

Analysis of Aggregate Incidence Rate Data in Real-World Evidence Studies

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Background

In pharmacoepidemiology, there are many contexts in which incidence rates are used to characterize risk of adverse events after exposure to a drug. Although comparative risk estimates are often preferred, there are several settings in which these may not be feasible. A drug may be new to the market and there may be relatively few patients exposed for short durations, the outcome may be rare and lead to few or no events, and/or comparative analyses may not be possible if certain diagnostic thresholds are not met (e.g., covariate balance) [1].

The objective of this work is to determine how best to summarize the incidence rates numerically across data sources. There are several important challenges that this work attempts to address: availability of few data sources, a non-trivial degree of between data-source variability, and events are often rare. We use Monte Carlo simulations to evaluate the bias and coverage of several methods, including meta-analysis and Poisson regression models, utilizing both frequentist and Bayesian approaches.

Methods

Three data generation factors were manipulated, the conditional rate (0.01, 0.001 or 0.0001 events per year), the standard deviation of the random effect in the data (0 or 1) and the number of studies (5 or 10). Data generation was based on a Poisson model with random data source effects: $\ln(Y_k) = \alpha + b_k + \ln(T_k)$. The intercept (α) was set to either $\ln(0.01)$, $\ln(0.001)$ or $\ln(0.0001)$. The data source random-effects, $b_k \sim \text{Normal}(0, \tau)$, were sampled from a distribution with $\tau=0$ or $\tau=1$. Exposure times were fixed for each data source (T_k), consisting of five data sources with exposure times: 500, 1000, 2000, 3000, and 4000 years. With 10 data sources the exposure times were repeated.

Six models are used to produce various methods of point estimation and confidence/credibility intervals.

- 1) Summing the number of events over the data sources divided by the sum of person time
- 2) Frequentist fixed effect Poisson regression model
- 3) Frequentist random-effects Poisson regression model
- 4) Frequentist random-effects meta-analysis model
- 5) Bayesian random-effects meta-analysis model
- 6) Bayesian random-effects Poisson regression model

For Poisson regression models if there are no events, the method will fail to converge, in which case zero is used as a point estimate of the incidence rate and confidence intervals use an exact method. For meta-analysis models, if any data source has zero events, a small expected count (0.00001 per person-year) is added to all data sources to compute the log incidence rate as $\ln(\widehat{IR}_k) =$

$$\ln\left(\frac{E_k + 0.00001 \cdot T_k}{T_k}\right) \text{ and } \text{var}_k(\ln(\widehat{IR}_k)) = \frac{1}{E_k + 0.00001 \cdot T_k}.$$

For both Bayesian models $\tau \sim \text{HalfNormal}(1)$ and $\alpha \sim \text{uniform}(\log(.000000000001), 10 * \exp(\alpha))$, where α is the simulated population-level incidence rate. For the Bayesian models we report point estimates using both the posterior mean and the posterior median, as well as equal-tailed and highest posterior credibility intervals. Any Bayesian model run that failed predefined convergence or sampling-quality diagnostics was excluded (e.g., proportion divergent transitions > 0.1%). The brm package [] was used to fit the Bayesian models by calling Stan's MCMC sampler to draw samples from the posterior distribution

