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Graphical Representation of Multiple Quantitative Bias Analysis Scenarios for Unmeasured Confounding

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DISCLOSURES

This methodological presentation received no external funding and uses deidentified results for illustrative purposes from a study that was funded by a pharmaceutical company.

OBJECTIVE

- To evaluate and graphically display the potential impact of an array of unmeasured confounding scenarios on an observed incidence rate ratio (IRR) estimate from a cohort study comparing the incidence of an outcome between treatment and comparator groups.

BACKGROUND

- The prevalence of a variable must be imbalanced between treatment groups to be a confounder.
- Quantitative bias analyses can correct effect-measure estimates for unmeasured confounding caused by an independent, binary confounding variable that was not adjusted for in the analysis.
- These analyses use assumptions of the strength of the association between the unmeasured confounder with the outcome and the prevalence of the confounding variable in the 2 treatment groups.
  - When these parameters are unknown or vary for a specific, known unmeasured confounder, evaluating a wide spectrum of assumptions may be of interest.
  - If there is no specific, known unmeasured confounder of interest, researchers may be interested in evaluating the potential impact of a single hypothetical confounding variable under a range of reasonable assumptions.

METHODS

- As an example, an IRR comparing the risk of an outcome in users of a specific medication (exposure group) compared with users of different medications with similar indications (comparator group) was estimated from a cohort study.
  - The observed IRR from the cohort study was 0.85.
- Quantitative bias analysis methods for unmeasured confounding require 3 bias parameters[1]:
  - The expected association between the unmeasured confounder and the outcome (RR_{CD})
  - The prevalence of the unmeasured confounder among the exposure group (ρ_1)
  - The prevalence of the unmeasured confounder among the comparator group (ρ_0)
- IRR estimates can be "corrected" for unmeasured confounding with the following formula:

$$IRR_{adj} = IRR_{obs}\left(\frac{RR_{CD}\rho_0 + (1-\rho_0)}{RR_{CD}\rho_1 + (1-\rho_1)}\right)$$

  - IRR_{adj} is the IRR associating the exposure with the outcome adjusted for the unmeasured confounder.
  - IRR_{obs} is the observed IRR without adjustment for the unmeasured confounder.

- 3 scenarios of the strength of the unmeasured confounder (RR_{CD}) were evaluated, with assumed RRs for the association between the confounder and the outcome of the following:
  - RR_{CD} = 1.5 (moderate confounder)
  - RR_{CD} = 3.0 (strong confounder)
  - RR_{CD} = 4.5 (very strong confounder)
- For each hypothetical confounder strength scenario, we calculated a matrix of IRRs corrected for the unmeasured confounder at every possible imbalance level:
  - Prevalence in the exposure group ranged from absent in all exposure patients (0% prevalence) to present in all patients (100% prevalence).
  - Prevalence in the comparator group ranged from absent in all comparator patients (0% prevalence) to present in all patients (100% prevalence).
  - A given confounder imbalance could result from multiple different combinations of treatment group prevalences.
    - For example, a 20-percentage-point difference in the confounder prevalence between the exposure and comparator groups could result from confounder prevalences of 100% and 80% in the exposure and comparator groups, respectively, or 30% and 10%, respectively (Table 1).
- At each imbalance level, the range and mean of all possible corrected IRR values were identified (Table 2).
- For each confounder strength scenario, each possible corrected IRR_{adj} estimate was plotted as a function of the confounder imbalance on a single graph using SAS (Figure 1A).

Table 1. Simplified Matrix of Corrected IRR Values for a Confounder at Multiple Imbalance Levels

