PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk of Obstructive Sleep Apnea in Patients with Rheumatoid Arthritis: A Nationwide Population-Based Retrospective Cohort Study
AUTHORS	Shen, Te-Chun; Hang, Liang-Wen; Liang, Shin-Jye; Huang, Chien-Chung; Lin, Cheng-Li; Tu, Chih-Yen; Hsia, Te-Chun; Shih, Chuen-Ming; Hsu, Wu-Huei; Sung, Fung-Chang

VERSION 1 - REVIEW

REVIEWER	PICKERING Marie-Eva, MD Rheumatology Department, Hospices Civils de Lyon, Laboratoire INSERM UMR 1033, France
REVIEW RETURNED	11-Jul-2016

GENERAL COMMENTS	This is an interesting retrospective cohort study based on a large population. The main problem with the study is that the primary endpoint is not properly defined. The gold standard of OSA diagnosis is polysomnography : the ICD 9 was used to define OSA and is not sufficient to assess the objective presence of OSA. There is a real need for prospective studies analyzing the link between RA and OSA, including confounding factors, not only of obesity, but also of BMI as a continuous variable.

REVIEWER	Patricia Katz University of California San Francisco USA
REVIEW RETURNED	03-Aug-2016

GENERAL COMMENTS	A major factor in evaluating studies using administrative data sets is the validity of the diagnosis information. It appears from the Discussion section that the RA diagnosis was peer-reviewed in some manner, and that cases were required to have 2 diagnoses in a year to be classified as RA. This information should be more clearly explained in the Methods section. Similarly, information on the validity of the OSA diagnosis is needed. At a minimum, some type of sensitivity analysis should be conducted; for example, requiring two diagnoses in one year or requiring a diagnosis following an indication of physician claim for OSA testing. Do the records represent independent patient observations, or is it possible that patients are represented by more than one observation in the data set? Independent observations would be preferable, but if the latter, analyses need to take multiple observations per person

	into account. Minor: • In reviewing the literature, it would be helpful to identify which, if any, studies have identified OSA using objective measures rather than self-report. • In the discussion, the authors state that the data are valuable because the study population is primarily female. RA is more prevalent in females, so this is what would be expected from an RA cohort. • Page 15, top paragraph: what is meant by "inadequate lifestyles"?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Comments to the Author:
This is an interesting retrospective cohort study based on a large population. The main problem with the study is that the primary endpoint is not properly defined. The gold standard of OSA diagnosis is polysomnography: the ICD 9 was used to define OSA and is not sufficient to assess the objective presence of OSA. There is a real need for prospective studies analyzing the link between RA and OSA, including confounding factors, not only of obesity, but also of BMI as a continuous variable.
Reply:
Thanks for the inspirational comment. Yes, the gold standard of OSA diagnosis is polysomnography (PSG); however, it is expensive and not widely available. Therefore, the physicians may reach the diagnosis just depended on self-reported symptoms or results of screening questionnaires (Berlin questionnaire or Wisconsin sleep questionnaire…). Anyway, we would like to modify our primary endpoint by changing the definition of OSA to: “people with a diagnosis of OSA (ICD-9-CM codes 327.23, 780.51, 780.53, and 780.57) following a diagnostic examination of polysomnography (PSG, examination codes: 17008A and 17008B in NHIRD).” (Please see page 10 lines 4−6.). We hope you will accept the new definition.
In addition, information on height and body weight was not provided in the database we used. We therefore unable to calculate BMI. We have stated in the revision as a study limitation:
“the NHIRD did not provide detailed information on the severity of RA or OSA, and potential confounding factors, such as height, body weight, family history of RA and/or OSA, and life styles including drinking and smoking habits.” (Please see page 17 lines 1−5.)

