Author's response to reviews

Title: On the use of propensity scores in case of rare exposure

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Author's response to reviews: see over
Dear Editor,

Please find enclosed the manuscript "On the use of propensity scores in case of rare exposure" by Hajage et al. that we would like to submit for publication in *BMC Medical Research Methodology* as a Research Article.

Post-marketing assessment of the risk and the benefit of a drug in real-world setting frequently rely on observational studies, with the need to account for imbalance of baseline characteristics between exposed and unexposed subjects. Propensity score (PS) analysis has become one of the most popular methods to overcome this problem.

The appropriateness of the estimation of treatment effect using PS relies on correct modelling of the probability of exposure conditionally to baseline confounding factors. This estimation could therefore be challenging in the case of rare exposure. This situation is frequently encountered in observational studies when study design does not require a high prevalence of exposure, for example studies performed on databases constituted with a nonspecific objective or analyzed for a different purpose than initially defined, or the evaluation newly marketed drugs in real world setting. However, there is a paucity of research examining the relative performance of different propensity score methods in case of infrequent exposure.

We addressed this issue by conducting an extensive series of Monte Carlo simulations to examine the performance of the two most recommended PS methods (PS-matching and inverse probability of treatment weighting) to estimate marginal hazard ratios, under the condition of infrequent exposure (10% down to 1%). We have focused on the estimation of hazard ratios, because 1) of the frequency with which they are reported in the medical literature, and 2) they are by nature not collapsible (conditional and marginal treatment effects will coincide), and there is therefore less of alternative methods to estimate the marginal effect of exposure.

Overall, we observed that the less biased results were obtained with estimators of the average treatment effect in the treated population (ATT) in comparison with estimators of the average treatment effect in the overall population (ATE). Among ATT estimators, IPTW using ATT weights outperformed PS-matching in all settings. Therefore, if consistent with clinical objectives, applied researchers are encouraged to estimate ATT with IPTW for studying the relative effect of a rare treatment. Further work in this area is needed to provide improved analytical strategies.

We believe these findings could be of great interest to the broad readership of *BMC Medical Research Methodology*. We hope that the present manuscript is acceptable for publication in the journal.

The submitted material has not been published and is not under consideration for publication elsewhere.

Sincerely yours,
David Hajage, Florence Tubach, Philippe Gabriel Steg, Deepak L Bhatt, and Yann De Rycke
Changes requested by editor (28th May 2015)

- Ethical approval and consent from patients/participants.
Concerning the real dataset illustration (REACH registry), manuscript was amended as follows: “Patients were enrolled 44 countries between December 2003 and December 2004. In each country, the protocol was submitted to the institutional review boards according to local requirements, and signed informed consent was obtained for all patients.” (page 8)
- Include line numbers.
Line numbers were added.

Conflicts of Interest
This article reports the results of a simulation study, and all the following disclosures are thus unrelated to the submitted work.

PG Steg discloses the following relationships (unrelated with submitted work):
– Research grants (to INSERM U1148): Servier, Sanofi
– Speaker or consultant (including steering committee, DMC and CEC memberships) : Amarin, AstraZeneca, Bayer, Boehringer-Ingelheim, BristolMyersSquibb, Daiichi-Sankyo-Lilly, GlaxoSmithKline, Medtronic, Merck-Sharpe Dohme, Novartis, Otsuka, Pfizer, Regado, Sanofi, Servier, The Medicines Company, Vivus
– Stockholder: Aterovax

DL Bhatt discloses the following relationships (unrelated with submitted work):
– Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences
– Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care
– Chair: American Heart Association Get With The Guidelines Steering Committee
– Data Monitoring Committees: Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Population Health Research Institute
– Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Associate Editor; Section Editor, Pharmacology), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today’s Intervention), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor)
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