A composite outcome: another example of thought bias

A composite outcome, such as “cancer or death”, is often modeled in trials or observational cohorts, but the logic is rarely spelled out. Nor is it clear how to draw the line between a sensible composite outcome and a ridiculous one. May I create the outcome “cancer or death or retired or divorced”? Why not? Can’t I be interested in the effect of some exposure on either of the four, rolled into one variable?

Fortunately, a solid answer can be given: with one exception, don’t combine outcomes. A composite outcome is a made-up (derived) variable, and like any made-up variable it is not a property of any human being. Whatever exposure you have in mind, it has no effect—not null effect—on your composite outcome, because your made-up variable does not show up in the causal diagram of the universe. For instance, “cancer” has causes and so does “death”, but “cancer or death” does not. “Birth” has causes and so does “death”, but “born dead” does not. Whenever you study the causes of stillbirth, you are locked in thought bias. I know: you were never taught to think this way.

A composite outcome is acceptable only when the made-up variable serves to impute the values of a natural variable. For instance, the natural variable MI status (yes) may be imputed by the following derived variable: ST position (elevated, 4mm), or TROPOIN T (4μg/L), or AUTOPSY (infarct), or CHD (yes) and VITAL STATUS (dead) and LOCATION (home). Each component of that composite outcome provides information on MI status.

Hernan, Schisterman, and Hernandez-Diaz have recently proposed to solve a problem of colliding bias by modeling a composite outcome: stillbirth or postbirth death. In a commentary on an article by Kramer, Zhang, and Platt, they wrote:

“There is, however, a fourth strategy [to avoid colliding bias], which is to define a composite outcome that encompasses both the outcome of interest and the competing event. This strategy is the default approach to the handling of competing risks in many randomized trials. For example, the primary outcome of many trials is a composite endpoint that includes both cardiovascular disease and death from any cause. Kramer et al. support the use of the composite outcome “perinatal death,” which includes both stillbirth and neonatal (postbirth) death, like many randomized trials do. By engulfing both the outcome of interest and the competing events, composite endpoints effectively eliminate the problem of competing risks, circumvent the selection bias, and allow us to escape the paradox.”

They are wrong twice over.

First, “perinatal death” is not truly a composite outcome of stillbirth and neonatal (postbirth) death—as Kramer et al. mistakenly thought. It is simply “death”! The baby is dead (VITAL STATUS=dead), regardless of the baby’s location in the world at the time of death (uterus, birth canal, or crib), and regardless of the baby’s title at the time of death (fetus or neonate). By analogy, think about combining the outcomes “in-hospital death” and “out-of-hospital death”—Second, and more important, their generic solution for competing risks shifts the problem from colliding bias to thought bias. A composite outcome circumvents colliding bias only to fall into the trap of thought bias.

Lastly, neither the causal diagram of Hernan et al. nor that of Kramer et al. corresponds to the theories of Kramer et al. My version of the diagram, before and after conditioning on “birth status” (B) and “vital status” (D), is shown on the next pages (Figures 1 and 2), and the lesson is clear: If you want to estimate the effect of an exposure on the baby’s vital status at some time point, stay away from conditioning on the baby’s vital status at earlier times and the baby’s location in this world. The message of both parties was correct; the explanations were not.

References


Figure 1. The causal structure before conditioning*

$E = $ exposure

$B = $ birth status

$D = $ vital status

$I = $ an intermediary

* The total effect of interest is $E$ on $D_{281}$
Figure 2. Restriction to “born alive”: colliding bias and causal-pathway bias