PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The association between benzodiazepine use and risks of chronic-onset post-stroke pneumonia: A population-based cohort study
AUTHORS	Lin, Shu-Man; Yang, Shih-Hsien; Liang, Chung-Chao; Huang, Huei-Kai; Loh, Ching-Hui

VERSION 1 – REVIEW

REVIEWER	Connie Wong Monash University, Australia
REVIEW RETURNED	15-Jun-2018

GENERAL COMMENTS	This is a well-designed large population-based cohort study with thorough and transparent methodology to assess the effect of benzodiazepines on post-stroke pneumonia. The results were presented clearly and not overstated. However, please include the following in your discussion of your data: 1) How does stroke impact on the effect of BZDs on pneumonia risk? The authors referred to 3 observational studies in the general population, with risk ratios ranging widely. How does your result here fit into the general population? 2) What is the effect of BZDs dosage? It appears from your data that the use rather than the dosage or duration of BZDs elevates the risk of pneumonia. This should be discussed in reference to the proposed mechanisms. 3) Please alter text in the introduction: "As modulators of the γ-amino butyric acid type A receptor (GABAA), benzodiazepines (BZDs) are widely used for treating a variety of conditions, such as insomnia, anxiety, muscle spasm, and epilepsy8, previous studies have postulated that BZDs may increase the risk of pneumonia. The cause may be related to nocturnal and daytime sedation, an increased risk of aspiration, and the possible depression of immune cells..."

REVIEWER	Karl Matz Danube University Krems, Austria
REVIEW RETURNED	27-Jun-2018

GENERAL COMMENTS	The authors report a large retrospective analysis of insurance data of a large Taiwanese patient cohort. They found an independent association of pneumonia with benzodiazepine prescriptions in stroke survivors. The problem of the case control study is the definition of cases: pneumonia cases were recorded as attributed diagnoses in the

	insurance data base at non specified time points after stroke. Post stroke pneumonia is defined as pneumonia occurring during the first two weeks after the stroke event, later cases during the hospital stays are called hospital acquired pneumonia. Thus, the cases recorded include possible post stroke pneumonia hospital acquired pneumonia and even community acquired pneumonia to undefined amounts. The study therefor can only state the occurrence of pneumonia in general is associated with benzodiazepine prescription. Consequently, it is not known if this association is seen in other patient groups not only in stroke survivors

REVIEWER	Yousef Hannawi, MD The Ohio State University, USA.
REVIEW RETURNED	12-Jul-2018

GENERAL COMMENTS	In this study, authors investigate the relationship between benzodiazepine use and the risk of pneumonia among patients with stroke. They report an increased incidence of pneumonia following stroke chronically in benzodiazepine users. The study reports new interesting findings. However, there are multiple methodological issues that need to be addressed: 1- Post stroke pneumonia, stroke-associated pneumonia, is a term that is used to describe pneumonia that occurs following stroke most commonly acutely typically within the first week (Smith et al, Stroke 2015). The pathophysiology of this pneumonia is attributed to the combination of stroke-induced immunodepression in the setting of aspiration which can be gross or microaspiration. Following stroke recovery, the effect of stroke induced immunodepression starts to decrease and pneumonia occurrence decreases subsequently. Thus, the effect of stroke starts to decrease except for the presence of aspiration. The major issue with this study is that in-hospital pneumonia (major proportion of pneumonia following stroke) is being eliminated and selection of pneumonia is in the chronic phase. Such pneumonia occurring late after stroke may be due to other pathologies separate from the stroke itself. Additionally, the adjustment for baseline variables (propensity matching) is only done at time of stroke for variables that were present within a year prior to the index date (stroke occurrence) which may long predates the occurrence of pneumonia. 2- As mentioned above, since pneumonia is considered long after the stroke, comorobidities may have occurred after stroke and they were not accounted for in the multivariate analysis. It will be needed to add the new Charlson comorbidity index at time of pneumonia diagnosis to the multivariate analysis. 3- Another concern is that many of the pneumonia cases were excluded if they did not lead to hospitalization which may have confounded the results. Are these cases of pneumonia the same for the both groups? 4- Since the BDZ may increase sleepiness and potentially aspiration. Is it possible based on the ICD codes and the available database to divide pneumonia into aspiration vs non-aspiration to understand the incidence and the effect of BDZ on each of them? This may add some explanation to the pathophysiology of pneumonia following stroke in chronic benzodiazepine users. 5- The indication for benzodiazepine prescription is missing. Another finding which increases the concern about the indication for benzodiazepine prescription is that at baseline, more patients were on anxiolytics prior to stroke in the group that were not given

