Assessing unmeasured confounding using negative control outcomes

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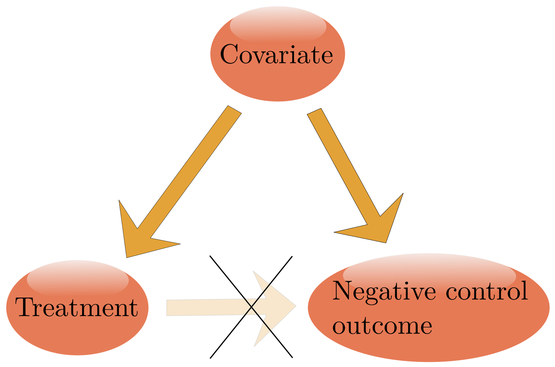
Unmeasured confounding: a primary threat to study validity

- Causal inference in real world studies requires there *to not be any unmeasured confounding variables* after controlling for confounding
- Important variables may not be present in the data or we may not know which variables to include
- Unmeasured confounding is often considered to be one of the primary challenges to performing real world studies

Negative control outcomes

- Negative control outcomes (NCOs) are a valuable tool to assess whether a study suffers from unmeasured confounding
- A negative control outcome is a variable that is both:
  - Known to not be causally affected by the treatment of interest
  - Shares the same confounding structure as the treatment and outcome of interest relationship
- The presence of an association between the NCO and the exposure constitutes evidence of residual confounding bias caused by an unmet modeling assumption such as unmeasured confounding

Figure 1: A negative control outcome is known to not be caused by the treatment



Negative control outcome study recipe

- Design the study that you would like to perform with the treatment and outcome of interest
- Select an NCO to use in place of the outcome of interest
- Perform the same study as you would if you were analyzing the outcome of interest *but using the NCO in its place*
- If the risk difference or risk ratio is far from the null value then it suggests that unmeasured confounding is present

Identifying negative controls

- Identify the mechanisms that drive treatment choice and outcomes. Physician input can often be valuable here
- A device that can help us frame our search for NCOs based on the previous step is the idea of *domains of confounding*
  - An informal collection of scenarios that have been learned through experience to cause confounding
  - E.g. confounding by indication or contraindication, confounding by frailty, confounding by health-seeking behavior or access to care
- As studies are presented in the literature, we can borrow NCOs for domains of confounding that could plausibly affect a given study

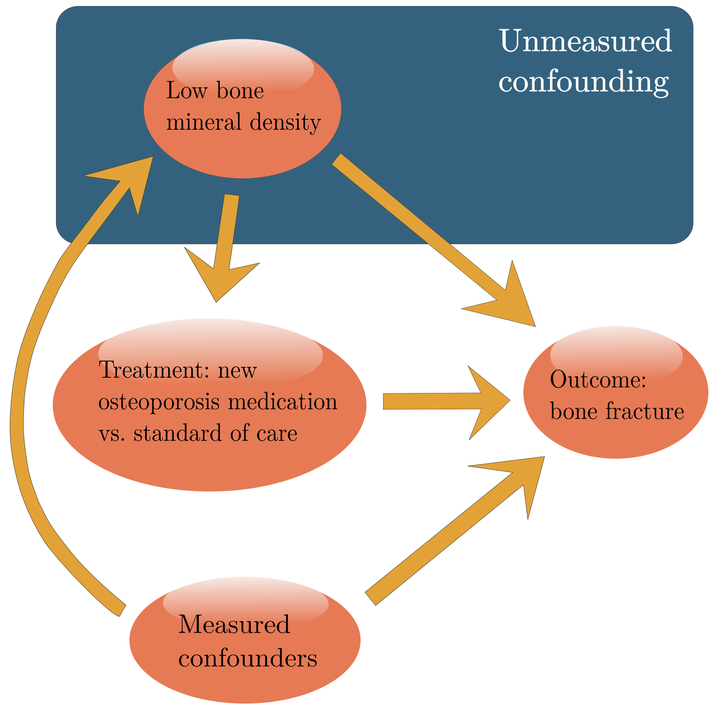
Managing unmeasured confounding

If you discover that your study has unmeasured confounding, consider the following options:

