Supplementary File 3

Details of instrumental variable (IV) analysis

One of the key limitations of observational epidemiological studies is the existence of unmeasured confounding that may render effect estimates of a particular exposure to be biased. Instrumental variables can be leveraged if fulfilling certain key assumptions, in order to deal with this issue of unmeasured confounding and yield unbiased results (1).

We here a-priori identified the time-specific preference for prescribing biologics among each of the consultants who recruited patients into the BSRBR-RA. This variable we called ‘physician preference’, as estimated and applied elsewhere (2). We calculated this preference variable in a time-dependent manner by sorting BSRBR-RA patients according to recruiting consultant and registration date, and then by calculating the relative frequency of biologics prescribed over the previous 12 patients recruited into the registry by each consultant ID. If this relative frequency for a given patient was >=0.5 then we defined the consultant (at that point in time) as “preferring biologics”, if it was <0.5 then they were considered as “preferring csDMARDs”. In such manner the first 12 prescriptions per consultant ID were excluded from the effect estimate as they were only used to generate the preference IV variable.

The IV was used in a 2-stage least squares linear regression. Treatment exposure was the dependent variable in the first model containing the IV (consultant preference) and measured covariates. This first model provided the estimated probability of being exposed depending on IV status and measured confounders. These fitted values were then included along with measured confounders as independent variables into the second stage which had THR/TKR (analysed separately) as the outcome. This used a fixed 12-year observation window (as this was the point of censoring in the main analysis). The coefficient for the predicted probability of being treated (given the IV and measured covariates) was the result of intrinsic interest.

We identified 5,018 patients whose consultant preferred biologics and 2,901 whose consultant preferred csDMARDs. The IV was found to be strongly associated with use of biologics (87% vs. 13% of patients were biologics users amongst consultants preferring biologics vs. csDMARDs, respectively). However the IV was also found to be associated with many of the measured confounders, thereby suggesting it would probably also be associated with unmeasured confounders, and in which case would undermine it’s validity as an instrument.

Supplementary file 4 reports on the crude associations between the IV and the study outcomes. Supplementary file 5 reports the unadjusted and adjusted absolute risk difference (per 100 patients) according to consultant preference for biologics.

1. Ertefaie A, Small DS, Flory JH, Hennessy S. A tutorial on the use of instrumental variables in pharmacoepidemiology. Pharmacoepidemiol Drug Saf. 2017;26(4):357-67.

2. Brookhart MA, Wang PS, Solomon DH, Schneeweiss S. Evaluating short-term drug effects using a physician-specific prescribing preference as an instrumental variable. Epidemiology. 2006;17(3):268-75.