	BDZ after stroke (as seen in the table). This means there was a shift in the opposite directions to become a benzodiazepine user following the stroke. This also raises the question about the need for the medication. Authors should be able to extract the diagnoses that led to prescribing benzodiazepines from the insurance claim data. 6- Given the rate of pneumonia is higher immediately after stroke; it will be interesting to report the numbers of pneumonia for the first year of follow up among (Benzodiazepine vs non-benzodiazepine) group. Since, the start of benzodiazepine use was defined after the index hospitalization. It was not clear to me whether the authors included only those who received benzodiazepines prior to pneumonia diagnosis. There is no mention of this. Is it possible that benzodiazepine use happened much later in the course following stroke and for some patients may have started even after the diagnosis of pneumonia?

VERSION 1 – AUTHOR RESPONSE

To Reviewer #1

Editor's and Reviewer's Comments	Our Response
This is a well-designed large population-based cohort study with thorough and transparent methodology to assess the effect of benzodiazepines on post-stroke pneumonia. The results were presented clearly and not overstated. However, please include the following in your discussion of your data:	Thank you for your kind comments and helpful suggestions.
1) How does stroke impact on the effect of BZDs on pneumonia risk? The authors referred to 3 observational studies in the general population, with risk ratios ranging widely. How does your result here fit into the general population?	Thank you for your question. In our revised manuscript, we have discussed the possible association and underlying mechanisms among stroke, BZD use, and pneumonia risk in the Discussion (P.14-15, Line 276-285). In addition, in our present study, we specifically evaluate the effect of BZDs on chronic-onset post-stroke pneumonia in stroke survivors [1]. This was not yet evaluated in any previous studies, and thus our study results cannot be applied directly to a general population. However, as pneumonia is one of the most common serious medical complications following stroke and can cause not only poor functional outcomes but also high mortality and financial burden, we believe that our study still features clinical value regarding the clinical management of patients after stroke. Reference: 1. Teramoto S. Novel preventive and therapuetic strategy for post-stroke pneumonia. Expert review of neurotherapeutics 2009;9(8):1187-200. doi: 10.1586/ern.09.72 [published Online First: 2009/08/14]

2) What is the effect of BZDs dosage? It appears from your data that the use rather than the dosage or duration of BZDs elevates the risk of pneumonia. This should be discussed in reference to the proposed mechanisms.	Thank you for your comments. In our initial study protocol, we planned to perform analyses according to the different cumulative doses of BZDs to evaluate whether a dose-effect relationship might exist. Unfortunately, in our revised manuscript, we did not find an obvious dose-effect relationship of BZD effect on the risk of contracting pneumonia. The significant association between pneumonia and low-dose BZD use was unexpected on account of the relatively low levels of associated drug exposure. This reminded us that potentially unidentified residual confounders could exist in non-randomized observational studies. Thus, further prospective clinical trials are necessary to determine the cause-and-effect relationship between post-stroke BZD use and risk of developing pneumonia. We have added this to our consideration of the study limitations in the Discussion section of our revised manuscript (P.16, Line 323-329). We hope that this statement can facilitate a more appropriate interpretation of our findings.
3) Please alter text in the introduction: "As modulators of the γ-amino butyric acid type A receptor (GABAA), benzodiazepines (BZDs) are widely used for treating a variety of conditions, such as insomnia, anxiety, muscle spasm, and epilepsy8, previous studies have postulated that BZDs may increase the risk of pneumonia. The cause may be related to nocturnal and daytime sedation, an increased risk of aspiration, and the possible depression of immune cells..."	We have amended this paragraph according to your suggestion. Thank you for your helpful comments and for giving us the opportunity to revise our manuscript.