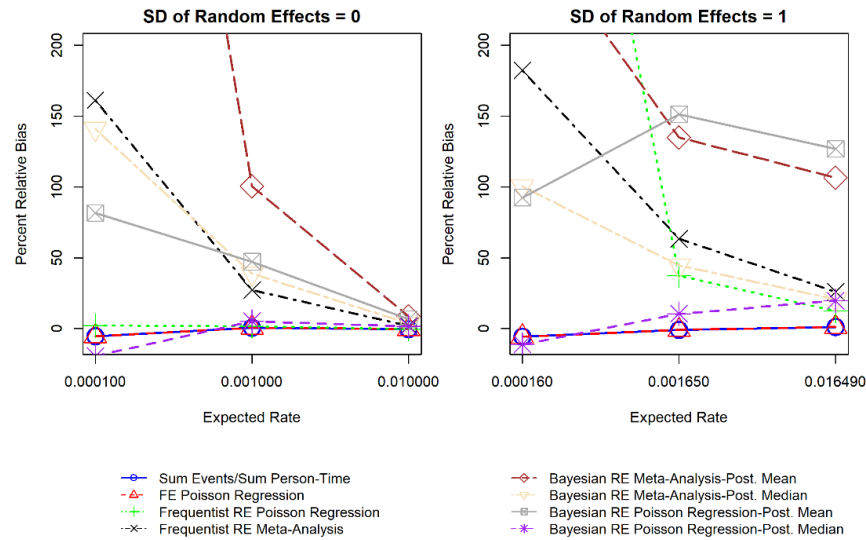
The outcomes evaluated were percent relative bias and coverage. Percent relative bias is calculated as: $100 * (\widehat{IR} - IR) / IR$, where IR is either the marginal or conditional incidence rate and $\widehat{IR} = \sum_{s=1}^S \widehat{IR}_s / S$ ($s = 1, \dots, S$; $S = 500$ simulated data sets). Coverage was calculated as the proportion of estimated 95% confidence/credibility intervals that covered the marginal/conditional population incidence rate across the 1000 simulated datasets for each condition.

Results

Marginal Incidence Rate

Methods of point estimation that had little bias for estimating the *marginal* incidence rate across the simulated conditions were sum Events/sum person-time across data sources, frequentist fixed-effect Poisson Regression, and a Bayesian random-effects Poisson regression where the posterior median is estimated (Figure 1). The poor performance of other methods for estimating the marginal incidence rate where the marginal effect is calculated from $\exp(\hat{\alpha} + 0.5 * \hat{\tau}^2)$ can be explained in part by the convexity of the exponential map (Jensen's inequality) and the sampling variability of the parameter estimates, particularly between-data source variability.

Figure 1. Percent Relative Bias of Marginal Estimates for the Incidence Rate by Method and Standard Deviation of the Random Effects (5 Data Sources)

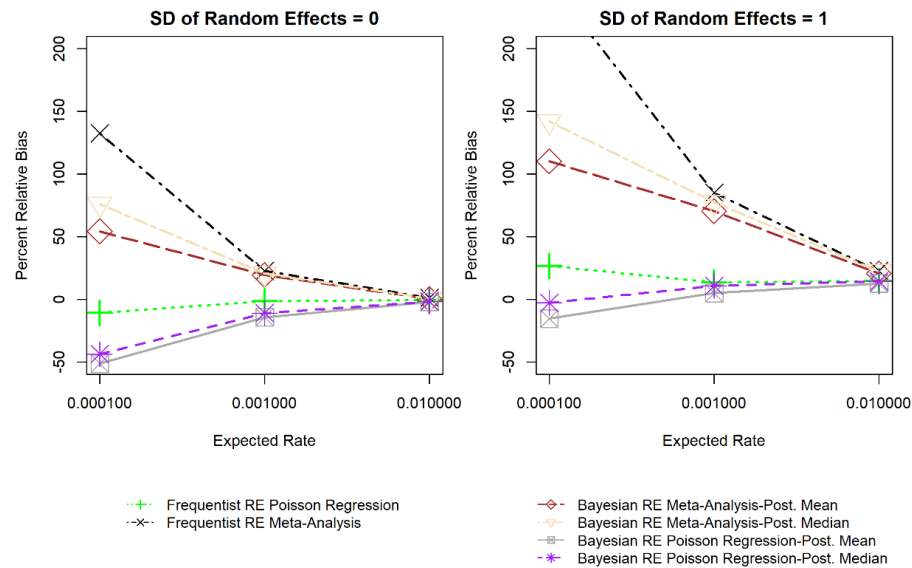


Conditional Incidence Rate

Methods of point estimation that had little bias for estimating the *conditional* incidence rate across the simulated conditions were frequentist and Bayesian random-effect Poisson Regression models (Figure 2).

