Practical Guidance and Tools for Sensitivity to Unmeasured Confounding "Tipping Point" Analyses

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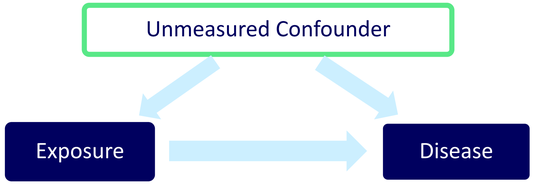
Background

- Strength of evidence provided by epidemiological and observational studies is limited by the potential of **unmeasured confounding**
- A review of 90 observational studies with statistically significant findings published in 2015 in JAMA, NEJM, and AJE revealed
  - **Less than half, 41 (45.6%),** mentioned the issue of unmeasured confounding as a limitation
  - **Only 4 (4.4%)** included a quantitative sensitivity analysis
- This disparity reveals the need **for practical guidance and simple tools**
  - To help the medical research community **incorporate sensitivity analyses** into their papers
  - To allow the readers of medical research **to easily perform such analyses** when a paper has not included one



Tipping Point Method

- **Main Objective:** Report the size and prevalence of an unmeasured confounder needed to **change the significance of your findings**.
- For example, if you have a finding with a hazard ratio of 1.25 and a 95% confidence interval (1.1,1.5), this would no longer be significant at the α=.05 level if adjusting for a hypothetical unmeasured confounder caused the **lower bound to cross 1**.
- The "tipping point" analysis would find the smallest potential **unmeasured confounder** that would cause this to happen.

Methods

Building on the methods put forth by Lin et al. (1998), we propose the following to determine the size and prevalence of an unmeasured confounder necessary to change the significance of an observed association:

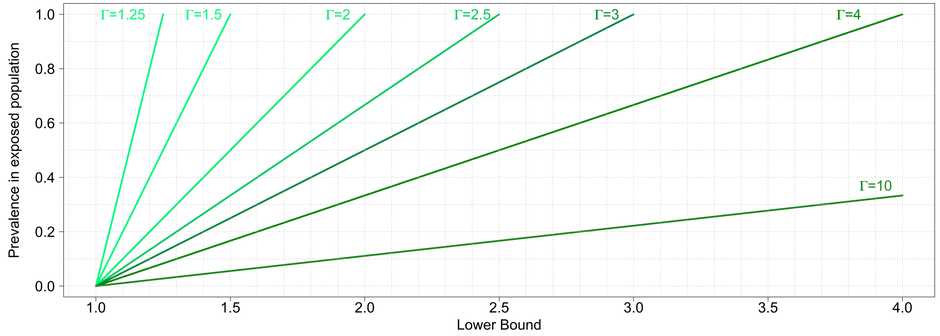
$$\mathrm{P}(\mathrm{LB}, \Gamma) = \frac{\mathrm{LB} - 1}{\Gamma - 1}$$
$$\text{for } 1 < \mathrm{LB} \leq \Gamma$$

- **P** is the threshold prevalence of the unmeasured confounder in the treatment population
- **LB** is the observed lower confidence limit
- **Γ** is the effect size of the unmeasured confounder

This would allow investigators to state,

> "In order for our association to no longer be significant, there would need to exist an unmeasured confounder of size **Γ** that is prevalent in **P** of the exposed population."

Figure 1. Sensitivity thresholds to given unmeasured confounders for observed odds ratio lower confidence bounds ranging from 1 to 4.



Example

Here is how to easily incorporate this into your study:

1. **State the primary analysis results:**
The primary analysis yielded a greater risk of congestive heart failure (CHF) with Sulfonylurea use over Metformin use; HR (95% CI): 1.40 (1.30, 1.50).

2. **State a size and prevalence of a hypothetical "tipping point" confounder:**
A hypothetical unobserved binary confounder with a 10% prevalence difference between the therapies would need to have an association with CHF of HR=4.0 to tip this analysis to nonsignificance at a 5% level.

3. **Ground this in an example from your study:**
For a comparison from the observed confounders, baseline CHF history had a prevalence difference of 5% in the pre-matching cohort and an association with CHF of HR=2.30; which would have been insufficient to tip this analysis had we not adjusted for it.

Conclusions

- We focus on the Lin et al. approach, however many other useful methods exist for a wide variety of settings. Our objective is to popularize the use of these sensitivity methods in general.
- Our universal figures can be applied **to both past and future research**, allowing readers to understand the sensitivity of studies that do not include such an analysis, and allowing future investigators to readily include such an analysis.