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Bidirectional Association Between Psoriasis and Obstructive Sleep Apnea: A Systematic Review and Meta-Analysis

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The link between psoriasis and obstructive sleep apnea (OSA) has not been confirmed. We aimed to investigate the relationship between psoriasis and OSA. We conducted a systematic review and meta-analysis of case-control, cross-sectional, and cohort studies on the association between psoriasis and OSA. We searched MEDLINE and Embase for relevant studies on May 11, 2019. The Newcastle-Ottawa Scale was used to evaluate the risk of bias of included studies. We performed random-effects model meta-analysis to calculate pooled odds ratio (ORs) with 95% confidence intervals (CIs) for case-control and cross-sectional studies as well as pooled incidence rate ratio (IRR) with 95% CIs for cohort studies in association between psoriasis and OSA. A total of 4 case-control or cross-sectional studies and 3 cohort studies with a total of 5,840,495 subjects were included. We identified a significantly increased odds for OSA in psoriasis patients (pooled OR 2.60; 95% CI 1.07–6.32), and significantly increased risk for psoriasis in OSA patients (pooled IRR 2.52; 95% CI 1.89–3.36). In conclusion, our study identified a bidirectional association between psoriasis and OSA. Sleep quality should be inquired in patients with psoriasis. Respiriologist consultation or polysomnography may be indicated for those presenting with night snoring, recurrent awaking, and excessive daytime sleepiness.

Psoriasis is a chronic inflammatory skin disease with characteristic feature of sharply circumscribed erythematous plaques with silvery scales on the trunk and limbs¹. The prevalence was estimated 0.5–11.4% in adults². Psoriasis is considered as a multisystemic disease involving proinflammatory cytokines such as tumor necrosis factor (TNF), interleukin (IL)-1, and IL-17^{3,4}. Various comorbidities have been linked to psoriasis including cardiovascular disease, metabolic syndrome, chronic kidney disease, uveitis, thyroid diseases, vitiligo, and inflammatory bowel disease^{5–11}.

Obstructive sleep apnea (OSA), also called obstructive sleep apnea-hypopnea syndrome, is a chronic disorder of intermittent upper airway collapse during sleep resulting in recurrent hypoxia^{12,13}. OSA is characterized with night snoring, recurrent awaking, and excessive daytime sleepiness¹⁴. The gold standard test for diagnosing OSA is polysomnography¹⁵. The prevalence of OSA ranges from 3 to 17%¹². Risk factors of OSA include obesity, aging, male gender, anatomical predisposition, and alcohol consumption^{12,13}. OSA induces systemic inflammatory and increases the risk of hypertension, stroke, cardiovascular disease, and metabolic disorder, in particular of diabetes mellitus type 2 and metabolic syndrome regardless of the obesity^{15–17}.

Psoriasis and OSA share a common pathogenesis of inflammatory and immune imbalance^{18,19}. The association between psoriasis and OSA has been examined in many studies but the results were limited and inconsistent^{20–27}. The objective of this study was to assess the evidence regarding the bidirectional association between psoriasis and OSA.

Methods

We conducted a systematic review and meta-analysis of observational studies (case-control, cross-sectional, and cohort studies) on the association between psoriasis and OSA. The reporting of this study followed the Meta-analysis of Observational studies in Epidemiology (MOOSE) guidelines²⁸. We have registered the study protocol with PROSPERO (CRD42019129605; see https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=129605).

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Literatures search. We searched the MEDLINE and Embase for relevant studies from inception to May 11, 2019. The search terms included psoriasis and sleep apnea and their synonyms. The search strategy is shown in the Supplement. No geographic or language limitations were imposed.

Study selection. The criteria for studies to be included were as follows: (1) observational studies investigating the association between psoriasis and OSA, including case-control, cross-sectional, and cohort studies; (2) research on human subjects; (3) the case group consisted of patients with psoriasis and the control group consisted of people without psoriasis in studies that examined the odds or risk of OSA in psoriasis patients; the study group was composed of patients with OSA and the control group was composed of people without OSA in studies that evaluated the odds or risk of psoriasis in OSA patients. We screened titles and abstracts for the initial study selection and obtained the full text of potentially eligible studies to confirm if they met our inclusion criteria. Two authors (T.G. and Y.F.) independently selected studies and disagreement was resolved by consulting the other author (C.C.).

Data extraction. We extracted the following data from the included studies: first author, year of publication, country of study, number and gender of study subjects, definition of the case group, definition of outcome, and risk estimates including hazard ratio (HR), incidence rate ratio (IRR), and odds ratio (OR) with 95% confidence interval (CI) on the association between psoriasis and OSA.

