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

Author: Xi-Lin Yang, Xiao-Xu Huo, Juliana CN Chan

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 pragraph 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 thorougly. 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.

3rd August 2015
Dr. Yue-Li Tian
Science Editor, Editorial Office
Baishideng Publishing Group Inc
E-mail: y.l.tian@wjgnet.com

Dear Dr. Tian,

Ref: Manuscript NO: 18245-review

Title: Methodological Challenges to Control for Immortal Time Bias in Addressing Drug Effects in Type 2 Diabetes

We would like to express our thanks again for the editor's comment. We have revised the manuscript with full consideration of your and the reviewers' comments as marked in the revised version of the manuscript using the Word tracking function. Our responses to the comments are listed below:

Response:

Thanks. We have revised these two sentences to:

"Immortal time refers to a period in cohort studies when non-exposure to a drug treatment from the baseline to the time of initiation of the drug treatment in the "drug exposure group" is misclassified as exposure to the drug treatment[1]. This misclassification may lead to a deflated HR of the treatment for the endpoint due to addition of the non-drug exposure period into the drug exposure period."(Page 9, the last paragraph).

In addition, we have refined the manuscript as marked in the attached manuscript using the WORD tracking function.

Sincerely,

Xilin Yang
PhD, Professor, Director
Department of Epidemiology and Biostatistics
School of Public Health
Tianjin Medical University
22 Qixiangtai Road, Heping
Tianjin 300070, China
Tel: +86 22 8333 6727
Fax: +86 22 8333 6608
Email: yxl@hotmail.com or yangxilin@tmu.edu.cn