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CORRESPONDENCE

Metformin use and asthma: Further investigations

To the Editor:

I read with interest the article entitled 'Metformin use and asthma outcomes among patients with concurrent asthma and diabetes' by Li *et al.*[1] I appreciate the authors for their work in investigating the risk of asthma outcomes with metformin use among patients with concurrent asthma and diabetes diagnoses using a large population-based retrospective cohort – the Taiwan National Health Insurance Database. This study supplements the possible mechanistic role of metformin in activating 5-adenosine monophosphate-activated protein kinase (AMPK), which is shown to attenuate allergic eosinophilic airway inflammation,[2] to inhibit TNF-α-induced inflammatory signalling[3] and to decrease oxidative stress,[4] thus providing evidence for possible beneficial role of metformin in asthma patients.

There are significant strengths to the study along with several limitations just like other retrospective cohort studies involving large administrative medical claims data. Lack of information on important confounders, including BMI, allergens or environmental triggers, dietary and socio-economic factors, limits the study findings and future epidemiological studies should address these limitations.

I have a few concerns about the study and would like to hear from the authors on the following: First, the study identified metformin use as lowering the risk of asthma hospitalizations and exacerbations, but not emergency department visits. An explanation about this important finding might help us in understanding the characteristics of asthma patients where metformin is beneficial. Second, the study excluded patients if they had an International Classification of Disease (ICD)-9 code for COPD, thereby possibly excluding patients with severe asthma. The survival benefit of metformin in COPD patients has been demonstrated in an earlier study, with COPD not to present as a barrier to the clinical use of metformin.[55] Additional analyses with the inclusion of these patients, and matched on severity, will further help understand the role of metformin use in reducing asthma morbidity. Finally, a rationale for 3 years of follow-up for outcome assessment should be provided.

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From the Authors:

We would like to thank Dr Veeranki for the thoughtful comments regarding our study.[1] Dr Veeranki rightly points out that studies utilizing administrative claims have limitations. We agree with this point and realize that the importance of studies utilizing claims data is to identify potential problems which require a more stringent study design to investigate.

Regarding the insignificant association between metformin use and asthma-related emergency department visits, a potential explanation is that the airway inflammation reduction effect of metformin works better on more severe asthma patients. In addition, there are other potential factors that may influence the decision of patients to be hospitalized or treated in emergency room and then sent home. These factors that can include personal decisions, procedural variables and admission rules[2] may not be fully identified from the

administrative claims data. A further investigation is warranted.

The study conducted by Hitchings *et al*. showed that metformin was associated with a survival benefit among patients with concurrent COPD and diabetes.[3] We conducted a new analysis to include patients with COPD. Similar to our main findings and study results reported by Hitchings *et al*., we found that metformin users were significantly associated with a lower risk of asthma-related hospitalization (OR = 0.16, 95% CI: 0.06–0.42) but not for asthma-related emergency department visits (OR = 0.57, 95% CI: 0.28–1.12) or asthma exacerbation (OR = 0.68, 95% CI: 0.46–1.02) in the new analysis. We suggested clinicians to be aware of the benefits of metformin in reducing airway inflammation.

Regarding the concern of the 3-year follow-up period, we intended to investigate the long-term effect of metformin use on airway inflammation. Both asthma and diabetes are chronic diseases. Due to the length of our data (11-year administrative claims dataset), we were able to use a 3-year follow-up period to conduct the study.

In the end, we appreciate the comments made by Dr Veeranki and hope our responses provide further clarification of our work. We look forward to further demonstrate whether metformin use by patients with asthma leads to an improved symptom control. There appears to be justification for considering the notion that metformin may have a beneficial effect on the airway inflammation. Clinical trial work that utilizes clinical outcomes as well as health services research work that includes a broader set of predictors known to be associated with treatment decisions related to emergency room visits and hospitalization are warranted.

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