Risk of bias evaluation. The risk of bias of included studies was assessed by using the Newcastle-Ottawa Scale²⁹. For case-control and cross-sectional studies, we examined the following eight domains: adequacy of case definition, representativeness of cases, selection of controls, definitions of controls, comparability of cases and controls, ascertainment of exposure, same method of ascertainment for cases and controls, and non-response rate. For cohort studies, we evaluated the following eight domains: representativeness of exposed cohort, selection of non-exposed cohort, ascertainment of exposure, absence of outcome of interest at start of study, comparability of cohorts, assessment of outcome, follow-up duration, and adequacy of follow up of cohorts.

Statistical analysis. The Review Manage version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for conducting all analyses. We calculated the OR with 95% CI in included case-control and cross-sectional studies and IRR in included cohort studies. If OR was not reported in an included study, we calculated the crude OR based on published data for example the number of events in the case and control groups. The most fully adjusted OR, HR, or IRR were adopted if reported. We performed meta-analyses to evaluate the bidirectional association between psoriasis and OSA. For included case-control and cross-sectional studies, we calculated pooled OR to examine the association between the two diseases. For cohort studies, we treated HR as IRR and calculated the pooled IRR³⁰. The statistical heterogeneity was assessed by the I^2 statistic across the included studies. An I^2 of $>50\%$ represents substantial heterogeneity³¹. We chose random-effects model for meta-analyses because clinical heterogeneity was anticipated. Therefore the DerSimonian and Laird method that takes between-study variability into account was used to obtain the pooled OR and IRR estimates³². Also, we conducted a sensitivity analysis after excluding studies that were rated with a high risk of bias.

Results

Characteristic of included studies. The PRISMA flow chart of study selection is shown in Fig. 1. Our systematic literature search yielded 98 records after removing duplicates. We identified one additional relevant study in a review article. After screening the titles and abstracts, 54 records were excluded. After assessing the full text for eligibility, 38 articles were excluded due to no relevant data, review articles, no comparison group or irrelevant comparison group. Ultimately seven studies with a total of 5,840,495 study subjects were included. One cohort study, two case control studies, and one cross-sectional study investigated the association of psoriasis with OSA. Three cohort studies and one case-control study investigated the association of OSA with psoriasis. There was one cohort study that reported the bidirectional association between psoriasis and OSA. The main characteristics of included studies are summarized respectively in Table 1.

Risk of bias of included studies. The risk of bias of included studies was summarized in Figs. 2 and 3. Of four included case-control and cross-sectional studies, no items were rated as high risk of bias (see Fig. 2). The Tsai 2011 study was rated with an unclear risk of bias in the 'adequacy of case definition' domain because only the International Classification of Disease (ICD) diagnostic codes were used to identify patients³³. Two studies were rated with an unclear risk of bias in the 'representativeness of cases' and 'selection of controls' domains because patients were selected from hospital not community^{34,35}. We rated two studies as unclear risk of bias in the 'comparability of cases and controls' domain because only age and gender, but not body mass index, were controlled^{33,35}. Moreover, three studies were rated as unclear risk in the 'ascertainment of exposure' domain because only medical records or ICD codes were employed^{24,33,34}. In three included cohort studies, we rated the Cohen 2015 study at high risk of bias in the 'representativeness of exposed cohort' domain (see Fig. 3)²³. The reason was that the study subjects were all female nurses.

Bidirectional association between OSA and psoriasis. One cohort study²⁵, one cross-sectional study³⁵, and two case-control studies^{24,33} demonstrated an increase in OSA among patients with psoriasis. The meta-analysis of two included case-control and one cross-sectional studies with 295,464 study subjects showed a significant association of psoriasis with OSA (pooled OR, 2.60; 95% CI, 1.07–6.32; Fig. 4)^{24,33,35}. Considerable statistical heterogeneity was found ($I^2 = 89\%$; $P < 0.0001$). One included cohort study illustrated a consistently

