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CLINICAL REVIEW

Worldwide and regional prevalence rates of co-occurrence of insomnia and insomnia symptoms with obstructive sleep apnea: A systematic review and meta-analysis

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SUMMARY

Recent investigations have established that patients with obstructive sleep apnea (OSA) and insomnia have greater daytime impairments and reduced quality of life compared to those with either disorder alone. The present study reviewed current data on the co-occurrence prevalence of insomnia and insomnia symptoms with OSA and assessed its worldwide and regional prevalence based on World Health Organization (WHO) regions. A total of 37 studies were included in the analysis. The overall prevalence rates of insomnia, any insomnia complaints, difficulty falling asleep (DFA), difficulty maintaining sleep (DMS) and early morning awakening (EMA) found in OSA patients were 38%, 36%, 18%, 42%, and 21%, respectively. According to the regional classification of the WHO, the rates of DFA, DMS and EMA in OSA patients in the Western Pacific Region were lower than those in the European Region and the Region of the Americas. We also analyzed the pooled prevalence rates of OSA based on different apnea-hypopnea index (AHI) criteria in insomnia patients. The rates were 35% (AHI≥5) and 29% (AHI≥15), respectively. Regional differences of DFA, DMS and EMA in OSA patients may be related to sex, age and body mass index.

Introduction

Obstructive sleep apnea (OSA) and insomnia are common sleep disorders. OSA is a condition characterized by repeated episodes of partial or complete obstruction of the respiratory passages during sleep [1–3], with estimated prevalence in the general population ranging from 9% to 38% [4]. Insomnia has similar prevalence with estimates ranging from 10% to 40%, depending on whether it is viewed as a specific disorder (5–10% prevalence) or a symptom (30% prevalence) [5–8]. Both OSA and insomnia are implicated in diseases such as hypertension [9,10] and diabetes [11,12], which are responsible for enormous health care costs [13,14].

In 1973, Guilleminault et al. provided the first report describing the co-occurrence of OSA and insomnia [15], and there has recently been a growing interest in their association [16–21]. This is due to the fact that patients with OSA and insomnia suffer from greater daytime impairments [18,22,23] and reduced quality of life [18,24] compared with patients with OSA or insomnia alone. Furthermore, different insomnia symptoms (difficulty falling asleep (DFA), difficulty maintaining sleep (DMS) and early morning awakening (EMA)) actually respond differently to OSA treatment and/or vary with different levels of OSA treatment adherence [25,26]. Thus, determining the prevalence and distribution of the co-occurrence of OSA and insomnia or different insomnia symptoms may raise awareness of the limitations in treatment for this patient population and encourage development of new treatment modalities.

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Abbreviations

AASM	American Academy of Sleep Medicine
AHI	apnea hypopnea index
BMI	body mass index
CI	confidence interval
CVD	cardiovascular diseases
CPAP	continuous positive airway pressure
DFA	difficulty falling asleep
DMS	difficulty maintaining sleep
DSM	Diagnostic and Statistical Manual for Mental disorders
EMA	early morning awakening
HPA	hypothalamic-pituitary-adrenal
ICSD	International Classification of Sleep Disorders
ISI	Insomnia Severity Index
JBIPCAT	Joanna Briggs Institute Prevalence Critical Appraisal Tool
OR	odds ratio
OSA	obstructive sleep apnea
PG	polygraphy
PSG	polysomnography
SNS	sympathetic nervous system
WHO	World Health Organization

Moreover, it may help in setting priorities for public health policy, guiding funding for public health initiatives, and for healthcare planning.

Several studies have reported on the prevalence of co-occurrence of insomnia/insomnia symptoms with OSA, but estimates vary across studies. One recent review summarized data in studies published between 2010 and 2015 [18], but meta-analytic data exploring prevalence rates of co-occurrence across large numbers of studies and participants are lacking. Furthermore, our preliminary literature search revealed more than 20 articles in this area published before 2010 or after 2015. Therefore, a review of the literature is timely and important. In addition, the information on the regional prevalence of co-occurrence is lacking. The World Health Organization (WHO) divides the world into six WHO regions (i.e., Africa, Americas, South East Asia, Europe, Eastern Mediterranean, and Western Pacific) for the purposes of reporting, analysis and administration [27,28]. Evaluating the co-occurrence prevalence of insomnia and OSA according to the WHO regional classification using a meta-analytic strategy may also help identify targets for the development of preventive and therapeutic programs in different regions.

