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Original Article

Higher risk of psoriasis in people with obstructive sleep apnea: a meta-analysis

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Abstract: Objectives: The aim of this study was to evaluate the risk of psoriasis in people with objective sleep apnea. Methods: A meta-analysis of studies was conducted investigating the risk of psoriasis in people with objective sleep apnea according to meta-analyses rules. PubMed, EMBASE, Ovid and Cochrane libraries were searched from inception to 20 November 2018. Two assessors independently selected the eligible studies, and extracted data. Results: Three studies with a total of 85468 participants were identified. The random effects model was applied. The psoriasis risk in people with objective sleep apnea was increased compared to the controls. The risk ratio (RR) of psoriasis was 2.58 (95% confidence interval (95% CI) = 1.29-5.16). The I^2 value was 47.4% (p = 0.149), which indicated that there was no substantial heterogeneity. Conclusions: Patients with objective sleep apnea have a higher likelihood of psoriasis. Further studies are required to provide data for psoriasis area and severity index (PASI) scores, severity of objective sleep apnea, and different age and sex groups to illustrate if there is a higher risk of psoriasis is associated with these factors.

Keywords: Psoriasis, objective sleep apnea, OSA, meta-analysis, NOS

Introduction

Psoriasis is a persistent, immune-mediated inflammatory skin disease that affects 2-4% of the population worldwide [1]. Psoriasis is not only a skin disease, but also a multisystem disease. Increasing evidence demonstrates the association of psoriasis with metabolic syndrome, inflammatory bowel disease, dyslipidemia, cardiovascular diseases and so on [2, 3]. It is thought that 73% of people with psoriasis suffer from at least one comorbidity [4]. Obstructive sleep apnea (OSA) is a sleep disorder affecting 2-4% of men and 1-2% of women of middling age, whose clinical manifestations are headache when the patient wakes up, daytime sleepiness, night-time snoring and a decrease in cognitive function [5]. There is mounting interest in the link between psoriasis and sleep. The two-way interactions between OSA and psoriasis might exist [6]. On one hand, a higher proportion of individuals with psoriasis would be expected to experience OSA [7]. On the other hand, evidence has indicated that patients with OSA have a higher risk of several comorbidities, such as stroke, cardiovascular disease, insulin resistance, and type 2 diabetes mellitus. Several studies have revealed the possibility that psoriasis is higher in individuals with OSA compared to controls [8, 9]. There is a gap in the comprehensive analysis of the association between psoriasis and OSA. The aim of this study was to search the literature for publications matching inclusion criteria, and to assess the probability of psoriasis in people with OSA.

Materials and methods

Literature search

The MOOSE (Meta-analysis of Observational studies in Epidemiology) guidelines were followed to carry out and report this study. The PubMed, EMBASE, Ovid and Cochrane libraries were searched from inception to 20 November 2018. The search strategy included ("psoriasis" [MeSH Terms] OR "psoriasis") AND ("obstructive sleep apnea" OR "sleep apnea, obstructive" [MeSH Terms] OR ("sleep" [All

Fields] AND "apnea" [All Fields] AND "ob-structive" [All Fields]) OR "obstructive sleep apnea" [All Fields] OR ("obstructive" [All Fields] AND "sleep" [All Fields] AND "apnea" [All Fields]). Only English-language studies were included. The initial search yielded 88 references, and two additional articles were identified for inclusion through a manual search of article references.

Study selection

Observational studies (e.g., cohort studies, case-control, cross-sectional, and randomized controlled trial) were included to detect the link between OSA and psoriasis. The following inclusion criteria were selected: the article was written in English; the exposure group was comprised of those diagnosed with OSA and the controls without OSA; the diagnosis of OSA and psoriasis must be documented. Psoriasis must have been assessed in conjunction with OSA and reported numerically (percent values, numbers of patients affected, odds ratio [OR], hazard ratio (HR) or rate ratio [RR]). Exclusion criteria included: case reports, review articles, case series, and commentaries. Two independent examiners performed the literature search and read titles and abstracts impartially to determine eligibility, and when a disagreement occurred a third examiner was utilized. Two authors identified 33 articles for review in full, and excluded the publications with the following characteristics: full-length article inaccessible (n = 2), case report/comment/review article/letter/meeting abstract (n = 17), intervention studies (n = 3) and inappropriate subjects of study (n = 8). After these exclusions, three publications met the inclusion criteria and were appropriate for subsequent meta-analysis.

