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Issues in interpreting and estimating the excess risk in case of count data

1. On the interpretation of the excess risk

Redelmeier, D. and Tibshirani, R. (2018) [1] introduce the concept of "excess risk" for matched studies when outcomes are count variables. Authors suggest the excess risk as an effective measure of exposure for people whose observed individual outcome (in the case of the article, "deadly accident" vs. "no deadly accident") depends on the exposure status itself. I believe such interpretation is questionable for three reasons:

1. The outcome is a stochastic measure, so for which people exposure status is decisive (i.e., they would have the outcome under one treatment status and would not have it under the alternative one) also depends on a random part. On the contrary, authors seem to suggest that whether the outcome changes or not depending on exposure status is a deterministic variable, the stochastic part only intervening in deciding whether such people would undergo the event only as exposed or only as unexposed.
2. One cannot rule out that, even in case there is no effect of the exposure at the global level, there are some people affected by it. For example, if there are 119 car accidents in a day in case of election and 119 in case of no election, it could happen that there are some people only having the accident in case of elections and others only in case of no-election (it may even happen that 238 different people would be involved, so that no one would have the accident under both the factual and the counterfactual situation). This holds unless we want to assume that, for every election day, only one possible effect may take place for each person (i.e., there are either only people who would not undergo the accident as unexposed but would as exposed or only people who would undergo the accident as unexposed but would not as exposed).
3. By calculating, for each observation, the difference with respect to its matched lowest value, we are also including differences between controls, i.e., between individuals sharing the same exposure status.

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2. On the issue of dependency of the excess risk estimate on the number of chosen controls

Although authors describe the situation with two controls for each exposed, it seems to me the use of a double control is due to the specific problem analyzed (i.e., the rate of deadly car accidents on the election days vs. days as similar as possible, apart for the fact there was no election) rather than to statistical reasons. In the case of doctors' diagnostic accuracy reported by authors for the binary case, for example, only one control is used for each exposed, thus suggesting that the concept of "excess risk" could be applied to the case of an arbitrary number of controls (or, at least, of one control per exposed as well). However, I believe that the distribution of estimated excess risk rate strongly depends on the number of chosen controls. For example, in case the exposed always have a higher rate than the controls (typically, if the effect is positive and strong enough with respect to the variance of the error to make the probability of the outcome value for a control being higher than its exposed counterpart negligible), with only one control per exposed individual the excess risk would be infinity (and symmetrically, in case of negative effect, 0). The more the number of controls increases, the more both the numerator and the denominator do (because we are subtracting the minimum among a larger number of observations in both cases). This addition of the same number (on average) to both the numerator and the denominator will result in an expected estimate of the excess risk closer to 1.

For example, let us suppose that the exposed follow a uniform discrete distribution from 6 to 10 and the controls from 1 to 6. It may be easily seen that the excess risk with only one control would always be infinity (or indeterminate, in the unlikely case of only having $<6, 6>$ couples). By introducing another control, we would have a denominator different from 0 (again, apart from the unlikely case of all pairs of controls being equal). In particular, the average values would be: in the controls a minimum of $91/36$ and a maximum of $161/36$, in the treated an average of 8. This implies a number of events in excess of 0 in one of the controls, and an average for the control with the maximum value of $35/18$, while for the treated of $8 - 91/36 = 197/36$. This implies the estimated excess rate would converge to $\frac{197}{36}/\frac{35}{36}=\frac{197}{35}=5.63$. By increasing the number of controls, the average minimum of the controls would converge to 1 (from above), and the mean of the excess risk of the controls to the average of the difference between 3.5 (the average of the control distribution) and the minimum, thus the average excess risk for the controls would converge to: $3.5-1 = 2.5$. The average excess number of events for the exposed would converge to the difference between the average outcome of the exposed and the average minimum of the controls, i.e., $8 - 1 = 7$, thus the excess rate would converge to $7/2.5 = 2.8$. To sum up, we would have an estimate of excess risk of infinity with 1 control, an estimate of excess risk converging to 5.63 with 2 controls, then expected to decrease with the number of controls, converging (as both sample size and the number of controls diverge) to 2.8. Even if (as in the case of [1]) the number of events is not always higher among the treated than in the controls (so that there would not be the problem of an infinite value), taking more than one control would move the estimated excess risk toward 1, due to the issue described above of a similar quantity added to both the numerator and the denominator of a fraction.

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Analyzing excess risk from matched designs with double controls: author's response

Tedeschi provides a thoughtful perspective on the interpretation and calculation of excess risk. We largely agree, and this was our rationale for raising the caution that excess risk is easily misinterpreted [1]. This was also our reason for providing a detailed exposition and concrete example to help explain the distinction to a larger audience of general medical readers. By contrast, clinical research studies sometimes publish findings expressed solely as an excess risk without fully considering these concerns [2].

The first concern from Tedeschi relates to the nature of underlying risk, whether outcomes reflect a stochastic or deterministic process, and how to consider the degree of individual heterogeneity. Such uncertainties underpin endless debates about the effect of random chance on patient outcomes and applying frequentist statistics to the care of individual patients [3]. We will not settle these debates anytime soon because the unknowns cannot be directly explored through a testable hypothesis.

A second concern from Tedeschi is on the idea that excess risk must require a comparator, thereby implying that different comparators can lead to different estimates. We agree and also endorse the additional point that an abundant collection of matched comparators could lead to particularly skewed estimates. We also agree that such discrepancies tend to be accentuated when the baseline count is small, excess count is large, variation is uneven, and comparisons are calculated as ratio statistics [4].

A tangential concern from Tedeschi is whether double controls are sufficient and what happens when a larger collection of matched comparators is available. Typically, an increase from solitary controls to double controls yields more statistical power, whereas an increase beyond seven matched controls provides minimal further gains. Higher assemblies of matched controls also raise pitfalls from mathematical complexity, missing data, and difficulties in visual displays. Double controls may be a useful compromise [5].

We agree with Tedeschi and reinforce the central point of consensus. Namely, that excess risk is easily estimated and easily misinterpreted. In addition, we underscore our main conclusion that, because implications can differ, a conservative approach can be to show results based only on total counts and not excess counts when analyzing a matched study. We thank Tedeschi for joining the conversation and providing a mathematical example that further illustrates the potential for misinterpretations.

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