Several factors (e.g., sex, age and body mass index (BMI)) have the potential to contribute to regional differences in the co-occurrence of insomnia and/or insomnia symptoms with OSA. Their associations with insomnia and OSA have been established in previous studies [4,5,29–32]. It has been demonstrated that being male, advancing age, and higher BMI are associated with an increased prevalence of OSA in the adult general population [4], whereas being female and advancing age are associated with an increased prevalence of insomnia [29]. In a recent review, Hnin et al. also considered age, sex and BMI as important contributors to differences in OSA prevalence observed across different ethnic populations [33]. Therefore, we speculated that exploring the effects of sex, age and BMI could aid in understanding reasons for potential regional differences in the co-occurrence prevalence of insomnia and/or insomnia symptoms with OSA.

The present review updates and extends previous findings, and uses a meta-analytic approach to identify the pooled effect size (and range of credible values) for the co-occurrence of OSA and insomnia. This approach confers advantages, such as enabling more accurate conclusions by summarizing the overall effect size and allowing a more nuanced understanding when statistically testing for factors that may impact effect size. It also avoids the tendency found in some reviews to simply tally and compare the number of significant versus non-significant findings. Meta-analysis also avoids the focus on results significance testing, which is affected by factors such as sample size and variability, and concentrates on effect size [34,35].

Our systematic review identified, meta-analyzed, and appraised literature contributions with any study design examining the co-occurrence of insomnia and OSA to answer the following questions: 1) what are the worldwide and regional prevalence rates of insomnia/insomnia symptoms (DFA, DMS and EMA) in adult patients with OSA? 2) what are the worldwide and regional prevalence rates of OSA in adult patients with insomnia? and 3) what are the regional prevalence rates of co-occurrence based on potential contributing factors such as sex, age, and BMI?

Methods

Eligibility criteria based on the PICOS approach

Participants (*P*): When exploring the prevalence rates of insomnia/insomnia symptoms in patients with OSA, the participants were adult OSA patients. The diagnosis of OSA required an objective sleep test such as polysomnography (PSG) or polygraphy (PG) using a cutoff (i.e., 5, 10 or 15) apnea hypopnea index (AHI) to define OSA. AHI is most often used to determine and indicate the severity of OSA and it continues to be the best index for evaluating and diagnosing patients with OSA [36]. Although the respiratory disturbance index (RDI) has sometimes been used to determine OSA in sleep research, the RDI and AHI algorithms are different, resulting in different values for across measures. Thus, combining the results of studies which used RDI and AHI cutoffs in our meta-analysis would have made our definition of OSA too complex, and the pooled effect sizes difficult to interpret. Thus, we only included studies which used an AHI cutoff to determine OSA.

When exploring the prevalence of OSA in patients with insomnia, the participants were adult insomnia patients. The diagnosis of insomnia required any one of the following three conditions: 1) it met Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria [37] or International Classification of Sleep Disorders (ICSD) criteria [38], 2) it was made by a health professional, or 3) it was based on a score above a given threshold on a valid insomnia questionnaire, such as the Insomnia Severity Index (ISI) $\geq$ 15 [39,40].

When exploring the prevalence of OSA in patients with insomnia, studies using subjects referred for sleep testing due to a high clinical suspicion for OSA were excluded, because of selection bias.

For explorations of both the prevalence rates of insomnia/insomnia symptoms in patients with OSA and of the prevalence of OSA in patients with insomnia, studies using trauma samples or highly suspected trauma samples (i.e., veterans) were excluded, due to the potential specific events underlying their insomnia [41,42] and OSA [43], and that they are not the routine cases seen in hospital or community samples. Traumatic events are defined formally in DSM [37] as an event involving serious injury or potential or actual death that an exposed person experiences (or witnesses), and responds with helplessness, intense fear or horror. Participants who had experienced traumatic events were judged as trauma samples.

Intervention (*I*): When exploring the prevalence rates of insomnia/insomnia symptoms in OSA patients, we did not exclude patients who were taking medication to improve insomnia symptoms

because we believed that taking sleep medications usually would not make patients deny their original insomnia symptoms. By comparison, continuous positive airway pressure (CPAP) treatment can present high pressure at the face, uncomfortable headgear, noise, mask discomfort, and nasal congestion, or dryness [44]. It is often seen as an intrusion into sleep [44]. Thus, we considered CPAP a potentially confounding factor which could bias the prevalence rates of insomnia/insomnia symptoms in OSA patients, and excluded studies which the OSA patients were under CPAP therapy when we explored the prevalence of insomnia/insomnia symptoms in OSA patients.

