing information on maternal depressive and anxiety symptom severity in pregnancy, measured via the Hopkins Symptom Checklist–25 (SCL-25) at gestational week 17 (5 items, SCL-5) and gestational week 30 (8 items, SCL-8),[26,27] was as follows: 5% and 10% on at least one of the SCL-5 or SCL-8 items, respectively, and 15% total missing information simultaneously on either scale. However, only a few women (<3%) completed none or less than one half of the items composing the individual SCL scales. The missing data mechanism in our study seemed to be linked to maternal age and to the extent of completion of the SCL items, but importantly, it did not seem to be associated with the outcome, late-onset preeclampsia. Based on this finding and under the MAR assumption,[25] we conducted 3 sets of analyses: (1) complete case analysis; (2) multiple imputation of missing data on the 2 SCL scales only (approach I); and (3) multiple imputation of missing data on the 2 SCL scales and on other maternal confounders (approach II). As shown in Table II, the adjusted and weighted

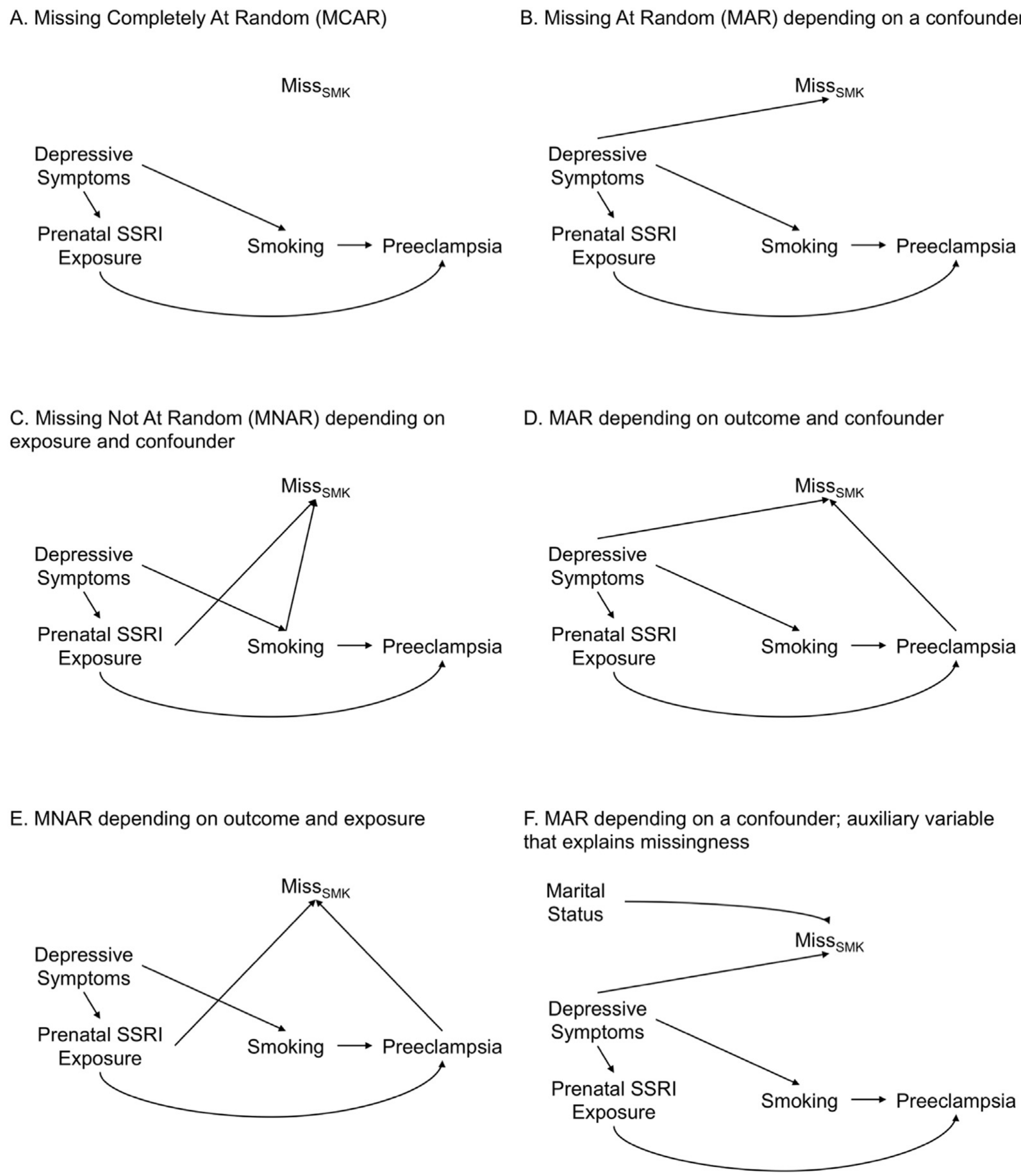

Figure 1. Causal diagrams showing relationships between prenatal selective serotonin reuptake inhibitor (SSRI) use, maternal depression severity, preeclampsia, and smoking, as well as a binary indicator ($Miss_{SMK}$) denoting missing information in the smoking variable. Panel A shows missing completely at random (MCAR) scenario; panel B shows missing at random (MAR) depending on a confounder; panel C indicates missing not at random (MNAR) depending on exposure and confounder; panel D shows missing at random (MAR) depending on outcome and confounder; panel E shows missing not at random (MNAR) depending on outcome and exposure; panel F shows missing at random depending on a confounder and auxilliary variable that explains missingness.

