adjusted for comedication, as well as duration of metformin use, dosage, diabetes duration, and glycated hemoglobin level. In our opinion, this study is the one with the least potential for bias.

The Meta-Analysis of Observational Studies in Epidemiology (MOOSE) group (10) noted that potential biases in the original studies make the calculation of a single summary estimate of exposure effect potentially misleading. We concur and suggest that the studies summarized by Zhang et al. cannot be assumed to have measured the same effect and that pooling the results of these 6 studies, given the high variance in study design, patient selection, and definitions of exposure and comparator, was not warranted.

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ONE AUTHOR REPLIES

I appreciate Hense and Geier’s interest (1) in our recent article (2). They believed that the bias, including variances in design, patient selection, and comparison definition, made it impossible to pool the 6 studies that were included. I do not agree. In my opinion, a systematic review and meta-analysis of the association between metformin and lung cancer risk will help call for caution in interpreting the current data and guide the design and analysis of future studies.

The first point raised in their letter is the concern that time-related bias was ignored in our article. In fact, the limitation of time-related bias was acknowledged in both that article (2) and in other articles by the same group published since 2011 (3, 4). It was noted that “[t]ime-related bias, particularly immortal time bias, is present in some previous studies, which results in an exaggerated beneficial effect” (2, p. 13). It was also noted that the study by Smiechowski et al. (5) accounted for time-related bias and showed a null association (2). In addition, the analysis described the bias from latency time (2), which was called time lag bias in the article by Suisse and Azoulay (6). Nonetheless, I do not agree that the presence of time-related bias in the 6 cited studies makes it impossible to pool the data if the limitation has been fully acknowledged. First, time-related bias, also known as time-dependent bias, has been found to be common in the clinical literature (7). The bias usually favors the treatment at interest; however, the magnitude of bias is difficult to quantify. It is not practical to discard studies that are subject to this bias, especially when data are lacking in this field. In addition, the subgroup analysis can provide useful information by comparing studies with or without evidence of time-related bias (8).

Hense and Geier also believe that the included studies may not have measured the same effect because of heterogeneity in study designs, patient selections, and the definitions for metformin exposure and comparator, and thus that a meta-analysis was not warranted. I disagree. A meta-analysis is not just about providing a single simple summary effect estimate. It has been emphasized in our papers that caution is needed in interpreting the results from meta-analyses in this field that combine data from observational studies that are subject to flawed study designs and various bias (2–4, 8, 9). Moreover,

a meta-analysis can provide more useful information, for example, by exploring the source of heterogeneity. Finally, relying on the one observational study (5) that is supposed to be subject to least potential for bias, as suggested by the authors (1), could be even more misleading than using a meta-analysis.

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