QUANTIFYING THE IMPACT OF EXPOSURE PREVALENCE AND SELECTION BIAS TO OPTIMIZE PATIENT SELECTION CRITERIA IN POST-AUTHORIZATION SAFETY STUDIES

MSR161

Elizabeth R. Packnett[1], Ryan Ross[1], Liisa A. Palmer[1]
[1]Merative, Real World Data Research & Analytics, Ann Arbor, MI, USA

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Background

- Regulators are increasingly requiring retrospective observational studies to assess the risk of major congenital malformations (MCM) following prenatal exposures [1].
- MCM are rare; the background rate of MCM in the United States is 3-4% [2]. Post-authorization safety studies of the risk of MCM following prenatal exposure will also require that pregnancies have evidence of the indication and then identify pregnancies as exposed or unexposed.
- Obtaining sufficient sample size with the indication and prenatal exposure to rule out increased risk of MCM can be challenging; modest changes to the patient selection criteria will affect the study's power to detect differences in exposed and unexposed.
- Database size, longitudinality, and infant linkage rate are important considerations when selecting a data source for post-authorization safety studies[3].

Objective

- To identify sample sizes where changes to patient selection criteria would impact the ability to detect an increased risk of MCM and assess how sensitive the estimated risk of MCM is to potential selection bias.

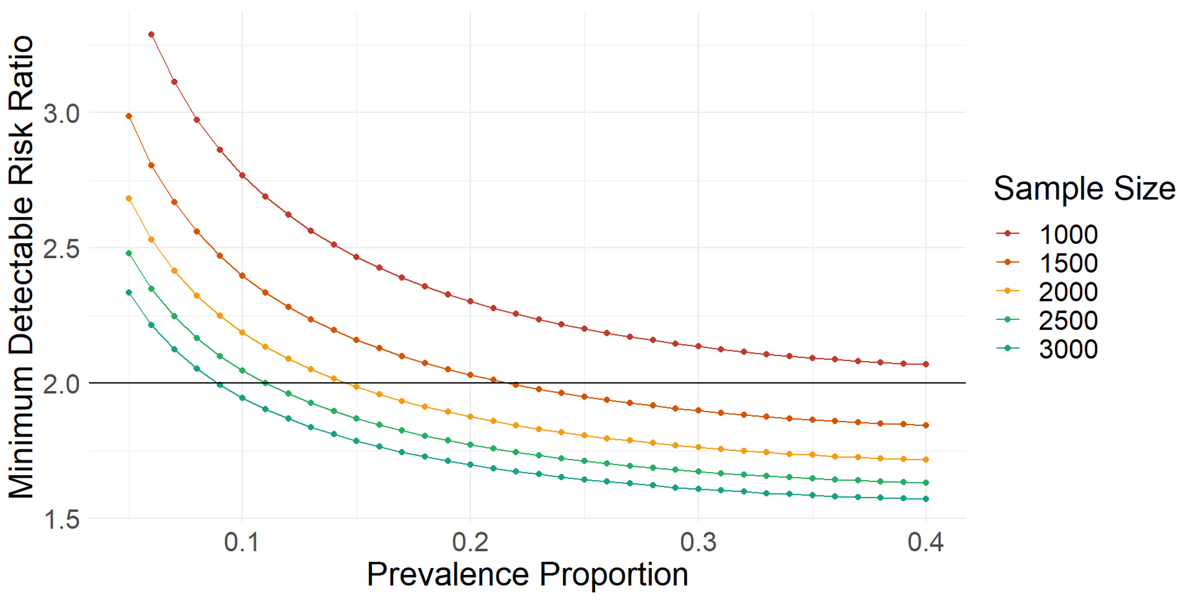
Methods

- A power analysis was conducted to determine the minimum sample size necessary to detect a two-fold increase in relative risk (RR) of MCM with a two-sided α=0.05 and 80% power.
- This analysis assumed a 4% rate of MCM in unexposed infants and varied exposure prevalence from 5-40%.
- Simulations were conducted to evaluate the sensitivity of the significance testing on the RR estimate to selection bias for different exposure prevalence, number of pregnancies, and assuming different pregnancy-infant linkage rates.
  - Three different levels of selection bias were considered:
    - No selection bias-equal probability of pregnancy infant linkage in all pregnancies.
    - Moderate selection bias-10% greater probability of pregnancy infant linkage in exposed pregnancies with the outcome
    - Severe selection bias-20% greater probability of pregnancy infant linkage in exposed pregnancies with the outcome.
  - Three different scenarios were used with number of pregnancies and rate of linkage of pregnancies to infants varied (Table 1)
  - Significance tests were conducted to evaluate the null hypothesis RR=1 and the alternative hypothesis RR=2 .