Reviewer: 2
Comments to the Author
Major points:
1) A major factor in evaluating studies using administrative data sets is the validity of the diagnosis information. It appears from the Discussion section that the RA diagnosis was peer-reviewed in some manner, and that cases were required to have 2 diagnoses in a year to be classified as RA. This information should be more clearly explained in the Methods section.
Reply:
Thanks for the comment. We used the “Catastrophic data file” to identified RA patients instead of “Those with ≥2 diagnoses in a year were identified to have RA”. A disease listed in the “Catastrophic data file” requires a careful evaluation by physician and the permit from the insurance. In the revised manuscript, we have stated:
“This cohort study used reimbursement claims data from the Longitudinal Health Insurance Database for Catastrophic Illness Patients (LHID-CIP), which is part of the NHIRD used for research purposes.” (Please see page 9 lines 1−3.)
In the revised manuscript, OSA was identified following your kindly suggestion. We have stated:

“The diagnostic criteria of OSA was that people with a diagnosis of OSA (ICD-9-CM codes 327.23, 780.51, 780.53, and 780.57) following a diagnostic examination of polysomnography (PSG, examination codes: 17008A and 17008B in NHIRD).” (Please see page 10 lines 3−6.)
In addition, we identified selected comorbidities by using “Those with ≥2 diagnoses in a year were identified to have the comorbidity”.

2) Similarly, information on the validity of the OSA diagnosis is needed. At a minimum, some type of sensitivity analysis should be conducted; for example, requiring two diagnoses in one year or requiring a diagnosis following an indication of physician claim for OSA testing.
Reply:
Thanks for the comment. We would like to follow your kindly suggestion. We have modified our definition of OSA as: “people with a diagnosis of OSA (ICD-9-CM codes 327.23, 780.51, 780.53, and 780.57) following a diagnostic examination of polysomnography (PSG, examination codes: 17008A and 17008B in NHIRD).” (Please see page 10 lines 4−6.). We hope you may accept the new definition. In the revision of the manuscript, we have stated:
“The diagnostic criteria of OSA was that people with a diagnosis of OSA (ICD-9-CM codes 327.23, 780.51, 780.53, and 780.57) following a diagnostic examination of polysomnography (PSG, examination codes: 17008A and 17008B in NHIRD).” (Please see page 10 lines 3−6.).

3) Do the records represent independent patient observations, or is it possible that patients are represented by more than one observation in the data set? Independent observations would be preferable, but if the latter, analyses need to take multiple observations per person into account.
Reply:
Thank you for raising the query. Yes, the records represent independent patient observations.

Minor points:
1) In reviewing the literature, it would be helpful to identify which, if any, studies have identified OSA using objective measures rather than self-report.
Reply:
Thank you for raising this significant point. In fact, the gold standard of OSA diagnosis is PSG; however, it is expensive and not widely available. Therefore, the clinicians may reach the diagnosis just depended on self-reported symptoms or results of screening questionnaires (Berlin questionnaire or Wisconsin sleep questionnaire…). There are many publications using screening questionnaires to identify the possible OSA, in particular for large scale studies (1−3).
We have made a search in PubMed for “rheumatoid arthritis” combined “sleep apnea” (2016/09/20, 70 Results) and found 6 relative articles (4−9). The largest study with RA cases (N=164) and non-RA controls (N=328) used Berlin Sleep Questionnaire (self-report, subjective measures) to evaluate sleep apnea. Other 5 small scale studies used PSG to confirm sleep apnea in RA (N= 8−62; sleep apnea rate: 37−100%). Collectively, it is hard to use PSG results to confirm OSA in a large scale study.
Reference:
1. Fawale MB, Ibigbami O, Ismail I, et al. Risk of obstructive sleep apnea, excessive daytime sleepiness and depressive symptoms in a Nigerian elderly population. Sleep Sci 2016; 9: 106−11. [Berlin Sleep Questionnaire]
2. Farajzadeh M, Hosseini M, Mohtashami J, et al. The Association Between Obstructive Sleep Apnea and Depression in Older Adults. Nurs Midwifery Stud 2016; 5: e32585. [Berlin Sleep Questionnaire]
3. Na-Rungsri K, Lertmaharit S, Lohsoonthorn V, et al. Obstructive sleep apnea and the risk of preterm delivery. Sleep Breath 2016; 20: 1111−7. [Berlin Sleep Questionnaire]
4. Gjevre JA, Taylor-Gjevre RM, Nair BV, et al. Do sleepy rheumatoid arthritis patients have a sleep disorder? Musculoskeletal Care 2012; 10: 187−95. [17 OSA in 25 RA cases - PSG] (Ref #21)
5. Mutoh T, Okuda Y, Mokuda S, et al. Study on the frequency and risk factors of moderate-to-severe sleep apnea syndrome in rheumatoid arthritis. Mod Rheumatol 2016; 26: 681–4. [23 OSA in 62 RA