association measures were higher and less precise in the complete case analysis than in the other 2 sets. However, the results of the complete case analysis expanded to pregnancies with only SCL imputed values (approach I) were similar to those obtained in the fully imputed models (approach II). Increasing

Table II. Association of prenatal selective serotonin reuptake inhibitor (SSRI) exposure with maternal risk of late-preeclampsia under 3 missing data—handling scenarios.

Exposure variable	Complete Case* (n = 3913)	Multiple Imputed, I† (n = 4361)	Multiple Imputed, II‡ (n = 5745)	Complete Case* (n = 3913)	Multiple Imputed, I† (n = 4361)	Multiple Imputed, II‡ (n = 5745)
	Adjusted Analysis (Unweighted)			Weighted Analysis		
	Adjusted RR (95% CI)	Adjusted RR (95% CI)	Adjusted RR (95% CI)	Weighted RR (95% CI)	Weighted RR (95% CI)	Weighted RR (95% CI)
SSRI, early pregnancy	1.22 (0.76—1.94)	1.07 (0.67—1.69)	0.96 (0.63—1.46)			
SSRI, midpregnancy	1.04 (0.49—2.21)	0.92 (0.43—1.95)	0.92 (0.48—1.79)	0.48 (0.21—1.11)	0.63 (0.30—1.32)	0.66 (0.33—1.28)
SSRI, late pregnancy	1.16 (0.55—2.46)	1.03 (0.49—2.17)	1.08 (0.57—2.07)	2.28 (0.88—5.87)	1.52 (0.65—3.56)	1.34 (0.61—2.93)
SSRI, any time	1.26 (0.80—1.98)	1.09 (0.70—1.71)	0.96 (0.64—1.45)			

Reference: unexposed pregnancies in the corresponding time window. The weighted analyses correspond to the marginal structural model with inverse probability of treatment weight. The adjusted analyses correspond to multivariate modified-Poisson regression models.

* Including only observations with complete data on all confounders.

† Including observations where multiple imputations were done for missing data on the 2 Hopkins Symptom Checklist scales only.

‡ Including observations where multiple imputations were done for missing data on the 2 SCL Hopkins Symptom Checklist as well as on other maternal confounders.

sample size and higher statistical power following multiple imputation can indeed explain these discrepancies. The extent of missing data on confounders other than the SCL between the complete case and approach I (31.9% vs 24.1%) analyses was, however, not substantial. Hence, because in this example missing data seemed to relate to the extent of completion of the SCL items, we could not exclude the possibility that a complete case analysis approach would yield biased estimates.[5,28,29] In the context of this applied example, results from approach II were thereby considered as those least biased.

Implications for applied researchers

Methods for identifying, analyzing, and mitigating bias from missing data have advanced significantly in recent years and are seeing greater uptake in applied perinatal pharmacoepidemiology research. Based on our survey of the literature, we have several recommendations for applied researchers who need to analyze data with missing values. These recommendations are made bearing in mind that there is no solution to handle missing data that fits all research contexts.

The first recommendation is to limit missingness, where possible, during collection of data. It should be recognized that no statistical method can make up for careful study design and data curation. Sometimes the assumptions that a specific case of missing data require are simply so unrealistic that the effect estimate is unlikely to be informative. The second recommendation is to carefully diagnose missingness and use subject-area knowledge as well as exploratory and descriptive data analysis to understand plausible mechanisms of missingness. We suggest that a minimum standard for missing data analysis should be a complete reporting of missingness within strata of exposure and outcome. Researchers should consider the use of causal graphs to make their assumptions about missingness mechanisms explicit. Third, researchers should be aware that the proportion of missing data should not be the major driver for the decision on how to handle missing data but rather the assumed mechanism as to why data are missing. The fourth recommendation is to include a statistical analyst with expertise in missing data methods. Inappropriate analyses using these complex methods can result in seriously biased results. Finally, researchers should apply strategies for missing data mitigation under different assumptions and include evaluations of robustness results under these assumptions. For example, including both the complete case analysis and the multiply imputed results can allow readers to decide which estimate they prefer, depending on assumptions about the missingness mechanism.

CONCLUSIONS

Careful attention to missing data, and to the assumptions required for analysis of missing data, is necessary in all areas of research, including perinatal pharmacoepidemiology. With transparent reporting of the extent and assumed mechanisms of missing data, and by applying strategies for missing data mitigation under different assumptions, future research can avoid the problems that result from failure to consider this important source of bias.

DISCLOSURES

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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