Results

- Sample size needed to detect a two-fold increase in RR was inversely related to exposure prevalence and varied from 5,114 with a 5% prevalence to 1,132 with a 40% prevalence (Figure 1).
- With moderate exposure prevalence (20-40%), reductions in sample size of less than 200 resulted in failure to detect two-fold differences in RR of MCM.

Figure 1. Sample size needed to detect a relative risk of MCM between 1.5 and 3.0 based on exposure prevalence



Results, cont.

- Statistical bias (accuracy of the RR estimate) was lowest when the total number of infants was larger (Figure 2).
- In all scenarios, statistical bias was higher in simulations with moderate or severe selection bias, though power to detect RR > 2 exceeded 80% for exposure prevalences from 10-40% (Figure 2).
- Probability of type I error was similar in all scenarios when no selection bias was present. However, when moderate or severe selection bias was present, the rate of rejection of a true null hypothesis (type I error) exceeded 0.05 for most simulations (Figure 3).

Table 1. Assumptions for number of pregnancies and infant linkage rate used for selection bias simulations

Scenario	*Total Pregnancies*	*Infant Linkage Rate*	*Total Infants*
1	*1,500*	*70%*	*1,050*
2	*1,200*	*80%*	*960*
3	*1,500*	*60%*	*900*

Figure 2. Statistical bias with A) no selection bias, B) moderate selection bias, C) severe selection bias

