Reckoning Risk Retrospectively:

Reply to Taipale et al

To the Editor: In case-control studies, we cannot calculate the relative risk (RR) because we do not have information on how many patients who were exposed vs unexposed to a risk factor did vs did not experience the outcome of interest; rather, because of the nature of the study design, we only have information on how many patients who experienced (case) vs did not experience (control) the outcome were vs were not exposed to the risk factor. The two scenarios may have the same row and column headings in a table but the cell contents are conceptually different.

Data from case-control studies are usually analyzed in logistic regressions. Logistic regressions yield odds ratios (ORs), not RRs, as the statistic of interest. ORs are lower or higher than the corresponding RRs for values below or above 1, respectively[1]; that is, ORs always overestimate the effect size. This is problematic when the outcome is frequent because the difference between the OR and its corresponding RR can then be quite large.[1,2] ORs are also more difficult to understand than RRs.

As a result, starting from several decades ago, more than half a dozen methods[3] have been suggested to estimate RRs from ORs, and from research designs in which RRs are usually not estimated. Dr Taipale and colleagues used the doubling of cases method[4] in a commendable re-analysis of data[5] from a previous study[6] and presented differences in risk for the outcome of interest using a more appropriate method[7] than that in their original paper.[6] It is reassuring that their results[5] are similar to the conclusions that they originally drew.[6]

Here, however, is a note of caution. An RR estimated from a case-control design differs conceptually from an RR obtained in a randomized controlled trial (RCT). The former RR may be biased by covariates that differ between the nonrandomized groups being compared; the biases cannot be completely adjusted for because there are always inadequately measured, unmeasured, and unknown confounds. Such an RR may be further biased by differences in durations of exposure to the risk factor, and by unavailability of outcome data from subjects who drop out early and those who are lost to follow-up.

In short, risks are best estimated prospectively in RCT designs. In situations in which RCTs are unavailable or cannot be performed, readers need to keep in mind that risks that are estimated in retrospective and/or nonrandomized designs, such as cohort and case-control studies, may be the best that are available but are nonetheless of unknown accuracy.

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