For exploring the prevalence of OSA in patients with insomnia, we did not exclude studies which contained insomnia patients using sleep medication because a previous systematic review found that sleep medications (i.e., eszopiclone, triazolam, nitrazepam, and zolpidem, etc.) did not significantly increase AHI (OSA severity) [45]. For the effects of CPAP, we believed that CPAP treatment usually would not make patients deny their original OSA diagnosis and did not exclude studies containing patients who had undergone CPAP treatment.

Comparison (C): This element was not applicable as we did not compare the pooled prevalence data with control groups.

Outcome (*O*): When exploring the prevalence of insomnia in patients with OSA, the outcome was prevalence of insomnia. The diagnosis criteria for insomnia was in accordance with that described in the "Participants (P)" section.

When exploring the prevalence rates of insomnia symptoms in patients with OSA, the outcomes were prevalence rates of insomnia symptoms (i.e., DFA, DMS, EMA, and any insomnia complaints). The definition of "insomnia symptoms" required that participants of the included studies answer questions to reflect the absence or presence of specific insomnia symptoms (DFA, DMS, or EMA) or any insomnia complaints. The questions asking about insomnia symptoms could be derived from a valid insomnia questionnaire (items in the questionnaire) or could be designed by the investigators of original studies.

When exploring the prevalence of OSA in patients with insomnia, the outcome was prevalence of OSA. The diagnosis criteria for OSA were as described in the "Participants (P)" section.

Studies with insufficient data for extraction of outcomes needed for the planned assessments were excluded.

Study design (S): Studies included any hospital- and community-based patient studies with any study design (i.e., cross-sectional, cohort, and case–control study) that included relevant cross-sectional data. Case reports, commentaries, and reviews were excluded.

Other inclusion criteria required that the studies were published in English and were obtained from peer-reviewed journals. If the same sample was used in more than one publication (overlap data), then only the dataset with the largest sample was chosen to avoid data duplication.

Information sources

We searched MEDLINE via OVID (up to May 16, 2018); EMBASE via OVID (up to May 15, 2018); Web of Science (up to May 17, 2018); PsyINFO via EBSCO*host* (up to May 25, 2018); CINAHL via EBSCO*host* (up to May 21, 2018); and all EBM databases via OVID (up to May 23, 2018). EndNote software was used to manage the references and removal of duplicates.

Search

The search strategies for all databases are included in Tables S1-S6. To supplement the electronic searches, the reference lists of included studies were also screened (Supplementary file).

Study selection

Studies were screened for relevance to the topic by title, followed by abstract and/or full text of the article. Articles were screened for inclusion by two reviewers (Zhang, Y. and Ren, R.). Studies that were conducted using animals or not written in English were excluded.

Data collection process

Data extraction was performed by two independent reviewers (Zhang, Y. and Ren, R.) using data collection forms. The data forms were piloted before use and included: 1) first author, 2) publication year, 3) research site (country), study design and recruitment setting (hospital or community), 4) total number of insomnia/OSA patients, 5) male%, age and BMI of OSA/insomnia patients, 6) clinical tools for insomnia symptoms, 7) oxygen desaturation for hypopnea ($\geq$3% or 4%), 8) diagnosis criteria of OSA/insomnia, 9) prevalence of insomnia in OSA patients, 10) prevalence rates of DFA, DMS and EMA in OSA patients, and 11) prevalence of OSA in insomnia patients. Additional details obtained from included studies were: 1) whether they had an exclusion criterion for co-occurrence of non-sleep conditions (Yes vs. No), 2) whether they had an exclusion criteria for patients taking sleep medications (Yes vs. No), and 3) rates of patients taking sleep medications. Disagreements were resolved with discussion, or if agreement could not be reached, a third author (Tang, X. D.) assisted in the resolution of any discrepancies. Data was obtained from the original papers and by contacting the authors when necessary (Table S7). If no clear answers were received from the authors after one month, the requested data was considered not performed or missing. The data were entered by a single author (Zhang, Y.) and verified by both reviewers (Zhang, Y. and Ren, R.).

Quality assessments

The methodological quality of the included studies was evaluated using the Joanna Briggs Institute Prevalence Critical Appraisal Tool (JBIPCAT) developed by Munn et al. [46,47]. This is an easy to use and validated tool for evaluating the methodological quality of studies reporting prevalence data in a systematic review [46]. The JBIPCAT revised version [46] includes nine questions used to evaluate the methodological quality of studies reporting prevalence data. These questions require responses of yes, no, unclear, or not applicable. The percentage of number of "yeses" was calculated for each included study.

