Appendix 4 (as supplied by the authors): Sensitivity analysis for unmeasured confounding

Method

We used the 'Array approach' proposed by Schneeweiss[1] to evaluate the impact of strong unmeasured confounding on our reported estimates. This approach uses a multiplicative bias term to understand the magnitude of, 1) the strength of the association between an unmeasured confounder and the outcome and, 2) imbalance in the distribution of the unmeasured confounder across the two exposure groups, is required to obtain substantially different exposure-outcome associations than the one reported in the presence of unmeasured confounding. This is achieved by applying a correction factor (the multiplicative bias term) for unmeasured confounding to the naïve or apparent RRs that do not account for unmeasured confounding as follows,

$$Corrected\ RR = \frac{Apparent\ RR}{Bias_M}\ ; where\ Bias_M = \frac{P_{C1}\,(RR_{CD} - 1) + 1}{P_{C0}(RR_{CD} - 1) + 1}$$

P_{C1} and P_{C0} – prevalence of the unmeasured confounder in the exposed and reference groups, respectively

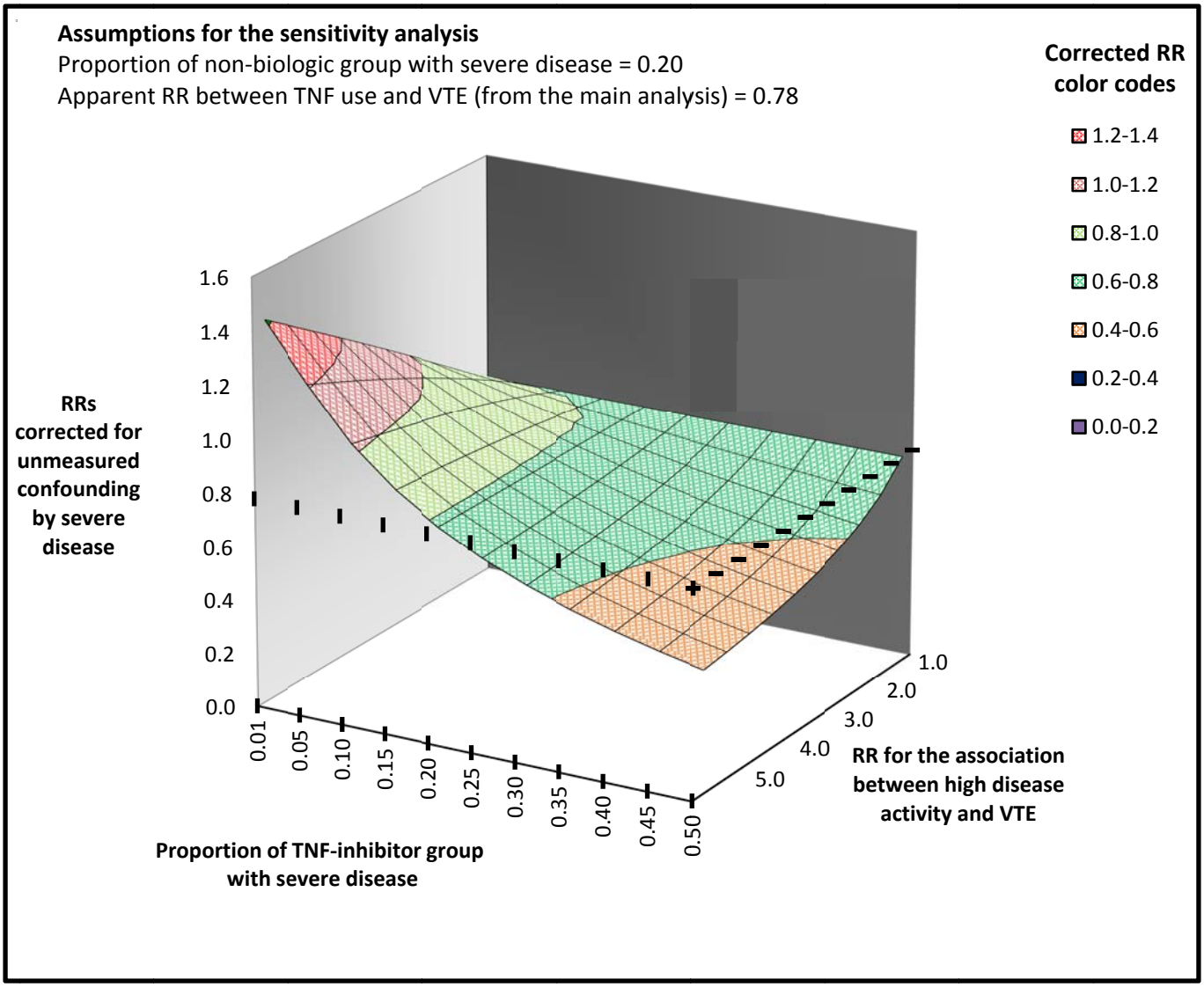
RR_{CD}- Risk ratio for the association between the unmeasured confounder and the outcome of interest

