Performance of Instrumental Variable Methods in Case-control and Cohort Studies: A Simulation Study

M. Jamal Uddin1, Rolf HH Groenwold1,2, Anthonius de Boer1, Svetlana V Beltser1, Kit CB Roes2, Olaf H Klungell1,2

1Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, University of Utrecht, Utrecht, The Netherlands
2Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

Background:
- Instrumental variable (IV) analysis is becoming increasingly popular to adjust for confounding in observational epidemiologic research
- An IV is a variable that is strongly related to the exposure, and only related to the outcome through exposure (Figure 1)
- When the IV is weakly related to the exposure, the IV estimation is highly biased. However, this has only been studied in a limited number of settings

Objective:
To assess the bias of IV estimates using simulated data in a variety of settings:
- cohort and nested case-control design
- different types (i.e. continuous and/or binary) of exposure, IV, and outcome
- different incidences of the outcome

Methods:
- We performed a simulation study based on the following parameters:
  - Sample size: 1,000 – 50,000
  - Incidence of the outcome: 1%, 5%, 10%, and 25%
  - True exposure effect: $\beta=1$ for continuous outcome (linear model) and $\beta=\log(OR)=\log(2)$ for binary outcome (logistic model)
  - Analysis of full simulated dataset (cohort) or cases and sample (1:1) of controls (case-control study)
  - Data analysis: two-stage IV methods (in case-control studies, subjects were weighted by the inverse of the sampling fraction)
  - Measures of the IV-exposure association: Pearson correlation ($\rho$), point bi-serial correlation (PBC), odds ratio (OR), and F-statistic
  - Bias: difference between the mean of IV estimates based on 10,000 simulation runs and the true exposure effect

Results:
- For all types of IV and exposure, IV estimates were biased when the IV was weak, especially for low (< 1%) incidences of the outcome
- When both IV and exposure were continuous in cohort data with $n=5000$, bias was considerable for $p<0.10$, but for $p>0.10$ bias was negligible
- For binary IV and continuous exposure (or vice versa) this was observed for $PBC=0.08$ and when both were binary at OR=1.30. For the case-control design these values were 0.20, 0.16 and 1.70 respectively
- IV estimates were less stable for rare outcome (e.g.1%), especially in the nested case-control design

Conclusions:
- Similar patterns of bias were identified for all considered scenarios of IV analysis and irrespective of study design. However, in case-control studies IVs should be stronger than when applying them in cohort studies to get consistent estimates.
- In all settings, IV estimates were unstable for weak instruments or rare outcomes
In such situations, it is not recommended to apply IV methods

Authors’ Disclosure Information
Conflicts of Interest: The department of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, has received unrestricted research funding from the Netherlands Organisation for Health Research and Development (ZonMw), the Dutch Health Insurance Board (CVZ), the Royal Dutch Association for the Advancement of Pharmacy (KMPH), the private-public funded Top Institute Pharma (www.ti-pharma.nl), includes co-funding from universities, government, and industry), the EU Innovative Medicines Initiative (IMI), EU 7th Framework Program (FP7), the Dutch Medicines Evaluation Board, the Dutch Ministry of Health and industry (including SmithKline, Pfizer, and others).

Acknowledgements: The research leading to these results has received funding from the European Union's Seventh Framework Programme (FP7/2007-2013) for the Innovative Medicine Initiative (www.imi-europa.eu) under Grant Agreement n° 115004. The research leading to these results was conducted as part of the PROTECT consortium (Pharmacoepidemiological Research on Outcomes of Therapeutics by a Euro pean ConsorTium, www.imi-protect.eu) which is a public-private partnership coordinated by the European Medicines Agency.