Data extraction and quality assessment

The data from included studies was extracted using a data-extraction form. For each study, the first author, study year, country, study design, subjects, and the risk estimates were recorded. Two assessors independently used the Newcastle-Ottawa Scale (NOS) to evaluate the quality of the included studies, where a study could be awarded a maximum of one star for each item within the selection and outcome domains, and a maximum of two stars for comparability. A study was considered to be of high quality if it was awarded seven stars or greater [10].

Statistical analysis

STATA software, version 14 (Version 14.0; Stata Corp., USA) was used to perform all analysis. The RR and 95% confidence interval (95% CI) were presented and heterogeneity was assessed using the I^2 statistic. An I^2 value indicated substantial heterogeneity. Using the RR data acquired from the publication results, the pooled RR for the prevalence of psoriasis in the patients with OSA was estimated. The OR value or HR value were approximately considered as RR value during to the low rate of psoriasis. The random effects analysis model was used to produce all pooled RRs due to study heterogeneity. Furthermore, in order to reduce the inclusion criteria bias and selector bias, a strict inclusion and exclusion criteria was established before this study, and two authors independently extracted the data based on the data form.

Results

In this study, literature was searched spanning a period from inception to the 20th November 2018 and synthesized data on 85468 study subjects was extracted. As displayed in **Figure 1**, 62 records were identified after removing duplicate data. The data from three studies were included in this meta-analysis [8, 9, 11]. The population of all three studies were from Greece, the USA and Taiwan. One case-control study was hospital-based, and the other two studies were based on the general population and Nurses' health study respectively. The features of the involved studies are described in **Table 1**. Furthermore, as shown in Table S1, all three studies were estimated using the NOS. None of the studies scored the maximum nine points using the modified NOS for quality assessment. The case-control study scored eight points. Furthermore, the other two studies conducted by Yang et al. [9] and Jeffrey et al. [11] scored eight and seven points respectively.

Of the three publications that studied patients with psoriasis, all described a higher prevalence or rate in patients with OSA than in controls without OSA. As illustrated in **Figure 2**, a random-effects model found that patients with