Statistical analyses

In this meta-analysis, to evaluate the pooled estimates of the prevalence of co-occurrence of OSA and insomnia, we obtained an estimate of the proportion of OSA in patients with insomnia, the proportion of insomnia in patients with OSA, and the proportion of DFA, DMS and EMA in patients with OSA from each study. To assess the worldwide geographical distribution of the prevalence of co-occurrence of OSA and insomnia, we performed a subgroup analysis according to the broad WHO regional classifications (i.e., Africa, Americas, South East Asia, Europe, Eastern Mediterranean, and Western Pacific) [27,28] (Details of how this classification was used is presented in Supplementary Data). When possible, sex differences in co-occurrence were explored across subgroup analyses and univariate meta-regression was used to assess variations of co-occurrence with age, BMI, and methodological variables (i.e., study design and recruitment). To strengthen the results, random-effects models were used in all of the tests. Publication bias was evaluated

with a funnel plot and tested for asymmetry using the Egger's test [48], with p values below 0.05 suggesting the presence of bias. All statistical analyses were performed using Comprehensive Meta-Analysis and STATA software.

Results

Study selection

Our search yielded 10,360 publications (Fig. 1). After removing the duplicates, we screened the title and abstract of the remaining 6441 articles. A total of 125 articles were selected for full paper review. Of these, 37 articles were found to meet the inclusion criteria (the excluded studies and reasons for their exclusion are provided in Table S8).

Insomnia/insomnia symptoms in OSA

Study characteristics. Seven studies involving a total of 8820 OSA patients reporting on prevalence rates of insomnia and 27 studies (one study was in both categories) involving a total of 25,987 OSA patients reporting on insomnia symptoms met our inclusion criteria (Table 1). Within WHO regions, one study [49] was a multi-center design (including patients from US, Australia, Germany, Brazil, Taiwan and Iceland), while nine studies [24,50–57] were conducted in the European Region, eleven studies [58–68] were conducted in the Western Pacific Region, one study [69] was conducted in the South-East Asia Region, and 11 studies [70–80] were conducted in the Region of the Americas. As for OSA diagnosis, 14 studies [50,57–60,62–64,69,70,72,74,78,80] used AHI≥5, five studies [55,66,73,75,79] used AHI≥10, nine studies [24,49,53,54,56,61,67,71,77] used AHI≥15, four studies [51,52,65,76] used criteria of AHI≥5 and AHI≥15, and one study [68] used AHI≥20. With respect to oxygen desaturation for hypopnea, six studies [56,58,66,68,70,71] used ≥3%, 18 studies [24,49,51–55,59,60,62–64,67,69,74,76,77,80] used ≥4%, eight studies [50,57,61,65,72,75,78,79] did not specify the oxygen desaturation for hypopnea, and one study [73] did not use desaturation. Of the seven studies that reported an insomnia diagnosis, four studies [51,60,70,71] used DSM or ICSD criteria, one study [50] reported that insomnia cases were physician diagnosed, and two studies [58,59] used an ISI score ≥15 to determine insomnia. The quality assessments of included studies are available in Table S11.

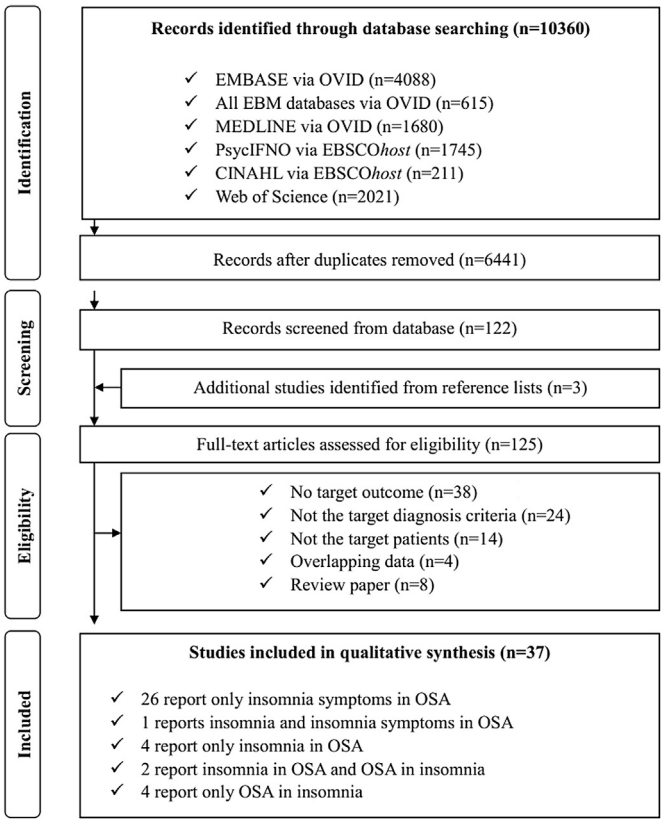

Fig. 1. Flow chart used for the identification of eligible studies.