To Reviewer #2

Editor's and Reviewer's Comments	**Our Response**
The authors report a large retrospective analysis of insurance data of a large Taiwanese patient cohort. They found an independent association of pneumonia with benzodiazepine prescriptions in stroke survivors. The problem of the case control study is the definition of cases: pneumonia cases were recorded as attributed diagnoses in the insurance data base at non specified time points after stroke. Post stroke pneumonia is defined as pneumonia occurring during the first two weeks after the stroke event, later cases during the hospital stays are called hospital acquired pneumonia. Thus, the cases recorded include possible post	Thank you for your insightful comments and for providing us with the opportunity to revise our manuscript. We apologize for the confusion caused by the indicated phrasing. To address your comments, acute-onset post-stroke pneumonia or stroke-associated pneumonia has been used to describe pneumonia that occurs early after stroke. The definition of pneumonia thus ranges across studies from occurring within the first 3 days, 1 week, 2 weeks, or 1 month following stroke [1-4]. However, our study aimed to evaluate the effect of BZDs in the chronic phase of post-stroke. The chronic-onset post-stroke pneumonia was defined as pneumonia that develops over 1 month after the stroke event[1]. Therefore, in our revised manuscript,

stroke pneumonia hospital acquired pneumonia and even community acquired pneumonia to undefined amounts. The study therefor can only state the occurrence of pneumonia in general is associated with benzodiazepine prescription. Consequently, it is not known if this association is seen in other patient groups not only in stroke survivors	we excluded patients who developed pneumonia within 30 days of stroke (P.8, Line 149-152). The effect of BZDs on the chronic-onset post-stroke pneumonia has not been evaluated by previous research; our study sought to address this dearth in the literature. We have amended the use of the term "post-stroke pneumonia" in our revised manuscript and replaced it with chronic-onset post-stroke pneumonia (P.3, Line 33; P.4, Line 59; P.5, Line 91; P.8, Line 146; P.12, Line 226; P.14, Line 260, 264; P.17, Line 341). In addition, as mentioned in your comment, our study specifically evaluated the effect of BZDs on chronic-onset post-stroke pneumonia in stroke survivors, which has hitherto yet to be evaluated in the literature. Thus, it is not known if our study results apply to other patient groups. However, as pneumonia is one of the most common serious medical complications following stroke and can cause not only poor functional outcomes but also high mortality and financial burden, we believe that our study still features clinical value regarding the clinical management of patients after stroke. Thank you for your insightful comments and suggestions. References: 1. Teramoto S. Novel preventive and therapuetic strategy for post-stroke pneumonia. Expert review of neurotherapeutics 2009;9(8):1187-200. doi: 10.1586/ern.09.72 [published Online First: 2009/08/14] 2. Hannawi Y, Hannawi B, Rao CP, et al. Stroke-associated pneumonia: major advances and obstacles. Cerebrovasc Dis 2013;35(5):430-43. doi: 10.1159/000350199 [published Online First: 2013/06/06] 3. Smith CJ, Kishore AK, Vail A, et al. Diagnosis of Stroke-Associated Pneumonia: Recommendations From the Pneumonia in Stroke Consensus Group. Stroke 2015;46(8):2335-40. doi: 10.1161/strokeaha.115.009617 [published Online First: 2015/06/27] 4. Hilker R, Poetter C, Findeisen N, et al. Nosocomial pneumonia after acute stroke: implications for neurological intensive care medicine. Stroke 2003;34(4):975-81. doi: 10.1161/01.str.0000063373.70993.cd [published Online First: 2003/03/15]