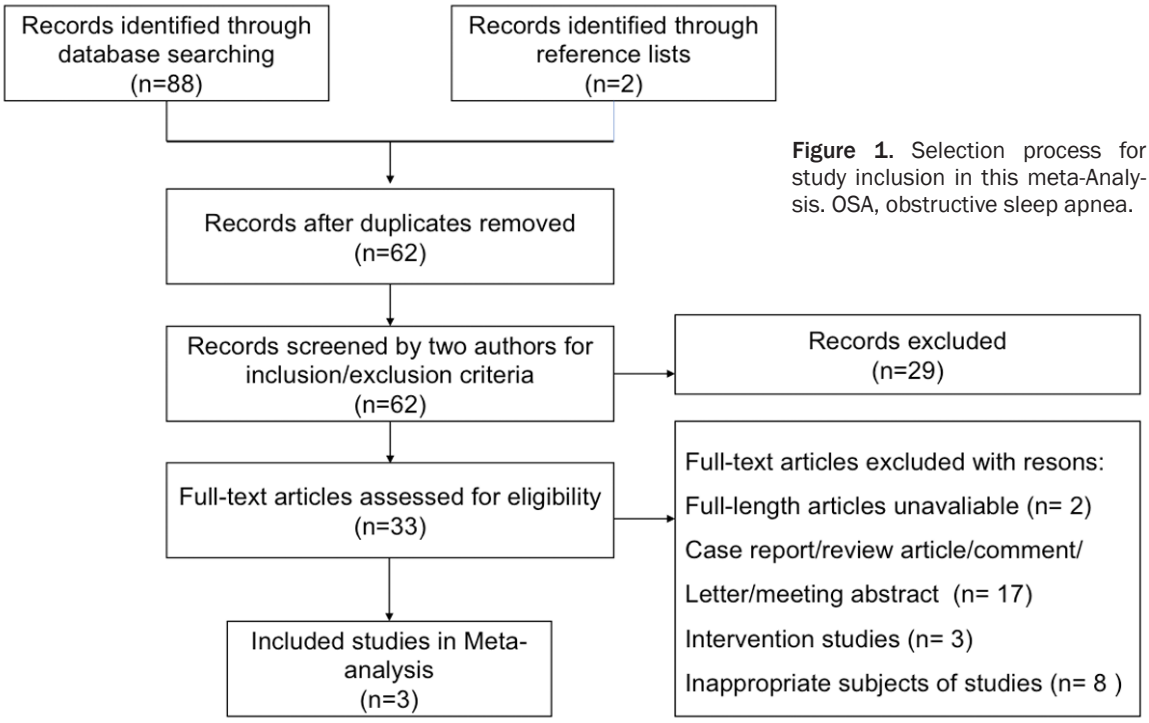

Figure 1. Selection process for study inclusion in this meta-Analysis. OSA, obstructive sleep apnea.

Table 1. Characteristics of included studies

Study, year	Country or region	Database used	Study subjects	Adjusted factors	Psoriasis*
Papadavid [12], 2017	Greece	Hospital patients	253 patients with OSA; 104 subjects without OSA	age, gender, obesity, hypertension, diabetes, smoking	13.31 (1.19-48.93)
Yang [13], 2012	Taiwan	Longitudinal Health Insuance Database 2000	2258 patients with OSA; 11255 matched comparison patients without OSA	age, BMI, shift worker, smoking, Alcohol, Physical activity, hypetension, Diabetes, Cardiovascular disease	1.91 (1.2-3.95)
Jeffrey [16], 2015	USA	Nurses' health study	71598 women in the Nurses' Health Study	geographic location, urbanization level, monthly income, obesity	2.3 (1.13-4.69)

OSA, obstructive sleep apnea; BMI, body mass index. *presented as adjusted risk ratio (95% confidence interval).

OSA were greater than two times as likely to have psoriasis than the controls that lacked OSA (pooled OR = 2.58; 95% CI = 1.29-5.16). There was no substantial heterogeneity across the studies (I^2 = 47.4%, p = 0.149). As showed in **Figure 3**, a funnel plot was used to evaluate publication bias through the Begg's test, and no significant asymmetry was detected, p = 0.296.

Discussion

Currently, many studies have presented that the link between psoriasis and the comorbidities [12-14]. Increasing evidence has indicated an association between psoriasis and sleep disorders, especially OSA [15, 16]. There was a larger prevalence of OSA in psoriatic patients (36%-81.8%) compared to in general population without psoriasis (2%-4%) [15]. The converse relationship was also demonstrated, which suggests that the chance of psoriasis in patients with OSA has compared to the population without OSA [8, 9, 11]. Similarly, in this study, the chance of psoriasis was greater in patients with OSA than the controls without OSA, with a RR of 2.58 (95% CI, 1.29-5.16). OSA is thought of a multifactorial inflammatory disease, characterized by sleep fragmentation, intermittent hypoxia and autonomic dysfunction. Which might cause abnormalities of the metabolic and cardiovascular systems [6]. It not clear whether or not OSA is a risk factor for the development of psoriasis. The potential mechanisms of OSA account for psoriasis are elaborated on below.