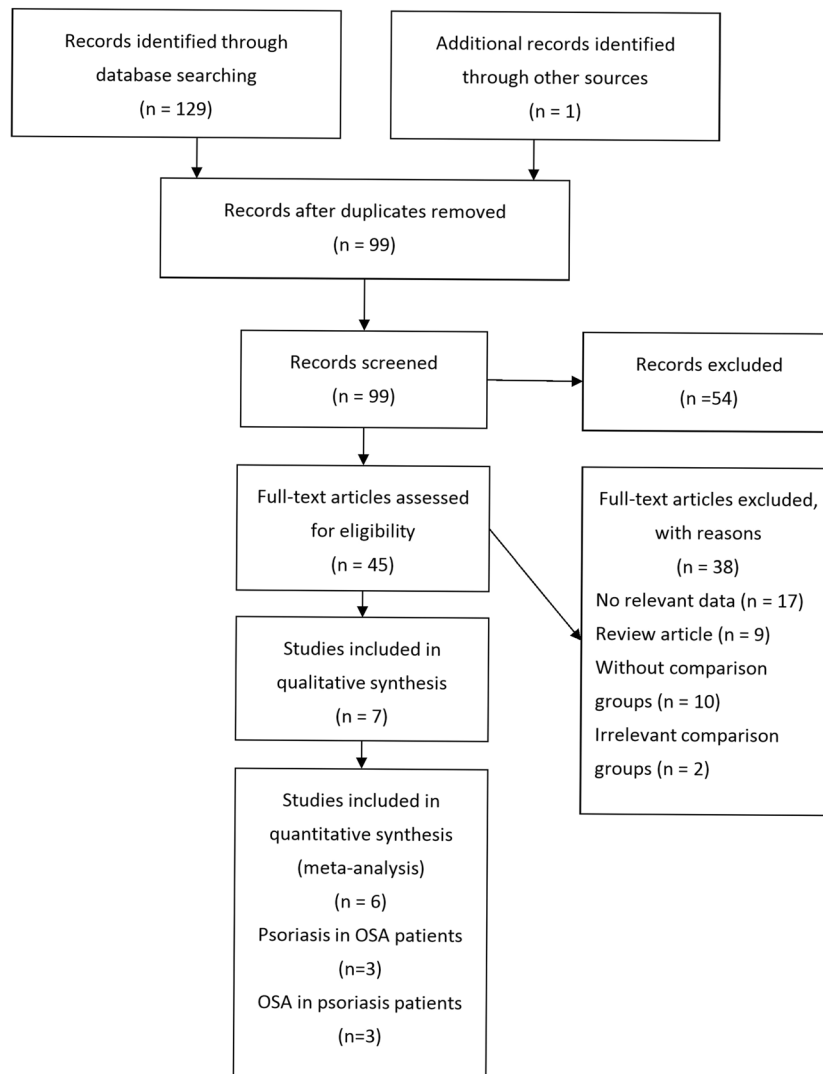


Figure 1. PRISMA study flow diagram.

increased risk for OSA in patients with mild psoriasis (adjusted IRR 1.36; 95% CI 1.21–1.53), severe psoriasis (adjusted IRR 1.53; 95% CI 1.08–2.18), and psoriatic arthritis (adjusted IRR 1.98; 95% CI 1.50–2.61)²⁵.

Conversely, three cohort studies^{23,25,27} and one case-control study³⁴ found a consistent increase in psoriasis among patients with OSA. The meta-analysis of three included cohort studies with 5,544,674 study subjects showed a significant association of OSA with psoriasis (pooled IRR, 2.52; 95% CI, 1.89–3.36; Fig. 5)^{23,25,27}. There was no statistical heterogeneity within these studies ($I^2 = 0\%$). The Cohen 2015 study was rated with a high risk of bias in the representativeness of the exposed cohort because all the study subjects were nurses²³. However, the association of OSA with psoriasis remained positive after excluding the Cohen 2015 study (pooled IRR 2.47; 95% CI 1.74–3.49). One case-control study showed a significantly increased odds for psoriasis in relation to OSA (adjusted OR 13.31, 95% CI 1.19–48.93)³⁴.

Discussion

To the best of our knowledge, the present study is the first meta-analysis investigating the bidirectional association between psoriasis and OSA. The evidence from included case-control and cross-sectional studies found a 2.6-fold greater odds for prevalent OSA in relation to psoriasis^{24,33,35} and a 13-fold increased odds for prevalent psoriasis in relation to OSA³⁴. Similarly, the evidence from an included cohort study demonstrated consistently increased risk for incident OSA among patients with mild and severe psoriasis as well as psoriatic arthritis²⁵. Conversely, OSA patients were 2.52-fold more likely to develop incident psoriasis when compared with non-OSA controls^{23,25,27}. Our meta-analysis possesses high generalizability because of including studies from various ethnicities for example the United States, France, Denmark, Greece, Israel, and Taiwan.