In the present study, we did not have direct information regarding the disease activity for the included inflammatory bowel disease patients. Disease activity can act as a confounder if patients with severe disease (Crohn's disease activity index of >450 or scoring 3 on at least one component of the Mayo clinic disease activity index for ulcerative colitis, for instance) are selectively treated with one of the two treatments being compared ($P_{C1} \neq P_{C0}$) and severe disease is an independent risk factor for VTE ($RR_{CD} >> 1$). Therefore, we tested the impact of unmeasured disease activity on our estimates. We assumed the prevalence of severe disease to be 20% in the reference group (non-biologic initiators). The apparent RR of 0.78, which was based on the estimate from our main analysis, was used to derive corrected RRs. We calculated a range of corrected RRs (the 'array') by varying the proportion of severe disease patients in the TNF-α inhibitor group (P_{C1}= 0.01 to 0.50) and RRs for the association between severe disease and VTE (RR_{CD} = 1.0 to 5.0) and plotted them on a 3-dimensional surface graph.

Results

As shown in the attached Figure, for a majority of plausible combinations of imbalances in the distribution of severe patients across the two treatment groups and severe disease-VTE associations, the corrected RRs fell within the confidence limits from our main analysis (0.6 to 1.0, all combinations on green-shaded surfaces). However, combinations where the proportion of severe disease patients were more than 2-fold higher in the reference group and having severe disease increased VTE risk by more than 3-fold, the corrected RRs were higher than 1 (1.0 to 1.4, all combinations on red-shaded surfaces). Conversely, combinations where the proportion of severe disease patients were more than 2-fold higher in the TNF-α inhibitor group and having severe disease increased VTE risk by more than 3-fold, the corrected RRs were less than 0.6 (0.4 to 0.6, all combinations on the orange-shaded surface).

Appendix to: Desai RJ, Gagne JJ, Lii J, et al. Comparative risk of incident venous thromboembolism in patients with inflammatory bowel disease initiating tumour necrosis factor-α inhibitors or nonbiologic agents: a cohort study. *CMAJ* 2017. DOI:10.1503/cmaj.161485.



Conclusion

Based on the results from this analysis, we note that a very high magnitude of the imbalances in the distribution of severe patients across the two treatment groups in combination with a very strong severe disease-VTE association is required to get results that are substantially different from the reported estimates. Considering that our propensity score models include a vast range of proxy variables to account for IBD severity, such large magnitudes of imbalances between the two treatment groups seem unlikely. Therefore, we conclude that residual confounding by disease activity is improbable to explain the effect of TNF-α inhibitors on the risk of VTE reported in this paper.

Reference

1. Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. *Pharmacoepi Drug Saf;* 2006; 15(5); 291-303.