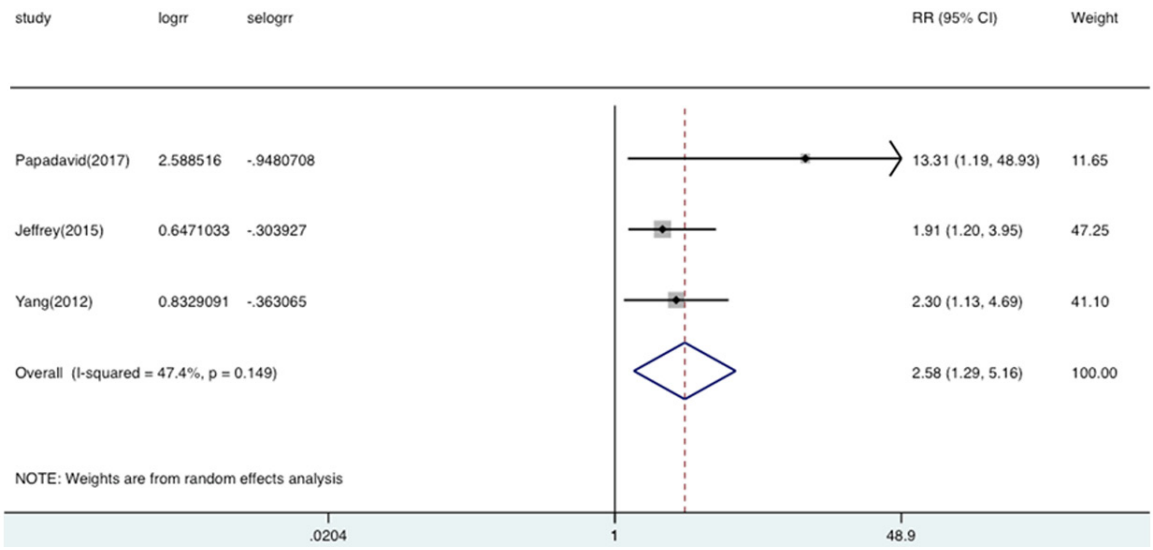

Figure 2. Meta-analysis of the risk of psoriasis in the people with obstructive sleep apnea. Shown is a forest plot, and the diamond represents the exact estimate from the study. The width of the line extending from each diamond represents the 95% confidence interval (CI). RR, risk ratio.

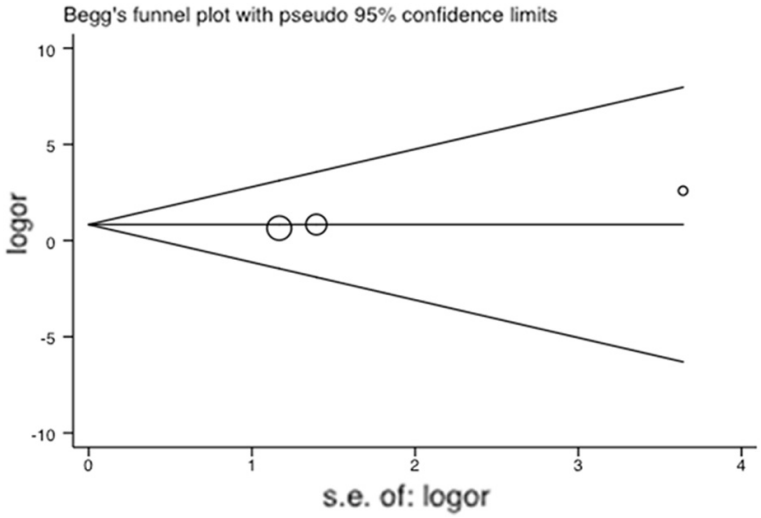

Figure 3. A funnel plot is shown for publication bias on selected studies.

The relationship between OSA keeps unknown and psoriasis is complicated and probably linked to systemic inflammation [17]. OSA patients typically possess inflammation of the upper airways, increased levels of oxidative stress and systemic inflammation specified by elevated levels of IL-6, TNF-α, IL-8, and C-reactive protein [18, 19]. The levels of inflammation initiated in OSA patients may contribute to the advancement and morbidity of autoimmune disorders. The levels of IL-6 and TNF-α were increased in psoriasis and correlated positively with severity of disease [20].

The serum concentration of vascular growth endothelial growth factor (VGEF), a protein expressed after HIF-1 activation, was raised in patients with severe OSA [21], which stimulates angiogenesis in psoriatic skin [22].

OSA may be related to hypothalamic-pituitary-adrenal (HPA) axis dysregulation [23]. OSA may affect cortisol secretion, and it tends to increase the level of cortisol [24]. Cortisol can interact with the immune system. For example, skin mast cells are activated by cortisol, which then modifies skin barrier function and upregulates pro-inflammatory cytokines which might aggravate the severity of psoriasis [6].