hospitalized cases - PSG] (Ref #22)
6. Reading SR, Crowson CS, Rodeheffer RJ, et al. Do rheumatoid arthritis patients have a higher risk for sleep apnea? J Rheumatol 2009; 36: 1869−72. [23 possible OSA in 164 RA cases and 30 possible OSA in 328 non-RA cases (total 53 possible OSA in 492 cases) - Berlin Sleep Questionnaire] (Ref #23)
7. Oyama T, Okuda Y, Oyama H, et al. Sleep apnea syndrome in rheumatoid arthritis (RA) patients complicated with cervical and temporomandibular lesions. Ryumachi 1995; 35: 3−8. [5 OSA in 10 RA cases with cervical and temporomandibular lesions - PSG] (Ref #32)
8. Shoda N, Seichi A, Takeshita K, et al. Sleep apnea in rheumatoid arthritis patients with occipitocervical lesions: the prevalence and associated radiographic features. Eur Spine J 2009; 18: 905−10. [23 OSA in 29 RA cases with occipitocervical lesions - PSG] (Ref #33)
9. Ataka H, Tanno T, Miyashita T, et al. Occipitocervical fusion has potential to improve sleep apnea in patients with rheumatoid arthritis and upper cervical lesions. Spine 2010; 35: E971–5. [8 OSA in 8 RA cases with upper cervical lesions who underwent occipitocervical fusion - PSG] (Ref #34)

2) In the discussion, the authors state that the data are valuable because the study population is primarily female. RA is more prevalent in females, so this is what would be expected from an RA cohort.
Reply:
Thanks for the comment. Yes, RA is a disorder more prevalent in women than in men in most of populations. It was 77.6% in this study. However, in most studies to evaluate the risk of OSA, the study populations were male or equal predominant. The incidence of OSA in a large female population has less been evaluated. We have revised the statements as:
“In addition, most studies to evaluate the risk of OSA were male or equal predominant. This study population, however, was predominantly composed of female individuals (77.6 %). Therefore, the data obtained is valuable because the incidence of OSA in a large female population has less been reported.” (Please see page 14 last 5 lines.)

3) Page 15, top paragraph: what is meant by "inadequate lifestyles"?
Reply:
Thank you for raising the query. The inadequate lifestyles may include fat and sugar-heavy diet, alcohol consumption, heavy smoking, or lack of exercise. We have revised the sentence as:
“In addition, genetic factors, environmental exposures, shared comorbidities, and inadequate lifestyles such as fat and sugar-heavy diet, alcohol consumption, heavy smoking, or lack of exercise may contribute to the occurrence of OSA in patients with RA.” (Please see page 15 lines 4−7.)

VERSION 2 – REVIEW

REVIEWER	Paricia Katz University of California San Francisco
REVIEW RETURNED	11-Oct-2016

GENERAL COMMENTS	The authors are commended on the revision of the manuscript. They may wish to note that their estimates of the elevated risk of OSA are likely conservative, due to the requirement for PSG to define OSA. It is likely that many people with OSA do not receive PSG. Further, because of the higher overall prevalence of OSA in men, it is likely that OSA is disproportionately under-recognized in women.

VERSION 2 – AUTHOR RESPONSE

Comment to the Author:
The authors are commended on the revision of the manuscript.
They may wish to note that their estimates of the elevated risk of OSA are likely conservative, due to the requirement for PSG to define OSA. It is likely that many people with OSA do not receive PSG. Further, because of the higher overall prevalence of OSA in men, it is likely that OSA is disproportionately under-recognized in women.
Reply:
Thanks for the suggestion. We totally agree with your viewpoints. We would like to state these in the Discussion section:
“In addition, our estimates of the elevated risk of OSA are likely conservative, due to the requirement for PSG to define OSA. It is likely that many people with OSA do not receive PSG. Further, because of the higher overall prevalence of OSA in men, it is likely that OSA is disproportionately under-recognized in women.” (Please see page 17 lines 5−9.)