- Change the study population to one that is comparable across treatments with respect to the unmeasured confounding variables
- Change the analytic approach to better capture or mitigate sources of confounding
- Use a different data source or wait until treatment groups become more comparable

What can go wrong: a hypothetical study suffering from unmeasured confounding

Figure 2: Bone mineral density is a factor that physicians incorporate to determine which medication to prescribe, but that is typically not available in claims data



Better coverage using multiple NCOs

- In practice, it is hard to be sure that a given negative control outcome variable will share the same confounding structure
- One approach is to select a set of negative control outcomes that collectively target multiple domains of confounding
- Can aggregate the results in order assess the presence of unmeasured confounding

Incorporating negative control outcomes as a gating mechanism for effectiveness or safety research

Figure 3: A workflow that attempts to ensure that unbiased estimates can be obtained prior to performing an analysis

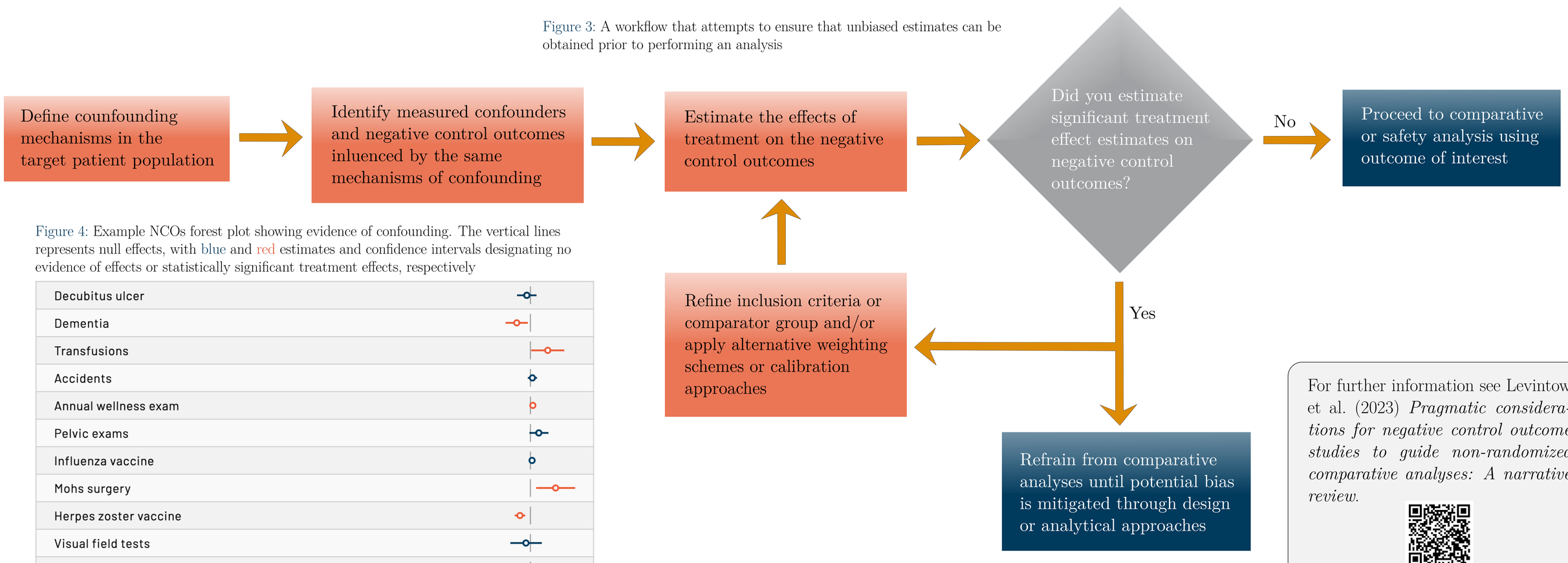


Figure 4: Example NCOs forest plot showing evidence of confounding. The vertical lines represents null effects, with blue and red estimates and confidence intervals designating no evidence of effects or statistically significant treatment effects, respectively

For further information see Levintow et al. (2023) *Pragmatic considerations for negative control outcome studies to guide non-randomized comparative analyses: A narrative review.*

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