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Title	Type 2 diabetes mellitus and risk of community-acquired pneumonia: a systematic review and meta-analysis of observational studies
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Reviewer 1	Bada Yang
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General comments (author response in bold)	Thank you for the opportunity to review this manuscript. In my view, this is generally a well-conducted and well-written and concise systematic review of an interesting topic. It was a pleasure to read. **Thank you for the positive feedback.** Nevertheless, I have some points to discuss. Please note that I am reading the work as a non-expert and I will mostly be focusing on the methodological aspects. General points 1. The review is already quite outdated. It may be a good idea to rerun the search up until the present moment. **We agree that the literature search was outdated and have updated it to include studies published through March 16th, 2020.** 2. This SR seems to be about type 2 diabetes, but 5 of 11 studies are about diabetes in general. I tend to think it would be better to change the focus of the review to 'diabetes in general' (unless there are good reasons to focus on T2D); otherwise to be more careful throughout the review to generalize the pooled results to T2D. **Please refer to our response to Comment 10 from the Manuscript meeting.** 3. The authors spent a lot of effort assessing study quality (using ROBINS-I), which is laudable, but the interpretation of review results do not seem to account for the serious limitations of included studies. **We thank the Reviewer for this comment. We agree that it is important to account for study quality when conducting knowledge syntheses and interpreting their results. We had originally intended to conduct subgroup analyses by study quality but were unable to do so because all included studies were of low or moderate quality. However, we do describe study quality in detail on pages 9-10 and mention that our results must be interpreted with caution because of the serious risk of bias of included studies on page 12 of the "Interpretation" section. We also added details regarding this issue in the limitations of the "Interpretation" section on page 14 of the manuscript, which now reads "Third, all of the included studies had a serious risk of bias, which prevented us from conducting subgroup analyses by study quality, and systematic reviews are inherently affected by the limitations of their included studies". In addition, we have revised the conclusion of the abstract, which now reads "Type 2 diabetes may be associated with an increased risk of CAP. However, the available evidence is from studies at serious risk of bias, and additional, high-quality studies are needed to confirm these findings". Similarly, we now explicitly mention the quality of this literature in our revised Conclusions on page 15.**

	Specific points ABSTRACT 4. Results: After mentioning the RR of 1.67 for cohort studies, please report how many studies contributed to this estimate and the overall risk of bias in this estimate (and please repeat this for the case-control studies). **We thank the Reviewer for these suggestions. We have added the number of studies contributing to the subgroup-specific estimates in the abstract. Unfortunately, due to word limitations, we were unable to add the risk of bias for these estimates. However, the risk of bias is discussed in detail in the "Results", "Interpretation", and "Conclusion" sections of the manuscript as well as the revised conclusions of the Abstract. In addition, the detailed quality assessment of each included study is reported in the appendices.** 5. Results: "..studies were of low quality" I suggest rephrasing this to "studies were at serious risk of bias". **We thank the Reviewer for this suggestion. We have changed the wording from "low quality' to "serious risk of bias" in the Results of the Abstract on page 3 of the manuscript. We now use this phrasing throughout the manuscript.** 6. Results: "There was evidence of publication bias" Publication bias cannot be concluded definitely from funnel plot asymmetry; I suggest 'There was evidence of small-study effects'. **We thank the reviewer for their suggestion. We have changed the wording from "publication bias" to "small-study effects" in the Results of the Abstract on page 3 of the manuscript. We have also modified our phrasing regarding this issue on pages 7, 11, and 13 of the manuscript.** 7. Conclusion: "Type 2 diabetes… risk of CAP". As I understand a large portion of studies were not specifically type 2 diabetes; does this need to be 'Diabetes of any type'? **Please refer to our response to Comment #10 from the Manuscript meeting.** 8. Conclusion: "Type 2 diabetes… risk of CAP" It is important that the conclusion takes the study limitations into account; for example by rephrasing: "…associated with an increased risk of CAP, but it is unclear whether this association is causal due to inadequate control of confounding factors in included studies". **We thank the Reviewer for their suggestion. We agree that it is important that the conclusion takes the study limitations into account, and we have rephrased it as "The available evidence suggests that type 2 diabetes is associated with an increased risk of CAP. However, this evidence is from studies at serious risk of bias, and additional high-quality studies are needed to confirm these findings. While awaiting such studies, patients should be informed to seek medical attention promptly if they develop symptoms to facilitate early detection and treatment of CAP given its associated morbidity and mortality. Physicians and patients should be aware of the importance of attaining glycemic control to prevent resulting infections in this patient population."** 9. Conclusion: The sentence "Physicians…type 2 diabetes" is not very informative.