	Prevalence of confounder in exposure group										
Prevalence in comparators	**0%**	**10%**	**20%**	**30%**	**40%**	**50%**	**60%**	**70%**	**80%**	**90%**	**100%**
0%	0.85	0.71	0.61	0.53	0.47	0.43	0.39	0.35	0.33	0.30	0.28
10%	1.02	0.85	0.73	0.64	0.57	0.51	0.46	0.43	0.39	0.36	0.34
20%	1.19	0.99	0.85	0.74	0.66	0.60	0.54	0.50	0.46	0.43	0.40
30%	1.36	1.13	0.97	0.85	0.76	0.68	0.62	0.57	0.52	0.49	0.45
40%	1.53	1.28	1.09	0.96	0.85	0.77	0.70	0.64	0.59	0.55	0.51
50%	1.70	1.42	1.21	1.06	0.94	0.85	0.77	0.71	0.65	0.61	0.57
60%	1.87	1.56	1.34	1.17	1.04	0.94	0.85	0.78	0.72	0.67	0.62
70%	2.04	1.70	1.46	1.28	1.13	1.02	0.93	0.85	0.78	0.73	0.68
80%	2.21	1.84	1.58	1.38	1.23	1.11	1.00	0.92	0.85	0.79	0.74
90%	2.38	1.98	1.70	1.49	1.32	1.19	1.08	0.99	0.92	0.85	0.79
100%	2.55	2.13	1.82	1.59	1.42	1.28	1.16	1.06	0.98	0.91	0.85

Note: Corrected IRRs estimated for a confounder strength of RR_{CD} = 3.00.

= 50% imbalance
= 40% imbalance
= 30% imbalance
= 20% imbalance
= 10% imbalance
= 0% imbalance

Table 2. Corrected IRR Estimates (IRR_{adj})

Covariate imbalance	Corrected IRR_{adj} estimates: Minimum	Mean	Maximum
0%	0.85	0.85	0.85
10%	0.71	0.76	0.79
20%	0.61	0.69	0.74
30%	0.53	0.62	0.68
40%	0.47	0.56	0.62
50%	0.43	0.50	0.57

Note: Corrected IRR_{adj} estimated for a confounder strength of RR_{CD} = 3.00.

RESULTS

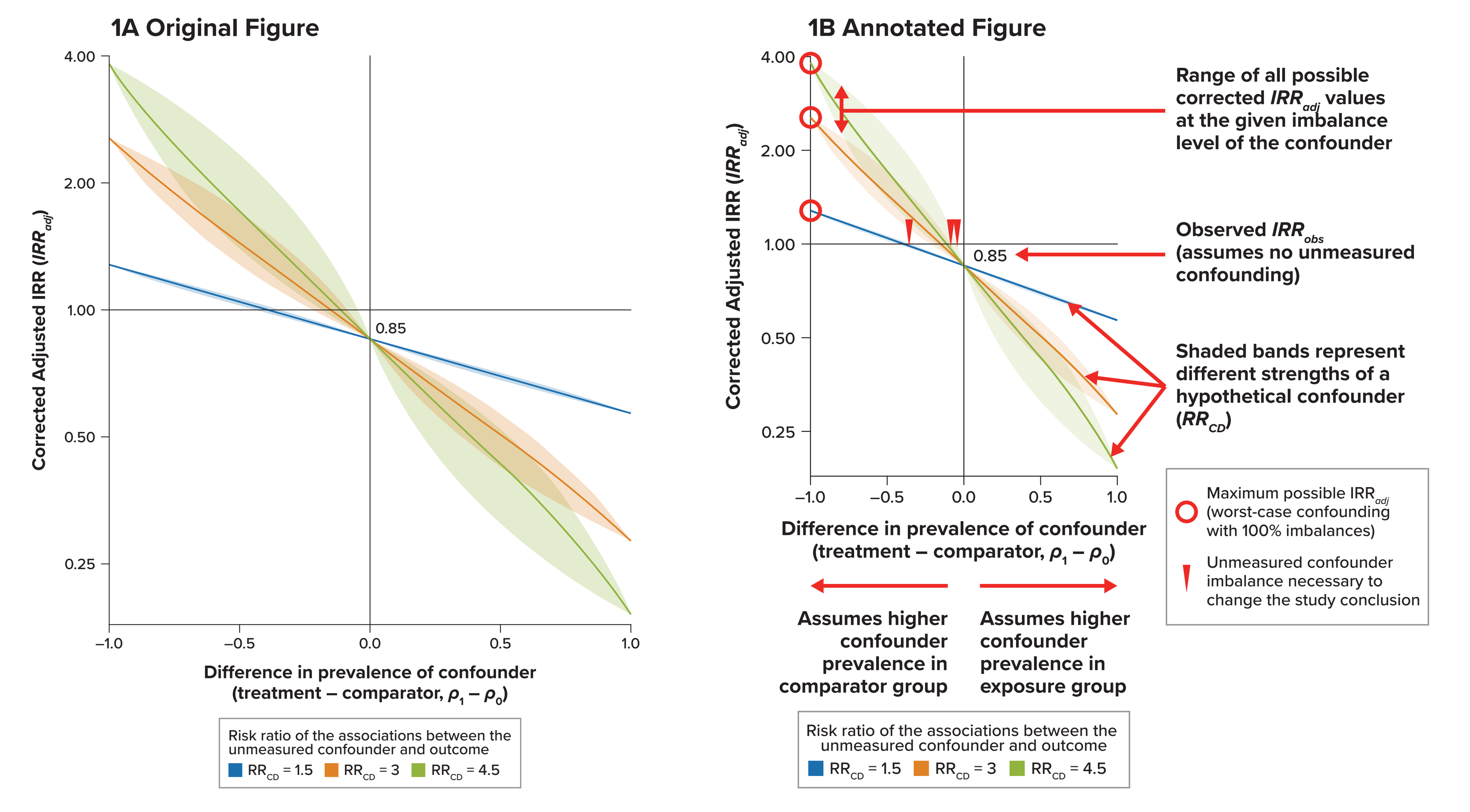
- The shaded bands represent the range of possible corrected IRR_{adj} estimates at each imbalance level for each RR_{CD} strength scenario (Figure 1B).
  - The solid line displays the mean corrected IRR_{adj}.
- In the cohort example, the observed IRR_{obs} was 0.85 (shown on the plot at an imbalance level of 0, as the observed IRR assumes no unmeasured confounding) (Figure 1B).
- The figure illustrates the worst-case confounding scenario for a hypothetical moderate confounder and how imbalanced an unmeasured confounder would need to be to mask a true elevated IRR > 1.00 (Figure 1B, Table 3).
  - Any imbalance less extreme than 100% would result in IRR_{adj} estimates lower than the maximum estimates shown in the second column.
  - Any imbalance less extreme than those shown in the third column would results in IRR_{adj} estimates below the null, similar to the IRR_{obs} estimate.