OSA can also result in metabolic syndrome [25, 26] whereby hypoxia-deoxygenation increase the production of reactive oxygen species, key mediators in the evolution of hypertension and coronary artery disease [27]. Obesity is a risk factor for OSA, as visceral adipocytes produce pro-inflammatory cytokines that can describe the link between obesity and OSA [28]. In contrast, metabolic syndrome and its compo-

nents play an important role in psoriasis pathogenesis [29]. Moreover, stress and sleep are closely linked, sharing pathways that disturb both the central nervous and immune systems and could establish the underlying mechanisms responsible. OSA is also known to increase stress, and stress is also a risk factor for psoriasis [30]. In summary, there is a potential link between psoriasis and OSA, and whether OSA is an independent risk factor awaits further research.

There are some limitations to this study. First, the number of included studies was limited, and there were potential sources of bias and heterogeneity amongst the studies included. Second, subgroup analyses based on age, sex, and severity of the disease were not possible, due to the studies not providing adequate data. Finally, the included studies were observational studies, and the quality of these studies are not as robust as randomized controlled trials. Additional studies may be needed in the future to expand the evidence with high quality.

In conclusion, this meta-analysis indicated that patients with OSA had a significantly greater likelihood of suffering from psoriasis. OSA might be a risk factor for psoriasis and physicians should be conscious of the relationship between OSA and psoriasis. OSA needs to be screened and treated, which may be a potential target for reducing the incidence of psoriasis and improving any therapeutic effect.

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Disclosure of conflict of interest

None.

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References

[1] Singh S, Taylor C, Kornmehl H, Armstrong AW. Psoriasis and suicidality: a systematic review and meta-analysis. J Am Acad Dermatol 2017; 77: 425-440.

[2] Ryan C, Kirby B. Psoriasis is a systemic disease with multiple cardiovascular and metabolic comorbidities. Dermatol Clin 2015; 33: 41-55.

[3] Grozdev I, Korman N, Tsankov N. Psoriasis as a systemic disease. Clin Dermatol 2014; 32: 343-50.

[4] Machado-Pinto J, Diniz Mdos S, Bavoso NC. Psoriasis: new comorbidities. An Bras Dermatol 2016; 91: 8-14.

[5] Maspero C, Giannini L, Galbiati G, Rosso G, Farronato G. Obstructive sleep apnea syndrome: a literature review. Minerva Stomatol 2015; 64: 97-109.

[6] Hirotsu C, Nogueira H, Albuquerque RG, Tomimori J, Tufik S, Andersen ML. The bidirectional interactions between psoriasis and obstructive sleep apnea. Int J Dermatol 2015; 54: 1352-8.

[7] Shalom G, Dreiher J, Cohen A. Psoriasis and obstructive sleep apnea. Int J Dermatol 2016; 55: e579-e584.

[8] Papadavid E, Dalamaga M, Vlami K, Koumaki D, Gyftopoulos S, Christodoulatos GS, Papiris S, Rigopoulos D. Psoriasis is associated with risk of obstructive sleep apnea independently from metabolic parameters and other comorbidities: a large hospital-based case-control study. Sleep Breath 2017; 21: 949-958.

[9] Yang YW, Kang JH, Lin HC. Increased risk of psoriasis following obstructive sleep apnea: a longitudinal population-based study. Sleep Med 2012; 13: 285-9.

[10] Chi CC, Chen TH, Wang SH, Tung TH. Risk of suicidality in People with psoriasis: a systematic review and meta-analysis of cohort studies. Am J Clin Dermatol 2017; 18: 621-627.

[11] Cohen JM, Jackson CL, Li TY, Wu S, Qureshi AA. Sleep disordered breathing and the risk of psoriasis among US women. Arch Dermatol Res 2015; 307: 433-8.

[12] Boehncke WH, Schön MP. Psoriasis. Lancet 2015; 386: 983-94.

[13] Yang YW, Keller JJ, Lin HC. Medical comorbidity associated with psoriasis in adults: a population-based study. Br J Dermatol 2011; 165: 1037-43.

[14] Hjuler KF, Bøttcher M, Vestergaard C, Bøtker HE, Iversen L, Kragballe K. Association between changes in coronary artery disease progression and treatment with biologic agents for severe psoriasis. JAMA Dermatol 2016; 152: 1114-1121.