	Instead, may I suggest to write a recommendation for further research. **We thank the Reviewer for this suggestion and have revised the last sentence on the Abstract to focus on future research. Please refer to our response to the previous comment.** MAIN TEXT 10. Introduction. In my view well-written, concise and easy to understand. **We thank the reviewer for this positive comment** 11. Introduction. Page 4, "Given the increasing prevalence… type 2 diabetes" I have the feeling that the real question of this SR is not whether T2D is merely associated with CAP, but whether T2D is a causal risk factor for CAP. I know that this distinction is often not made in the literature (and authors are often reluctant to use the word 'causal') but I believe in current times, where we have methods to infer causality from observational data, the use of this word is justified and will reduce a lot of confusion with readers (Hernan M, AJPH 2018). My suggestion is to rephrase the objective to make explicit that the review question is causal. **We agree that it would be interesting to draw causal inferences regarding this research question. However, while preparing the protocol for this study, we identified that this literature had several limitations and that most of the relevant studies had not used methods that would allow for causal inferences. Consequently, we felt that it would be more prudent to limit our knowledge synthesis and the interpretation of its results to associations. Importantly, we believe that the study of such associations remains important, as clinicians should consider that type 2 diabetes is associated with an increased risk of community-acquired pneumonia and institute preventative measures in patients with type 2 diabetes, regardless of whether this association is causal.** 12. Methods. Study selection: I feel that a great weakness in many SRs is that the eligibility criteria (PICO) are not very specific. The eligibility criteria are what gives body to the review question, and a well-defined review question is needed in order to adequately assess risk of bias and generalizability. I wonder if it is possible to elaborate more on the Patients, Exposures, Controls and the Outcomes. For example, in the current manuscript, disease (or outcome) definitions are not provided, and the control group is not specified in the eligibility criteria. **We agree with the Reviewer that it is helpful to frame eligibility using specific PICO criteria. In response, we have added a sentence mentioning that we have followed the PICO format suggested by the Cochrane handbook and for which elements of our inclusion criteria correspond to each of the PICO criteria. These changes were made in the sub-section "Study selection" in the Methods on pages 5 and 6 of the manuscript, which now reads "We defined our inclusion criteria using the population, intervention, comparator and outcome (PICO) format of the Cochrane Handbook, however defining an exposure instead of an intervention. Studies were included if they fulfilled the following criteria: 1) observational design (cohort or case-control study); 2) study population aged ≥18 years [population]; 3) reported at least one of the following two exposures: type 2 diabetes or diabetes with type not specified [exposure]; and 4) reported at least one of the following two outcomes: CAP or unspecified pneumonia [i.e., did not explicitly differentiate**

	between community-acquired and nosocomial (hospital- or ventilator-acquired); outcome]. We included studies for which the comparator group was individuals without type 2 diabetes [comparator]". Exposure and outcome definitions were not defined using the same specificity as would be reported in a primary study to allow for the inclusion of relevant studies that used varying definitions of diabetes and pneumonia as our objective was to synthesize the totality of the available evidence regarding this issue. In addition, we describe the various definitions of exposure and outcome from the included studies in detail in e-Table 3. 13. Methods. "After removal of duplicates…inclusion determined by consensus" this part belongs to the Study Selection paragraph, rather than Data extraction. **We thank the reviewer for this suggestion. We have moved this portion of text from the "Data extraction and quality assessment" sub-section to the "Study selection" sub-section of the Methods on page 6 of the manuscript.** 14. Methods. "As pneumonia is a rare outcome… pooled together". The Cochrane Handbook provides a formula to convert OR to RR by assuming a baseline risk. This seems to me the more elegant solution; baseline risk could for example be estimated using the data from the cohort studies included in the review. At minimum I would like to suggest to try this method and see if it differs from the current results. **We thank Reviewer 1 for their suggestion. We have calculated the RRs for the studies who only reported ORs, using the following formula, reported in the references below:** **Relative risk=odds ratio/(1−p0+(p0×odds ratio))** **We present here the results of these conversions. We used the risk of community-acquired pneumonia in the unexposed group in every study as the baseline risk.** **Author, Year Reported OR (95% CI) Calculated RR (95% CI)** **Hine, 2017 1.43 (1.18, 1.74) 1.42 (1.18, 1.74)** **Muller, 2005 1.30 (1.11, 1.52) 1.29 (1.10, 1.51)** **Ray, 2017 3.23 (1.24, 8.38) 2.91 (1.23, 6.10)** **Kornum, 2008 1.26 (1.21, 1.31) 1.23 (1.19, 1.27)** **Thomsen, 2004 1.50 (1.1, 2.00) 1.44 (1.09, 1.84)** **As the calculated RRs are fairly similar to the reported ORs, we believe that this approach supports the assumption that the OR approximates the RR since pneumonia is rare. Since our a priori plan was to assume that the OR approximates the RR given the rare disease assumption, we have elected to leave our primary analysis unchanged. However, in response to Reviewer 1's comment, we have added a sensitivity analysis that utilizes this approach. This sensitivity analysis is now described on page 8 of the Methods, page 11 of the Results, and in e-Table 5 and e-Figure 7.** **References:** **1. Grant, R.L., Converting an odds ratio to a range of plausible relative risks**