Obesity is a trigger for inflammation and has been linked to chronic inflammatory diseases³⁶. Patients with psoriasis have been found to have increased body mass index (BMI) than healthy controls³⁷. Besides, OSA was related to obesity and thus weight loss is the recommended first-line therapy^{38,39}. Obesity may promote upper

First author, year, country	Study design	Case group	Control group	Case definition and sampling population/ outcome definition	Results	
Studies investigating the odds of obstructive sleep apnea in psoriasis patients						
Tsai, 2011, Taiwan	Case-control	51,800 patients with psoriasis (31,923 males and 19,877 females)	207,200 age-, gender- and urbanization-matched controls (127,692 males and 79,508 females)	ICD-9-CM psoriasis code from national health insurance database in 2006/ICD-9-CM sleep apnea code	Crude OR: 3.30 (2.00–5.44)	Adjusted RR: 3.89 (2.26–6.71)
Shalom, 2016, Israel	Case-control	12,336 patients with psoriasis (6,441 males and 5,895 females)	24,008 age- and sex- matched controls (12,096 males and 11,912 females)	Diagnosis of psoriasis by dermatologists from medical database of Clalit Health Services/ICD-9-CM sleep apnea code	OR:1.74 (1.50–2.03)	Adjusted OR: 1.27 (1.08–1.49)
Egeberg, 2016, Denmark	Cohort study	66,523 patients with psoriasis (32,115 males and 34,408 females)	5,393,040 individuals in the reference population (2,659,620 males and 2,733,420 females)	ICD-10-CM psoriasis or psoriatic arthritis code from Danish National Patient Register from 1 Jan 1997 to 31 Dec 2011/ICD-10-CM sleep apnea code	IRR: Mild psoriasis: 1.88 (1.69–2.09) Severe psoriasis: 2.69 (2.00–3.62) Psoriatic arthritis: 3.08 (2.38–4.00)	Adjusted IRR: Mild psoriasis: 1.36 (1.21–1.53) Severe psoriasis: 1.53 (1.08–2.18) Psoriatic arthritis: 1.98 (1.50–2.61)
Sacmaci, 2019, Turkey	Cross-sectional	60 patients with psoriasis (30 males and 30 females)	60 sex- and age- matched controls (30 males and 30 females)	Diagnosis of psoriasis by dermatologists// Diagnosis of sleep apnea by neurologists according to Berlin Questionnaire for Sleep Apnea	Crude OR: 6 (1.89–19.04)	NA
Studies investigating the odds of psoriasis in obstructive sleep apnea patients					Crude (95% CI)	Adjusted (95% CI)
Yang, 2012, Taiwan	Cohort study	2,258 patients with sleep apnea (1,414 males and 844 females)	11,255 age- and sex-matched controls without sleep apnea and psoriasis	ICD-9-CM sleep apnea codes from national health insurance database from 1 Jan 2001 to 31 Dec 2005 after receiving polysomnography/Two consensus psoriasis diagnosis, with at least one made by dermatologist or rheumatologists	Crude HR: 2.21 (1.08–4.49)	Adjusted HR: 2.30(1.13–4.69)
Cohen, 2015, USA	Cohort study	490 patients with OSA (All females)	71,108 individuals in the reference population (All females)	Self-reported sleep apnea in 1997/Self-reported psoriasis, psoriasis within 2 years of onset of sleep apnea were excluded	Crude IRR: 2.65 (1.6–4.14)	Adjusted RR: 1.91(1.20–3.05)
Egeberg, 2016, Denmark	Cohort study	39,908 patients with sleep apnea (31503 males and 8405 females)	5,419,655 individuals in the reference population (2,660,232 males and 2,759,423 females)	ICD-10-CM sleep apnea code from Danish National Patient Register from 1 Jan 1997 to 31 Dec 2011/ICD-10-CM psoriasis or psoriatic arthritis code	IRR: Sleep apnea without CPAP Mild psoriasis: 1.97 (1.71–2.26) Severe psoriasis: 2.80 (2.02–3.87) Psoriatic arthritis: 2.38 (1.65–3.34) Sleep apnea with CPAP Mild psoriasis: 2.29 (1.79–2.93) Severe psoriasis: 4.77 (2.96–7.67) Psoriatic arthritis: 7.29 (4.88–10.88)	Adjusted IRR: Sleep apnea without CPAP Mild psoriasis: 1.62 (1.38–1.89) Severe psoriasis: 1.85 (1.25–2.74) Psoriatic arthritis: 1.98 (1.32–2.99) Sleep apnea with CPAP Mild psoriasis: 1.95 (1.48–2.57) Severe psoriasis: 3.75 (2.22–6.34) Psoriatic arthritis: 6.84 (4.49–10.4)
Papadavid, 2017, Greece	Case-control	253 patients with OSA (200 males and 53 females)	104 controls without OSA (82 males and 22 females)	Underwent full nocturnal polysomnography, cessation of airflow for ≥ 10 s, from July 2009 to July 2012/Diagnosed for psoriasis by the same dermatologist	NA	Adjusted OR: 13.31 (1.19–48.93)