Table 3. Corrected IRR Values at Selected Imbalance Levels

Confounder strength	Maximum possible IRR_{adj} (100% imbalance[a])	Imbalance[b] required for IRR_{adj} > 1.00
RR_{CD} = 1.5	1.28	40%
RR_{CD} = 3.0	2.6	10%
RR_{CD} = 4.5	3.83	< 10%

[a] Worst-case scenario: 0% prevalence in the exposure group and 100% prevalence in the comparator group.
[b] Higher prevalence in the comparator group: $\rho_0 - \rho_1$.

Figure 1. Adjusted IRRs Under Varying Assumptions of the Strength and Relative Prevalence of an Unmeasured Confounder Compared With the Observed IRR Estimate



DISCUSSION

- These figures simultaneously present the results of multiple quantitative bias analyses, testing variations of assumptions of the strength and prevalence of unmeasured confounding.
  - "Worst-case" scenarios involving extreme imbalances or confounder strengths can be evaluated, as can the degree of imbalance or confounder strength required to meaningfully alter the study's conclusion.
  - The reasonableness of these scenarios can be evaluated against known information.
- Many parameters are measured with uncertainty. These methods did not address the confidence intervals or variance of the IRR_{obs} estimate, but they could.
- These methods assume a single binary that the unmeasured confounder relationship is independent of the other measured confounders.
  - May be a simplification of true interconnectedness of confounding variables
  - Potentially still useful in evaluating the robustness of the study results

CONCLUSIONS

- An array of assumptions was evaluated and displayed on a single graph to visually assess the maximum possible impact of a single unmeasured confounder.
- Summary plots of multiple confounding scenarios provided an efficient method of displaying and evaluating the potential impact of unmeasured confounding on the results of an observed risk estimate.

References

1. Lash TL, Fox MP, Fink AK. Unmeasured and unknown confounders. In: Applying quantitative bias analysis to epidemiologic data. Springer Science and Business Media, LLC; 2009. p. 59-78.

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