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Title: The performance of preference-based instrumental variables to emulate a randomised clinical trial of comparative medical device effectiveness.

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Background:

Instrumental variables (IV) are used to minimize confounding in pharmacoepidemiology. There is a scarcity of data on the performance of preference-based IVs in medical device epidemiology.

Objectives:

We aimed to test the use of surgeon, centre and regional preferences for partial knee replacement (PKR) as IVs to replicate an ongoing RCT comparing PKR vs total knee replacement (TKR), the TOPKAT trial.

Methods:

Participants undergoing PKR or TKR according to the UK National Joint Registry, and with linked post-operative patient reported oxford knee scores (OKS) data were included. TOPKAT exclusion criteria were applied to maximise comparability.

We calculated preference as the % of PKR in the last 20, 30 and 50 knee replacement surgeries for lead and consultant surgeon, and the last 100, 300, 500, and 1000 for surgical unit and regional area. We estimated IV strength using F-statistic and odds ratio (OR) on a regression between IV and exposure (PKR). We evaluated balance per groups (IV>median vs IV≤median) with standardized mean differences (SMD) for known confounders. IVs with confounding (SMD ≥0.1) and those considered weak (OR 95% confidence intervals including 1 or F-statistic<10) were not further evaluated. A 2-stage IV regression was fitted to calculate the effect of PKR on one-year OKS compared to TKR. We used  $\chi^2$  to test differences in treatment estimates between TOPKAT and IVs results; and  $\tau^2$  to quantify between-studies variance.

Results:

A total of 69,269 patients were included for preference calculations; 34,576 had OKS data and were included, with 358 undergoing PKR. Lead surgeon preference based on 30 and 50 surgeries did not balance for age; while consultant preference based on previous 50 surgeries, and all area (surgical unit and region-based) IVs resulted in imbalances in socio-economic status.

The results from lead surgeon preference IV based on 20 previous surgeries were comparable to TOPKAT: 9.1 (CI95: 0.1 to 18.1) vs 1.9 (0.2 to 3.6) respectively;  $\chi^2$   $p=0.12$ ;  $\tau^2=15$ . Conversely, consultant preference IV based on 20 and 30 previous surgeries yielded significantly different results, with  $\chi^2$   $p=0.01$  and  $p<0.01$  respectively.

#### Conclusions:

Surgeon preference is a potentially valid IV, but treatment estimates are sensitive to decisions made during the construction of IVs. More research is needed on best practices for the estimation and diagnostics of surgeon preference IVs. Finally, caution is advised in the interpretation of area-based IVs, which fail to balance regional confounders such as deprivation.