To Reviewer #3

Editor's and Reviewer's Comments	Our Response

In this study, authors investigate the relationship between benzodiazepine use and the risk of pneumonia among patients with stroke. They report an increased incidence of pneumonia following stroke chronically in benzodiazepine users. The study reports new interesting findings. However, there are multiple methodological issues that need to be addressed:	Thank you for your helpful comments and for giving us the opportunity to revise our manuscript.
1- Post stroke pneumonia, stroke-associated pneumonia, is a term that is used to describe pneumonia that occurs following stroke most commonly acutely typically within the first week (Smith et al, Stroke 2015). The pathophysiology of this pneumonia is attributed to the combination of stroke-induced immunodepression in the setting of aspiration which can be gross or microaspiration. Following stroke recovery, the effect of stroke induced immunodepression starts to decrease and pneumonia occurrence decreases subsequently. Thus, the effect of stroke starts to decrease except for the presence of aspiration. The major issue with this study is that in-hospital pneumonia (major proportion of pneumonia following stroke) is being eliminated and selection of pneumonia is in the chronic phase. Such pneumonia occurring late after stroke may be due to other pathologies separate from the stroke itself. Additionally, the adjustment for baseline variables (propensity matching) is only done at time of stroke for variables that were present within a year prior to the index date (stroke occurrence) which may long predates the occurrence of pneumonia.	Thank you for the insightful comments. We agree with your comment that the term “post-stroke pneumonia” or “stroke-associated pneumonia” is commonly used when pneumonia develops in the acute phase of post-stroke.[3] Previous studies have actually divided post-stroke pneumonia into two types according to its time of occurrence: acute-onset and chronic-onset.[1 2] During the chronic phase of post-stroke, the risk of contracting pneumonia among stroke survivors is still higher than among non-stroke patients owing to dysphagia or impaired swallowing reflex and the consequent silent aspiration or microaspiration into lower airways. Besides, immobilization, post-stroke disability, and cognitive impairment are also risk factors for chronic-onset post-stroke pneumonia.[1] In the present study, we aimed to evaluate the effect of BZDs in the chronic phase of post-stroke. The chronic-onset post-stroke pneumonia was defined as pneumonia that develops over 1 month after the stroke event[1]. Therefore, in our revised manuscript, we excluded patients who developed pneumonia within 30 days of stroke and focused on evaluating the risks of pneumonia occurring over 1 month after stroke (P.8, Line 149-152). The effect of BZDs on the chronic-onset post-stroke pneumonia has never been evaluated in previous studies; our study addresses this dearth in the literature. To avoid confusion, we clearly defined our study outcome as the chronic-onset post-stroke pneumonia (develops over 1 month after the stroke) in our revised manuscript (P.8, Line 145-152). We hope that such revision helps readers to interpret our findings more clearly and appropriately. Additionally, as per your suggestion, the Charlson comorbidity index at the time of pneumonia diagnosis or other end-point of follow-up were calculated, matched, and adjusted in our revised analyses. Please refer to the reply below (Question 2). Thank you for your insightful comments. References: 1. Teramoto S. Novel preventive and therapuetic strategy for post-stroke pneumonia. Expert review of neurotherapeutics 2009;9(8):1187-200. doi:

	10.1586/ern.09.72 [published Online First: 2009/08/14] 2. Hannawi Y, Hannawi B, Rao CP, et al. Stroke-associated pneumonia: major advances and obstacles. Cerebrovasc Dis 2013;35(5):430-43. doi: 10.1159/000350199 [published Online First: 2013/06/06] 3. Smith CJ, Kishore AK, Vail A, et al. Diagnosis of Stroke-Associated Pneumonia: Recommendations From the Pneumonia in Stroke Consensus Group. Stroke 2015;46(8):2335-40. doi: 10.1161/strokeaha.115.009617 [published Online First: 2015/06/27]
2- As mentioned above, since pneumonia is considered long after the stroke, comorobidities may have occurred after stroke and they were not accounted for in the multivariate analysis. It will be needed to add the new Charlson comorbidity index at time of pneumonia diagnosis to the multivariate analysis.	Thank you for your suggestion. We absolutely agree with your viewpoint that some comorbidities may occur after stroke and possibly confound the association between BZD use and risk of contracting pneumonia and that these should be accounted for in our analyses. Therefore, as per your suggestion, we have calculated another Charlson comorbidity index at the time of pneumonia diagnosis (for pneumonia cases) or other end-point of follow-up (for those without pneumonia). The Charlson comorbidity index at the end-point of follow-up was calculated using the data on comorbidities from the year prior to the end-point date (P.9, Line 181-184). This Charlson comorbidity index was then included when performing propensity score matching, and was adjusted in multivariate Cox proportional hazard regression models. The results presented in the revised version were still similar to those found by our previous version and the conclusion was the same: BZD use is associated with an increased risk of pneumonia in stroke patients. These consistent results further strengthen our findings.
3- Another concern is that many of the pneumonia cases were excluded if they did not lead to hospitalization which may have confounded the results. Are these cases of pneumonia the same for the both groups?	As per your concern, to determine whether including pneumonia diagnoses made in an outpatient service may have influenced the study outcome or not, we performed a sensitivity analysis. The sensitivity analysis was conducted considering the pneumonia event diagnosed during the follow-up period regardless of whether the diagnosis was rendered by an inpatient or outpatient service. The results still revealed that BZD use was independently associated with increased risks of developing pneumonia (adjusted HR = 1.94, 95% CI = 1.77- 2.14, p < 0.001). The consistent results found by our sensitivity analysis further strengthened findings. The sensitivity analysis has been mentioned in Methods section (P.8, Line 159-162) and the results were briefly summarized in the Results section (P.13, Line 252-257). The detailed statistical values are shown in the Supplementary materials (Supplementary Table S1).

