

Format for ANSWERING REVIEWERS

10th June 2015



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 18245-review.doc).

Title: Methodological challenges to control for immortal time bias in addressing drug effects in type 2 diabetes

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Name of Journal: *World Journal of Methodology*

ESPS Manuscript NO: 18245

The manuscript has been improved according to the suggestions of reviewers:

Reviewer 1:

I received an article concerning pharmacoepidemiologic questions of drug effects in type 2 diabetes, what is very important topic of pharmacoepidemiologic and biostatistic analysis. I have some doubts if the proposed methods doesn't need further specific validations. After revision this article could be recommend for publication.

Response:

Yes, these methods validated in our database need further validations when used in other cohorts of patients with T2DM. More importantly, we believe that these biases should be taken into full consideration at the stage of designing the study and further research about how to simultaneously remove these biases is needed. So we revised the conclusion to highlight our points:

"... by documenting indications or variables at the time when drugs are introduced or changed. Our validation studies indicated that exclusion of immortal time in an analysis testing effects of RAS inhibitors while inclusion of immortal time in an analysis testing effects of statins on CVD, respectively yielded effect sizes in T2D close to that obtained in RCTs. Our findings call for further research in developing methodology to simultaneously remove immortal time bias and drug use indication bias. Meanwhile, in the absence of methods which can address effects of different drugs in multiple databases, it will be prudent to use reference drugs and test the quality of database and adjustment methods for immortal time and drug indication before testing for other drug associations with clinical outcomes to avoid erroneous conclusions." (Page 8, the last paragraph and page 9).

Also, we have revised the abstract with highlighting this point:

"Our results highlight the complexity and difficulty in removing these biases. We call for validations of the methods to cope with immortal time and drug use indications before applying them to particular research questions, to avoid making erroneous conclusions." (Page 3, the abstract, the last 4 lines).

Reviewer 2:

This is an interesting article concerning pharmacoepidemiologic questions of drug effects in type 2

diabetes. The topic is overall prospective, because question of bias is an important factor of pharmacoepidemiologic and biostatistic analysis. The article is well designed and well written and information is presented thoroughly. Therefore, I recommend this article for publication as Editorial in World Journal of Methodology.

Response:

Thanks.

Reviewer 3:

I am afraid the proposed methods need further extensive validations.

Response:

Yes, we agree. See our response to reviewer 1.