Table 1. Characteristics of included studies. CI, confidence interval; CM, Clinical Modification; HR, hazard ratio; ICD, International Classification of Disease; IRR, incidence rate ratio; N/A, not available; OR, odds ratio; OSA, obstructive sleep apnea; RR, risk ratio.

airway inflammation, reduce muscle contractibility, and induce airway collapse during sleep⁴⁰. BMI has been correlated with psoriasis severity³⁷ and OSA²⁶. Among most of included studies in our meta-analysis^{23–25,27,34},

	Adequacy of case definition	Representativeness of cases	Selection of controls	Definition of controls	Comparability of cases & controls	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate
Papadavid 2017	+	?	?	+	+	?	+	+
Sacmaci 2019	+	?	?	+	?	+	+	+
Shalom 2016	+	+	+	+	+	?	+	+
Tsai 2011	?	+	+	+	?	?	+	+

Figure 2. Risk of bias of included case-control and cross-sectional studies. Risk of bias were assessed base on Newcastle-Ottawa Scale. Green dots indicate low risk of bias; yellow dots indicate unclear risk of bias and red dots indicate high risk of bias.

	Representativeness of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Comparability of cohorts	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts
Cohen 2015	-	+	+	+	+	+	+	+
Egeberg 2016	+	+	+	+	+	+	+	+
Yang 2012	+	+	+	+	+	+	+	+

Figure 3. Risk of bias of included cohort studies. Risk of bias were assessed base on Newcastle-Ottawa Scale. Green dots indicate low risk of bias; yellow dots indicate unclear risk of bias and red dots indicate high risk of bias.

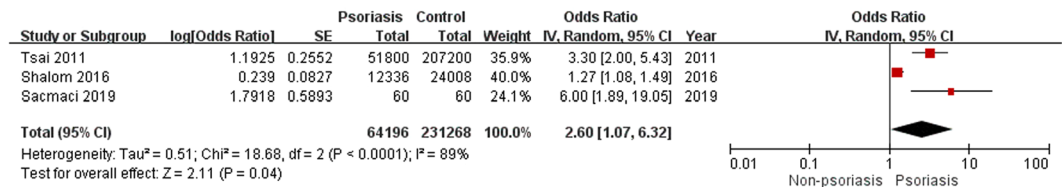


Figure 4. Forest plot for case-control and cross-sectional studies on the association of psoriasis with obstructive sleep apnea. The meta-analysis illustrated a significant association of obstructive sleep apnea with psoriasis (pooled odds ratio 2.60; 95% confidence interval 1.07–6.32).

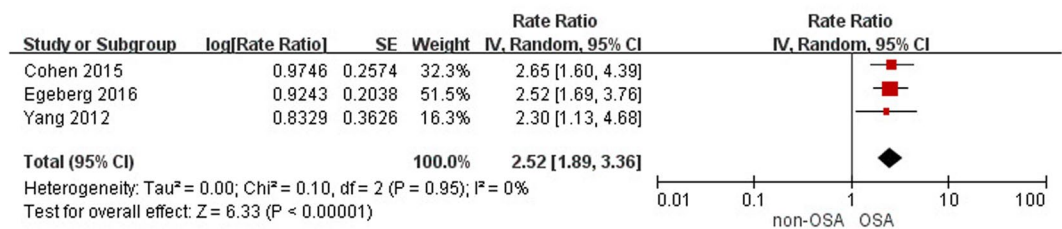


Figure 5. Forest plot for cohort studies on the association of obstructive sleep apnea with psoriasis. The meta-analysis illustrated a significant association of obstructive sleep apnea with psoriasis (pooled incidence rate ratio 2.52; 95% confidence interval 1.89–3.36).

the confounding from obesity has been considered and BMI was adjusted in the statistical analysis. The bidirectional association between psoriasis and OSA remained significant after adjustment for obesity or BMI. Only one included case-control study of Tsai 2011 did not contain any information about BMI or body weight³³. Another included cross-sectional study of Sacmaci 2019 did not perform adjustment for obesity, but there was no significant difference in BMI between psoriasis patients and non-psoriasis controls (28.5 kg/m² vs. 26.9 kg/m²; P = 0.051)³⁵. Therefore, confounding by obesity could not fully explain the association between psoriasis and OSA.