[15] Gupta MA, Simpson FC, Gupta AK. Psoriasis and sleep disorders: a systematic review. Sleep Med Rev 2016; 29: 63-75.

[16] Henry AL, Kyle SD, Chisholm A, Griffiths CEM, Bundy C. A cross-sectional survey of the nature and correlates of sleep disturbance in people

with psoriasis. Br J Dermatol 2017; 177: 1052-1059.
[17] Dalamaga M, Papadavid E, Vlami K. Unmasking the Janus face of the association between psoriasis, metabolic syndrome and obstructive sleep apnea. Sleep Breath 2013; 17: 449-50.
[18] Maari C, Bolduc C, Nigen S, Marchessault P, Bissonnette R. Effect of adalimumab on sleep parameters in patients with psoriasis and obstructive sleep apnea: a randomized controlled trial. J Dermatolog Treat 2014; 25: 57-60.
[19] de Lima FF, Mazzotti DR, Tufik S, Bittencourt L. The role inflammatory response genes in obstructive sleep apnea syndrome: a review. Sleep Breath 2016; 20: 331-8.
[20] Arican O, Aral M, Sasmaz S, Ciragil P. Serum levels of TNF-alpha, IFN-gamma, IL-6, IL-8, IL-12, IL-17, and IL-18 in patients with active psoriasis and correlation with disease severity. Mediators Inflamm 2005; 2005: 273-9.
[21] Briancon-Marjollet A, Henri M, Pépin JL, Lemarié E, Lévy P, Tamisier R. Altered in vitro endothelial repair and monocyte migration in obstructive sleep apnea: implication of VEGF and CRP. Sleep 2014; 37: 1825-32.
[22] Zablotna M, Sobjanek M, Nedoszytko B, Lange M, Kozicka D, Glen J, Roszkiewicz J. Association of psoriasis with the VEGF gene polymorphism in the northern Polish population. J Eur Acad Dermatol Venereol 2013; 27: 319-23.
[23] Bublitz MH, Monteiro JF, Caraganis A, Martin S, Parker J, Larson L, Miller MA, Bourjeily G. Obstructive sleep apnea in gestational diabetes: a pilot study of the role of the hypothalamic-pituitary-adrenal axis. J Clin Sleep Med 2018; 14: 87-93.
[24] Vgontzas AN, Pejovic S, Zoumakis E, Lin HM, Bentley CM, Bixler EO, Sarrigiannidis A, Basta M, Chrousos GP. Hypothalamic-pituitary-adrenal axis activity in obese men with and without sleep apnea: effects of continuous positive airway pressure therapy. J Clin Endocrinol Metab 2007; 92: 4199-207.
[25] Gowda S, Goldblum OM, McCall WV, Feldman SR. Factors affecting sleep quality in patients with psoriasis. J Am Acad Dermatol 2010; 63: 114-23.
[26] Ekstedt M, Akerstedt T, Söderström M. Microarousals during sleep are associated with increased levels of lipids, cortisol, and blood pressure. Psychosom Med 2004; 66: 925-31.
[27] Panaree B, Chantana M, Wasana S, Chairat N. Effects of obstructive sleep apnea on serum brain-derived neurotrophic factor protein, cortisol, and lipid levels. Sleep Breath 2011; 15: 649-56.
[28] Gaines J, Vgontzas AN, Fernandez-Mendoza J, Calhoun SL, He F, Liao D, Sawyer MD, Bixler EO. Inflammation mediates the association between visceral adiposity and obstructive sleep apnea in adolescents. Am J Physiol Endocrinol Metab 2016; 311: E851-E858.
[29] Rodríguez-Zúñiga MJM, Cortez-Franco F, Quijano-Gomero E. Association of psoriasis and metabolic syndrome in Latin America: a systematic review and meta-analysis. Actas Dermosifiliogr 2017; 108: 326–334.
[30] Remröd C, Sjöström K, Svensson Å. Subjective stress reactivity in psoriasis - a cross sectional study of associated psychological traits. BMC Dermatol 2015; 15: 6.