4- Since the BDZ may increase sleepiness and potentially aspiration. Is it possible based on the ICD codes and the available database to divide pneumonia into aspiration vs non-aspiration to understand the incidence and the effect of BDZ on each of them? This may add some explanation to the pathophysiology of pneumonia following stroke in chronic benzodiazepine users.	Thank you for your suggestion. Unfortunately, we could not obtain details from the medical records of the patients and therefore could not analyse medical histories to gain insight into the exact mechanisms of pneumonia contraction. There was no reliable method to distinguish between aspiration and non-aspiration pneumonia using our claims-based data. We have added this point to our discussion on study limitations in the revised manuscript (P.16, Line 321-323).
5- The indication for benzodiazepine prescription is missing. Another finding which increases the concern about the indication for benzodiazepine prescription is that at baseline, more patients were on anxiolytics prior to stroke in the group that were not given BDZ after stroke (as seen in the table). This means there was a shift in the opposite directions to become a benzodiazepine user following the stroke. This also raises the question about the need for the medication. Authors should be able to extract the diagnoses that led to prescribing benzodiazepines from the insurance claim data.	Thank you for your comments. We have summarized the possible indication of BZD prescription in the BZD cohort by obtaining the diagnoses which had been made during the follow-up period. In the BZD cohort, 35.8% patients had been diagnosed with insomnia, 25.7% with anxiety, 12.9% with depression, 8.1% with epilepsy, 3.2% with muscle spasm, and 2.5% with delirium. We recognize that possible confounding by indication may exist. Unfortunately, it is hard to completely avoid such indication bias in observational studies that evaluate the effect of medication or intervention. Thus, we have acknowledged this problem in our discussion of limitations in the revised manuscript and concluded that further prospective studies or clinical trials are necessary to determine the cause-and-effect relationship between post-stroke BZD use and the pneumonia risk (P.16, Line 324-329). Thank you very much for your having brought this to our attention.
6- Given the rate of pneumonia is higher immediately after stroke; it will be interesting to report the numbers of pneumonia for the first year of follow up among (Benzodiazepine vs non-benzodiazepine) group. Since, the start of benzodiazepine use was defined after the index hospitalization. It was not clear to me whether the authors included only those who received benzodiazepines prior to pneumonia diagnosis. There is no mention of this. Is it possible that benzodiazepine use happened much later in the course following stroke and for some patients may have started even after the diagnosis of pneumonia?	As per your suggestion, we have performed the analyses for the comparison of pneumonia risks within the first year of stroke. There were 271 (7.2%) and 184 (4.9%) patients who developed pneumonia in BZD and non-BZD cohorts, respectively, within the first year of stroke. Compared with the non-BZD cohort, the BZD cohort still featured higher risks of developing pneumonia (adjusted HR, 1.66 [95% CI: 1.37- 2.02, $p < 0.001$]). The results concerning the specific evaluation of the pneumonia risk factors in the first year were consistent with the overall analyses. In addition, we apologize for the confusion caused by the original manuscript. In our study design, the BZD cohort only included those who received BZDs during the follow-up period (from index date to end-point date, including the date of first occurrence of pneumonia, death, or until December 31, 2013) (P.7, Line 135; P.8, Line 154-156). Therefore, for cases of pneumonia, the BZDs were counted only when being used prior to pneumonia diagnosis. We thank you for your careful review and for providing us with the

	opportunity to further improve our manuscript in the revision process.

References
1. Teramoto S. Novel preventive and therapuetic strategy for post-stroke pneumonia. Expert review of neurotherapeutics 2009;9(8):1187-200. doi: 10.1586/ern.09.72 [published Online First: 2009/08/14]
2. Hannawi Y, Hannawi B, Rao CP, et al. Stroke-associated pneumonia: major advances and obstacles. Cerebrovasc Dis 2013;35(5):430-43. doi: 10.1159/000350199 [published Online First: 2013/06/06]
3. Smith CJ, Kishore AK, Vail A, et al. Diagnosis of Stroke-Associated Pneumonia: Recommendations From the Pneumonia in Stroke Consensus Group. Stroke 2015;46(8):2335-40. doi: 10.1161/strokeaha.115.009617 [published Online First: 2015/06/27]
4. Hilker R, Poetter C, Findeisen N, et al. Nosocomial pneumonia after acute stroke: implications for neurological intensive care medicine. Stroke 2003;34(4):975-81. doi: 10.1161/01.str.0000063373.70993.cd [published Online First: 2003/03/15]

VERSION 2 – REVIEW

REVIEWER	Connie Wong Monash University, Australia
REVIEW RETURNED	17-Oct-2018

GENERAL COMMENTS	No further comments.