	for better communication of research findings. BMJ : British Medical Journal, 2014. 348: p. f7450. **2. Deeks JJ, H.J., Altman DG, Chapter 10: Analysing data and undertaking meta-analyses., in Cochrane Handbook for Systematic Reviews of Interventions version 6.0 T.J. Higgins JPT, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, Editor. 2019, Cochrane** 15. Results. Quality assessment: "All studies were… information bias" There is no domain in ROBINS-I called 'information bias'; please specify the domain of bias. **We have modified the terms "information bias" for "exposure misclassification" and have added clarification in parentheses "classification of interventions in ROBINS-I" to clarify exactly what category we were referring to. We have revised the "Quality assessment" sub-section of the Results on page 9 of the manuscript accordingly.** 16. Results. Diabetes and pneumonia: "Estimates also varied… RR of 1.61" It seems to me that these two subgroups have very similar results; very close point estimates and overlapping CIs; could you motivate why you think estimates varied with outcome definition? **We agree with the Reviewer that the estimates of both outcome definitions were similar. We therefore modified our phrasing from "also varied with" to "were similar by" in the "Diabetes and pneumonia" sub-section of the Results (page 10).** 17. Results. Diabetes and pneumonia: "In subgroup analyses, the pooled estimate… had a RR of 1.61". Please specify whether these subgroup analyses were done with cohort studies, case-control studies or all studies. **These subgroup analyses were done with all studies. We have added "which included both cohort and case-control studies" to clarify this in the "Diabetes and pneumonia" sub-section of the Results section, page 10 of the manuscript.** 18. Interpretation. "…with greater risks reported in studies … any pneumonia diagnosis". Is it indeed the case that studies of general diabetes have greater risks? This is unsupported in the results; I suggest performing meta-regression if possible and computing the ratio of RRs with associated CIs. **We thank Reviewer 1 for this comment and apologize if this statement was not clear. We were attempting to highlight the fact that subgroup analyses that were stratified by type 2 diabetes versus diabetes in general suggested a slightly stronger association among studies of diabetes in general (pooled RR: 1.70, 95% CI: 1.59, 1.82) than in those where exposure was restricted to type 2 diabetes (pooled RR: 1.48, 95% CI: 1.26, 1.74). This stratified analysis is presented in e-Figure 1. As noted above, we now state that similar results were obtained when stratifying by outcome definition. Due to word limit constraints, we have removed this sentence from the Interpretation section.** 19. Interpretation. "Physicians may want to … preventative measures". I am only convinced of this if the authors are able to demonstrate that absolute risk increases are great. As authors themselves asserted, CAP baseline risk is low. I suggest illustrating based on assumed baseline risks, what the absolute risk increase would be.