The bidirectional association between psoriasis and OSA suggest the shared common systemic inflammatory pathogenic pathways¹⁹. OSA is considered a systemic inflammatory disorder. High levels of systemic inflammatory molecules are part of mechanism leading to OSA^{41,42}. The activities of IL-17, TNF, IL-6, IL-7 and C-reactive protein are significantly increased in patients with OSA compare to obese patients^{43–45}. These pro-inflammatory cytokines decreased after continuous positive airway pressure (CPAP) treatment⁴⁴. Studies have shown that the circadian rhythm of TNF release was significantly disturbed in patients with OSA^{46,47}. The inflammatory process may predispose them to the development of psoriasis²⁷. Elevated circulating levels of IL-17, TNF, IL-6, and IL-22 were also associated with psoriasis⁴⁸. One previous study found that treatment with etanercept significantly improved symptoms of OSA in moderate to severe psoriasis⁴⁹. The increase of IL-17 is related to atherosclerotic vascular disease, which is a risk factor for OSA⁵⁰. Moreover, psoriasis causes pruritus and may lead to sleep disturbance, which contributes to systemic inflammation and consequently induces OSA^{51–53}.

Autonomic activation is considered an important factor between OSA and psoriasis^{53–55}. Some scholars assumed that psoriasis-related itching and pain could disrupt sleep and thus increase autonomic activation, which possibly induces OSA^{18,54}. On the other hand, Gabryelska *et al.* proposed low grade inflammation in OSA patients with elevated levels of IL-1 and TNF could stimulate hypothalamus and increase hypothalamic-pituitary-adrenal activity with resultant surging of autonomic activity⁵⁶. The inflammation and autonomic activation involved in OSA may be a risk factor for psoriasis⁵⁵.

Intermittent hypoxia during sleep in OSA patients induces oxidative stress. Some markers including nuclear factor- κ B (NF- κ B) and hypoxia-inducible factor-1 α (HIF-1 α) could detect the oxygen stress and activate the inflammatory pathway⁵⁷. HIF-1 α , a transcriptional regulator of cell oxygen metabolism, is a specific marker for diagnosing OSA⁵⁸. The levels of HIF-1 α correlate with the severity of OSA and can be effectively reduced by CPAP treatment⁵⁷. Besides, vascular risk response to hypoxia was detected in OSA patients. A significant upregulation of NF- κ B, HIF-1 α , endothelial nitric oxide synthase, vascular cell adhesion molecule 1, and vascular endothelial growth factor (VEGF) were expressed in the skin biopsy specimens of OSA patients⁵⁹. Increased circulation of VEGF promotes angiogenesis which is also an important process in initiating psoriasis^{59,60}. VEGF is a marker of tissue response to hypoxia and activated by HIF-1 α ⁵⁹. There is evidence indicating activation of excess HIF-1 α and VEGF in psoriatic skin when compare to normal skin^{61,62}. In addition, HIF-1 α is involved in T-cell regulation and survival which are crucial in psoriasis formation⁶². The effects of hypoxia with elevated levels of HIF-1 α and VEGF may explain the association between OSA and psoriasis.

There are a few limitations of the present study. First, OSA was identified by the use of ICD codes in four included studies^{24,25,27,33} and misclassification bias might have been present. Second, high statistical heterogeneity was detected as to the association of psoriasis with OSA (I² = 89%; see Fig. 4), but all the include studies consistently reported positive association.

In conclusion, the evidence to date supports a bidirectional association between psoriasis and OSA. All patients with psoriasis should be informed about the risk of OSA, and vice versa. OSA is a comorbidity of psoriasis that should not be ignored, and sleep quality should be inquired in patients with psoriasis. Respiriologist consultation or polysomnography may be indicated for those presenting with night snoring, daytime sleepiness, and insomnia.

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Author contributions

This study was designed by C.C. Data extraction was performed by T.G. and Y.F. Data review was done by all authors. First draft was written by T.G. All authors commented on the first draft and agreed with the final version. C.C. is the guarantor of the study.

Competing interests

The authors declare no competing interests.

Additional information

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