REVIEWER	Karl Matz Danube University Krems Austria
REVIEW RETURNED	08-Nov-2018

GENERAL COMMENTS	Definition of outcome , ie. chronic post stroke pneumonia is now appropriate.

REVIEWER	Yousef Hannawi The Ohio State University
REVIEW RETURNED	14-Nov-2018

GENERAL COMMENTS	In this revised manuscript, authors report on the association between benzodiazepine use and pneumonia risk among patients with stroke. Authors responded well to the reviewer comments and revised their manuscript accordingly. The revised manuscript has much improved compared to the previous version. In particular the noted following changes ensure the results further: first, inclusion of only chronic onset pneumonia when immunodepression has started to subside and changing the naming from stroke-associated pneumonia to chronic post-stroke pneumonia as the latter is more consistent with the current analysis. Second, including the Charlson comorbidity index at time of pneumonia diagnosis also ensures some adjustment for some of the baseline comorbidities. Third, adding sensitivity analysis for outpatient treated pneumonia will ensure further the reliability of the results. There, however, remain two limitations. These limitations are inherited to the retrospective design and sample nature of de-identified insurance claim data. These limitations necessitate

	future prospective studies to evaluate any underlying biases as suggested by the authors in their revision. First: the lack of data to discriminate the cause of pneumonia aspiration vs non-aspiration which makes it harder to link benzodiazepine use to an underling biological mechanism leading to pneumonia. Second, the inability to completely adjust for the underlying pathology necessitating benzodiazepine use. This may in part explain the lack of association of BDZ dose and pneumonia risk. Hence, I recommend the following minor changes to address these limitations: 1- Since this is mainly a chronic post stroke pneumonia study. Please add this to the title to read chronic post stroke pneumonia. 2- In the discussion section, on page 16, I would add a language to the unidentified residual confounders effect (i.e. effect of the underling etiologies needing BDZ prescription, other exposures, etc.) This will help address the effect of the unmeasured biases. In addition, explain further the design of these future studies to address these biases, this will help better inform the readers.

VERSION 2 – AUTHOR RESPONSE

To Reviewer #2

Editor's and Reviewer's Comments	Our Response
Definition of outcome , ie. chronic post stroke pneumonia is now appropriate.	Thank you for your previous helpful comments and suggestions.

To Reviewer #3

Editor's and Reviewer's Comments	Our Response
In this revised manuscript, authors report on the association between benzodiazepine use and pneumonia risk among patients with stroke. Authors responded well to the reviewer comments and revised their manuscript accordingly. The revised manuscript has much improved compared to the previous version. In particular the noted following changes ensure the results further: first, inclusion of only chronic onset pneumonia when immunodepression has started to subside and changing the naming from stroke-associated pneumonia to chronic post-stroke pneumonia as the latter is more consistent with the current analysis. Second, including the Charlson comorbidity index at time of pneumonia diagnosis also ensures some adjustment for some of the baseline comorbidities. Third, adding sensitivity analysis for outpatient treated pneumonia will ensure further the reliability of the results. There, however, remain two limitations. These limitations are inherited to the retrospective design and sample nature of	Thank you for your review and comments. We have revised our manuscript as per your suggestions, and hope that the current version of revised manuscript is satisfactory for publication.

de-identified insurance claim data. These limitations necessitate future prospective studies to evaluate any underlying biases as suggested by the authors in their revision. First: the lack of data to discriminate the cause of pneumonia aspiration vs non-aspiration which makes it harder to link benzodiazepine use to an underling biological mechanism leading to pneumonia. Second, the inability to completely adjust for the underlying pathology necessitating benzodiazepine use. This may in part explain the lack of association of BDZ dose and pneumonia risk. Hence, I recommend the following minor changes to address these limitations:	
1- Since this is mainly a chronic post stroke pneumonia study. Please add this to the title to read chronic post stroke pneumonia.	The title was now corrected as “The association between benzodiazepine use and risks of chronic-onset post-stroke pneumonia: A population-based cohort study.” Thank you for your suggestion.
2- In the discussion section, on page 16, I would add a language to the unidentified residual confounders effect (i.e. effect of the underling etiologies needing BDZ prescription, other exposures, etc.) This will help address the effect of the unmeasured biases. In addition, explain further the design of these future studies to address these biases, this will help better inform the readers.	We have revised the Discussion section as per your suggestions (Page 15). Thank you for your comments.