	We thank Reviewer 1 for this comment. While the baseline risk of CAP in patients with type 2 diabetes is sufficiently low to use the rare disease assumption to estimate the RR from the OR, their lifetime risk is higher, which suggests a potentially clinically important increased risk. We have revised the second paragraph of the "Interpretation" section to underscore that our findings support current treatment guidelines regarding the use of preventative measures in this population. The paragraph now reads "Pneumococcal and influenza vaccination are recommended by most guidelines and are suggested as a cost-effective strategy to prevent CAP in patients with type 2 diabetes. Although the included evidence contains important limitations, our results are compatible with current clinical treatment guidelines. The increased risk of CAP in patients with type 2 diabetes should be taken into consideration in clinical practice, and prevention of pneumonia should be discussed by physicians." 20. Interpretation. "Our results support…in these patients" I am a bit puzzled to read this paragraph since the evidence base consists of studies with serious risk of bias. There is for me too much uncertainty in the putative causal relationship to assert that 'the results support the hypothesis'. **We agree with Reviewer 1 that this sentence may have been strongly worded given the quality of the data. We have modified this sentence which now reads "The specific biological mechanism behind the increased risk of CAP in patients with type 2 diabetes has not been established". We have also modified our conclusion which now reads "The available evidence suggests that type 2 diabetes is associated with an increased risk of CAP. However, this evidence is from studies at serious risk of bias, and additional high-quality studies are needed to confirm these findings. While awaiting such studies, patients should be informed to seek medical attention promptly if they develop symptoms to facilitate early detection and treatment of CAP given its associated morbidity and mortality. Physicians and patients should be aware of the importance of attaining glycemic control to prevent resulting infections in this patient population." Please refer to Comment #6 of the Manuscript meeting, Comment #8 from Reviewer 1.** 21. Conclusion. "As hyperglycemia appears…patient population" this statement is unsupported by this systematic review. I recommend to remove this. **We have removed this part of the sentence on page 15 of the manuscript.** 22. e-Figure 5: I am not sure whether I agree with the observation of funnel plot asymmetry by the authors. It seems to be rather symmetrical; but I am open to discussion as to why this is indicative of publication bias. **We thank Reviewer 1 for pointing this out. In fact, the asymmetry was mostly driven by one small study. We have modified our explanation of this observation in the Results in the "Diabetes and Pneumonia" subsection on page 10. In addition, please see our response to Comment #6 from the Manuscript meeting.**
Reviewer 2	Bhagirath Singh
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General comments	In this manuscript the authors have perform systematic review and meta-analysis

(author response in bold)	of studies done over the past 70 years on type 2 diabetes (T2D) and community-acquired pneumonia (CAP). Overall the analysis and conclusions confirm the observational data from a larger number of studies that authors have reviewed. However, there are number of critical points that should to be addressed by the authors: 1. Type 2 diabetes impairs host immune responses that may allow development of CAP in these subjects. This could be strongly impacted by patients' age and sex. Due to the age-related changes the older patients are more likely to have impaired immune responses that may cause rapid CAP development. Therefore, authors should analyze the data in Table 1 and 2 to determine the role of age and sex related factors in CAP. It will be important to analyze if these factors contribute to CAP. **We agree that it would be interesting to examine the role of age and sex in the association between type 2 diabetes and community-acquired pneumonia. However, we were limited to the aggregate data presented in the published papers, and there were insufficient data (and data variability) to examine how the distributions of these characteristics impacted study-specific measures of association. We now discuss this issue in our revised limitations paragraph on page 14, which now reads "Eighth, due to insufficient data and data variability, we were unable to examine how the distributions of characteristics such as age and sex impacted study-specific measures of association".** 2. The authors have not defined and discussed the 'publication bias' in the context of studies they analyzed in the manuscript. This should be clarified and to show if there is evidence of publication bias in the reported studies using appropriate methodology. This is critical if no information is available of the unpublished data or the study may not have identified all the relevant factors as how the data was collected. **We thank Reviewer 2 for this comment. We now defined small-study effects on page 7 of the revised manuscript, which now reads "Small-study effects, i.e. where smaller studies may show larger treatment effects in a meta-analysis, were assessed via visual inspection of funnel plots" , and have added a reference for further details. We also specify that the asymmetry in the funnel plot (and our conclusion of the potential presence of small-study effects) appears to be driven by one small study. We have added details regarding this issue in the "Diabetes and pneumonia" sub-section of the Results on page 10 and we discuss this issue as part of our revised Limitations on page 14.** 3. The authors should be consistent to describe the data they analyzed. In various places in the manuscript authors have described the same data as "low quality" (page 4, line 42), "moderate quality" (page 14, line 15), "low to moderate quality" (page 13, line 32) etc. This qualitative description of the data and its inclusion in Supplemental e-Table 4 in a highly subjective manner further complicates the value of this meta-analysis. **We agree with Reviewer 2 that this may be confusing to read. We have modified the terminology through the manuscript, so it refers to "serious risk of bias". This applies to the sentences identified by the reviewer. In addition, please see our response to Comment #5 from Reviewer 1.**

	4. Appropriate figure legends must be provided for all the figures in the manuscript. This is critical to understand the data presented in each figure since not all information is included in the text of the manuscript. **We thank Reviewer 2 for this comment. We have expanded all figure legends to ensure that figures are 'stand alone' and have the information needed to understand the data presented. The details are available on page 22 for Table 1, page 25 for Table 2, page 26 for Figure 2, and below each e-figure in the Supplemental material.**