Table S1. The NOS Scores of three included references

The reference 12: "Psoriasis is associated with risk of obstructive sleep apnea independently from metabolic parameters and other comorbidities: a large hospital-based case-control study"	
Selection	Outcomes
1) Is the case definition adequate?	✳
a) yes, with independent validation ✳	
b) yes, eg record linkage or based on self reports	
c) no description	
2) Representativeness of the cases	✳
a) consecutive or obviously representative series of cases ✳	
b) potential for selection biases or not stated	
3) Selection of Controls	
a) community controls ✳	
b) hospital controls	
c) no description	
4) Definition of Controls	✳
a) no history of disease (endpoint) ✳	
b) no description of source	
Comparability	
1) Comparability of cases and controls on the basis of the design or analysis	✳✳
a) study controls for _____ (Select the most important factor.) ✳	
b) study controls for any additional factor ✳ (This criteria could be modified to indicate specific control for a second important factor	
Exposure	
1) Ascertainment of exposure	✳
a) secure record (eg surgical records) ✳	
b) structured interview where blind to case/control status ✳	
c) interview not blinded to case/control status	
d) written self report or medical record only	
e) no description	
2) Same method of ascertainment for cases and controls	✳
a) yes ✳	
b) no	
3) Non-Response rate	✳
a) same rate for both groups ✳	
b) non respondents described	
c) rate different and no designation	
Total score	8 points

The reference 13: "Increased risk of psoriasis following obstructive sleep apnea: a longitudinal population-based study"	
Selection	Outcomes
1) Representativeness of the exposed cohort	✳
a) truly representative of the average _____ (describe) in the community ✳	
b) somewhat representative of the average _____ in the community ✳	
c) selected group of users eg nurses, volunteers	
d) no description of the derivation of the cohort	
2) Selection of the non exposed cohort	✳
a) drawn from the same community as the exposed cohort ✳	
b) drawn from a different source	
c) no description of the derivation of the non exposed cohort	
3) Ascertainment of exposure	✳
a) secure record (eg surgical records) ✳	
b) structured interview ✳	
c) written self report	
d) no description	

4) Demonstration that outcome of interest was not present at start of study ✳

a) yes ✳

b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis ✳✳

a) study controls for _____ (select the most important factor) ✳

b) study controls for any additional factor ✳ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome ✳

a) independent blind assessment ✳

b) record linkage –

c) self report

d) no description

2) Was follow-up long enough for outcomes to occur ✳

a) yes (select an adequate follow up period for outcome of interest) ✳

b) no

3) Adequacy of follow up of cohorts

a) complete follow up-all subjects accounted for ✳

b) subjects lost to follow up unlikely to introduce bias-small number lost-> ____ % (select an adequate %) follow up, or description provided of those lost)

c) follow up rate < ____% (select an adequate %) and no description of those lost

d) no statement

Total score 8 points

The reference 16: “Sleep disordered breathing and the risk of psoriasis among US women”

Selection Outcomes

1) Representativeness of the exposed cohort

a) truly representative of the average _____ (describe) in the community ✳

b) somewhat representative of the average _____ in the community ✳

c) selected group of users eg nurses, volunteers

d) no description of the derivation of the cohort

2) Selection of the non exposed cohort ✳

a) drawn from the same community as the exposed cohort ✳

b) drawn from a different source

c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure ✳

a) secure record (eg surgical records) ✳

b) structured interview ✳

c) written self report

d) no description

4) Demonstration that outcome of interest was not present at start of study ✳

a) yes ✳

b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis ✳✳

a) study controls for _____ (select the most important factor) ✳

b) study controls for any additional factor ✳ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome ✳

a) independent blind assessment ✳

b) record linkage –

c) self report

d) no description

2) Was follow-up long enough for outcomes to occur ✳

a) yes (select an adequate follow up period for outcome of interest) ✳

b) no

3) Adequacy of follow up of cohorts

a) complete follow up-all subjects accounted for ✳

b) subjects lost to follow up unlikely to introduce bias-small number lost-> ____ % (select an adequate %) follow up, or description provided of those lost) .

c) follow up rate < ____% (select an adequate %) and no description of those lost

d) no statement

Total score	7 points