Assessing unmeasured confounding using negative control outcomes

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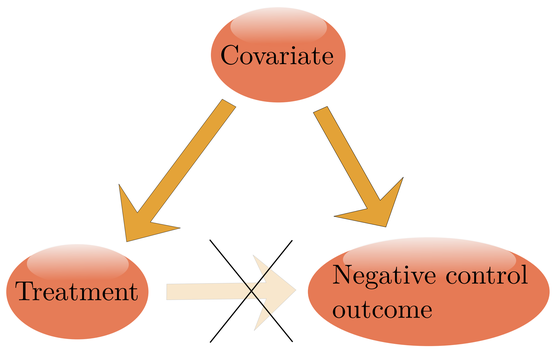
Negative control outcomes

- 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



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 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. Physician input can often be valuable to find outcomes with an appropriate confounding structure
- 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

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

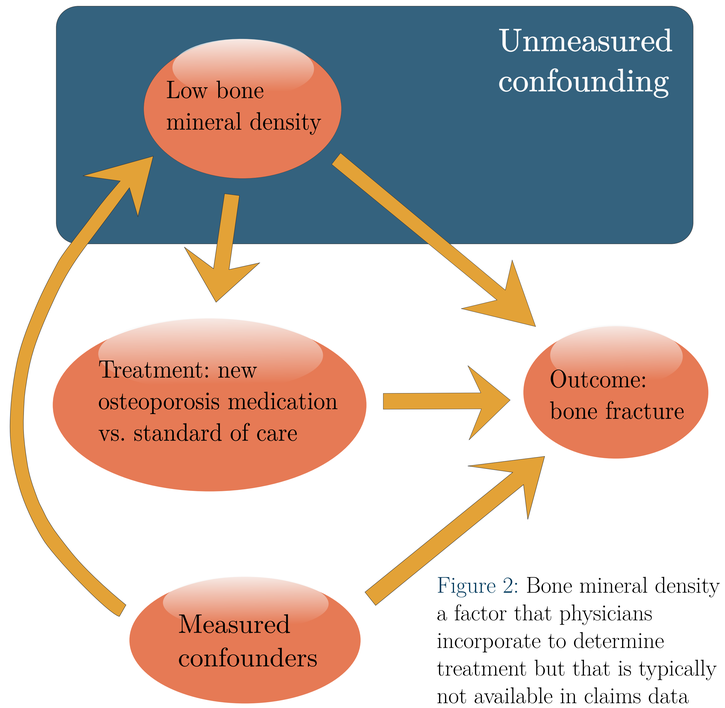


Figure 2: Bone mineral density is a factor that physicians incorporate to determine treatment but that is typically not available in claims data

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

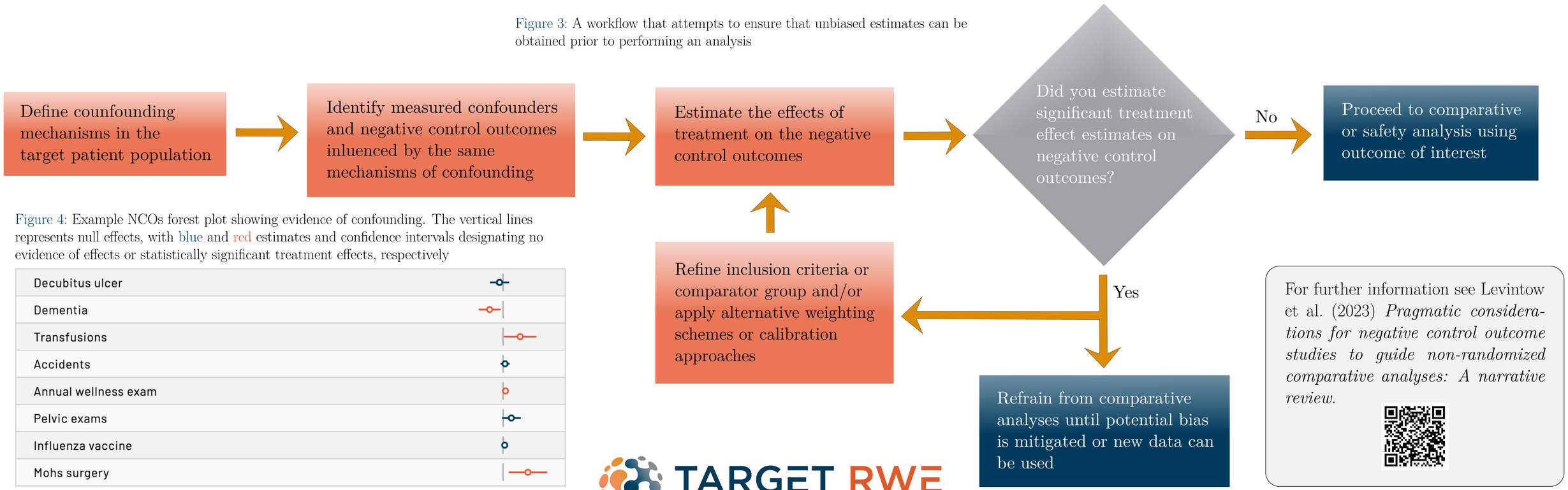


Figure 4: Example NCOs forest plot showing evidence of confounding. The vertical lines represents null effects, with blue and red estimates and confidence intervals designating no evidence of effects or statistically significant treatment effects, respectively

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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