For both marginal and conditional incidence rate same pattern with 10 data sources (not displayed)

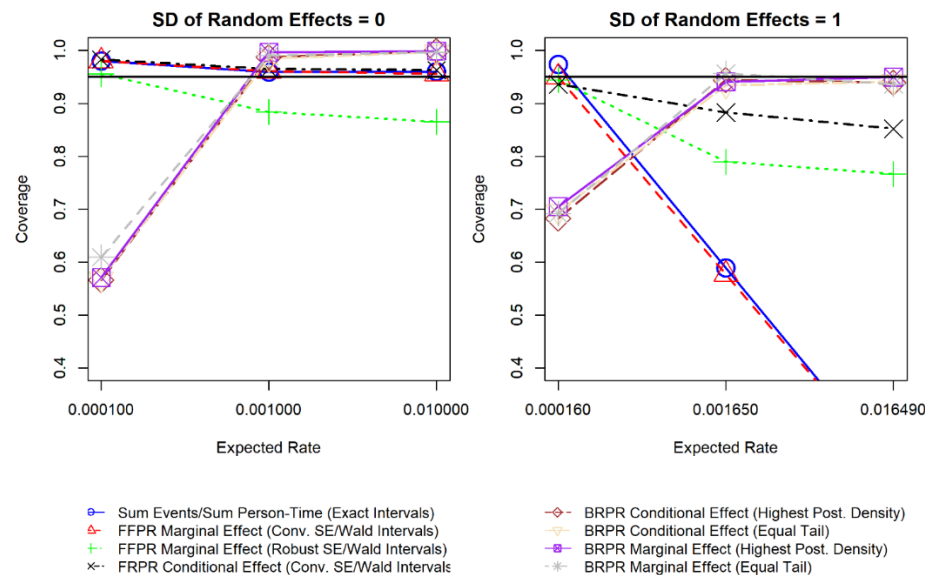
Figure 2. Percent Relative Bias of Conditional Estimates for the Incidence Rate by Method and Standard Deviation of the Random Effects (5 Data Sources)



Coverage of Marginal and Conditional Interval Estimates

Pooling, frequentist fixed-effect or random-effects Poisson regression interval estimates for the marginal or conditional incidence rates were below nominal coverage when $\tau = 1$ and the rate was at one of the two larger values, but close to nominal otherwise (Figure 3). Bayesian estimates of either the marginal or conditional rate from a Poisson regression only fell below nominal coverage at the rarest population rate simulated, and close to nominal otherwise. Bayesian and robust standard errors improved coverage with an increasing number of data sources (ie, 10-not displayed)

Figure 3. Coverage for Methods Demonstrating the Least Bias for Estimating Marginal and Conditional Incidence Rates (5 Data Sources)



Note: Solid black line represents nominal coverage level. FFPR=Frequentist Fixed-effect Poisson Regression. BRPR=Bayesian Random-effects Poisson Regression. FRPR=Frequentist Random-effects Poisson Regression.

Conclusion

Across simulations reflecting rare events and few data sources, simple aggregation of events over person-time, frequentist fixed-effect Poisson regression, and Bayesian random-effects Poisson regression using the posterior median provided the least biased estimates of the marginal incidence rate. For the conditional incidence rate, both frequentist and Bayesian random-effects Poisson regression models consistently minimized bias. No method achieved uniformly good coverage, but the following guidance can be provided: 1) For marginal rate intervals if the outcome is rare (0.0001 events per year), use pooled data with exact confidence intervals or a fixed-effect Poisson regression with robust standard errors and Wald intervals. If not as rare, then a Bayesian random-effect Poisson regression with equal-tail or highest density posterior credibility intervals, 2) For conditional rate intervals if the outcome is rare (0.0001 events per year) use frequentist random-effect Poisson

regression with conventional standard errors and Wald intervals. If not as rare, then use a Bayesian random-effect Poisson regression with equal-tail or highest density posterior credibility intervals.

References

1. Conover MM, Ryan PB, Chen Y, Suchard MA, Hripcsak G, Schuemie MJ. Objective study validity diagnostics: a framework requiring pre-specified, empirical verification to increase trust in the reliability of real-world evidence. *J Am Med Inform Assoc*. 2025 Mar 1;32(3):518-525.