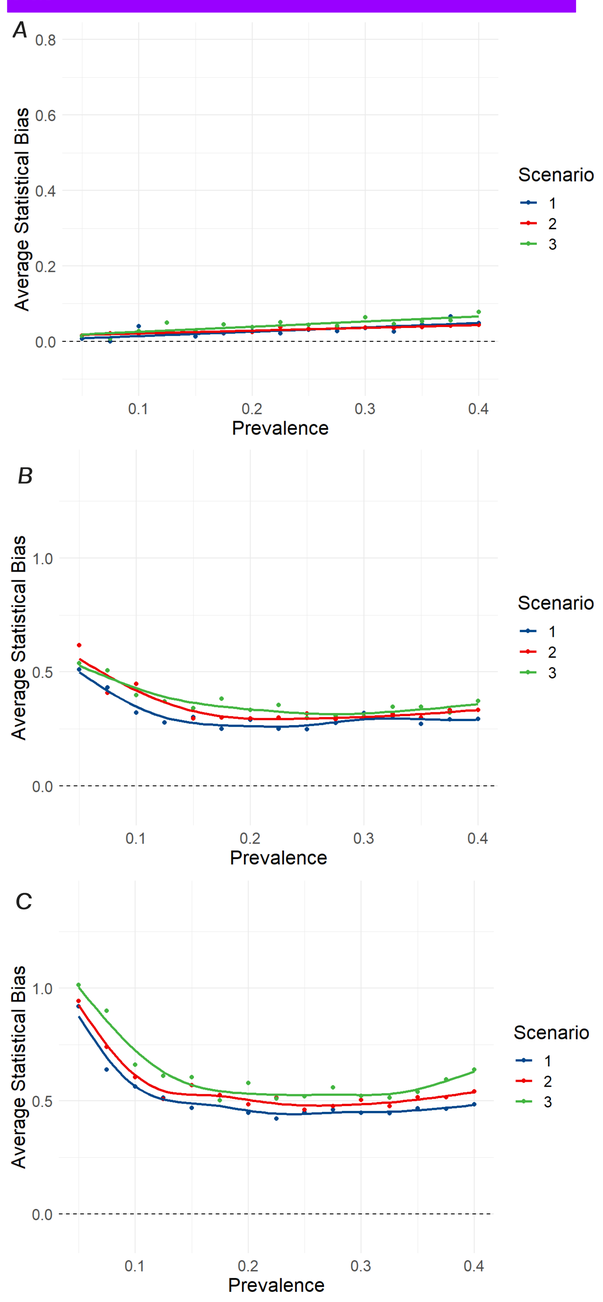
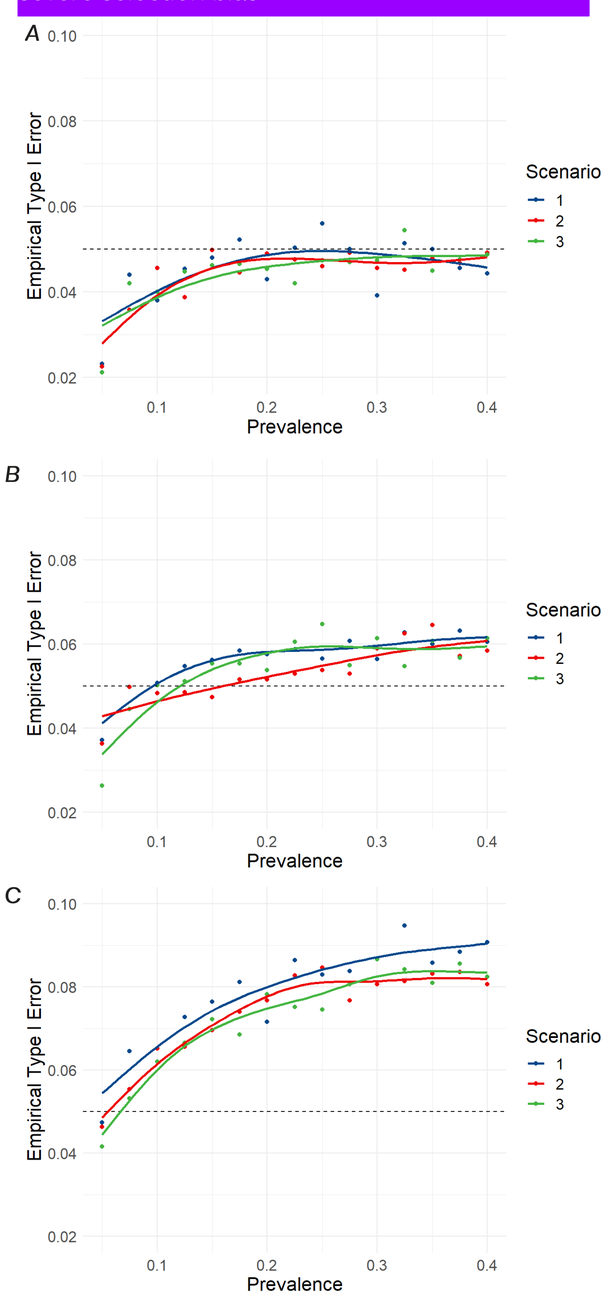


Figure 3. Probability of type I error with A) no selection bias, B) moderate selection bias, C) severe selection bias



Conclusions

- In these simulations, total number of infants had a larger effect on the accuracy of the RR estimate and ability to detect significant differences in risk of MCM in exposed and unexposed pregnancies regardless of the level of selection bias.
- Though alterations to patient selection criteria may have only modest effects on the total patients included in the study, these changes can impact the accuracy of the RR estimate and ability to detect differences in MCM risk.
- The ability to correctly detect differences in risk of MCM in infants with and without prenatal exposure is further decreased when the alterations to patient selection criteria introduce selection bias.

References
[1] FDA. Postapproval Pregnancy Safety Studies Guidance for Industry. May 2019
[2] MMWR Morb Mortal Wkly Rep. 2008; 57(1); 1-5.
[3] Regulatory Use of Real-World Data: Quantifying Drug Exposure Risk in Pregnancy with Retrospective Administrative Claims Data. DIA Real-World Data Conference 2023, 17 Oct.

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