Overall prevalence of insomnia/insomnia symptoms in patients with OSA

The pooled estimated prevalence rates of insomnia, any insomnia complaints, DFA, DMS, and EMA in patients with OSA were 38.0% (95% confidence interval [CI]: 15–64%), 36% (95%CI: 26–46%), 18% (95%CI: 14–23%), 42% (95%CI: 32–51%), and 21% (95% CI: 14–28%), respectively (Figs. 2–6).

Regional prevalence of insomnia/insomnia symptoms in patients with OSA

Data needed for calculating the regional prevalence of insomnia in patients with OSA were lacking from the African Region, the Eastern Mediterranean Region and the South-East Asia Region. Therefore, we were only able to assess prevalence in the other three geographic regions. The pooled prevalence of insomnia in patients with OSA in the European Region, Region of the Americas, and Western Pacific Region was 48% (95%CI: 2–97%), 49% (95%CI: 41–57%), and 28% (95% CI: 26–31%), respectively (Fig. 2). The rate of insomnia in patients with OSA in the Western Pacific Region was lower than in the other regions ($p < 0.001$).

The pooled prevalence rates of any insomnia complaints in patients with OSA in the European Region, Region of the Americas, and Western Pacific Region were 29% (95%CI: 14–47%), 51% (95%CI: 36–66%), and 31% (95% CI:17–48%), respectively (Fig. 3). The rate of any insomnia complaints in patients with OSA in the Region of the Americas appeared higher than in other regions, but the difference was not statistically significant ($p = 0.110$).

The pooled prevalence of DFA in patients with OSA in the European Region, Region of the Americas, and Western Pacific Region was 20% (95%CI: 12–30%), 24% (95%CI: 16–32%), and 9% (95% CI: 5–14%), respectively (Fig. 4). The rate of DFA in patients with OSA in the Western Pacific Region was significantly lower than in the other regions ($p < 0.001$).

The pooled prevalence of DMS in patients with OSA in the European Region, Region of the Americas, and Western Pacific Region was 52% (95%CI: 41–64%), 35% (95%CI: 22–48%), and 28% (95% CI: 19–38%), respectively (Fig. 5). The rate of DMS in patients with OSA in the European Region was significantly higher than in the other regions ($p < 0.001$).

The pooled prevalence of EMA in patients with OSA in the European Region, Region of the Americas, and Western Pacific Region was 27% (95%CI: 19–35%), 24% (95%CI: 15–35%), and 9% (95% CI:2–20%), respectively (Fig. 6). The rate of EMA in patients with OSA in the Western Pacific Region was significantly lower than in the other regions ($p < 0.001$).

Effects of sex, age and BMI

The meta-regression analysis of OSA patients found that being male was associated with lower prevalence rates of DFA and EMA

Table 1
Summary of included studies reporting the prevalence rates of insomnia and insomnia symptoms in patients with OSA used in the meta-analysis (for more information please see Table S9).

Study	Country	OSA sample size	Study design	Recruitment setting	Sample	Insomnia Diagnosis criteria	Evaluation of insomnia symptoms	OSA criteria	Oxygen desaturation for hypopnea	Prevalence of insomnia	Prevalence rates of insomnia symptoms
Saaresranta et al., 2016 [50]	17 European countries and Israel	6555	Baseline cross-sectional data of longitudinal design	Hospital	Consecutive patients; 75.4% male; mean age (range): 52.93 (18–80); mean BMI: 31.7; mean AHI: 34.57	Physician diagnosed	Questions designed by the investigators	AHI≥5 (PSG/PG in sleep lab)	Unspecified	5.6%	Any insomnia complaints (53.5%)
Lichstein et al., 2013 [70]	US	89	Cross -sectional	Hospital	Consecutive patients; age range: 15–86; unspecified gender, BMI and AHI	ICSD-2	N/R	AHI≥5 (sleep lab PSG)	≥3%	67.4%	N/R
Kline et al., 2014 [71]	US	64	Baseline cross-sectional data of longitudinal design	Community	Recruited patients; 100% female; mean age: 52.8; mean BMI: 36.4; unspecified AHI	DSM-IV	N/R	AHI≥15 (home PSG)	>3%	23.4%	N/R
Cho et al., 2018 [58]	Korea	476	Cross-sectional	Hospital	Consecutive patients; 75.8% male; mean age (range):50.9 (20–75); mean BMI: 25.56; mean AHI: 33.68	ISI≥15	N/R	AHI≥5 (sleep lab PSG)	≥3%	29.2%	N/R
		350	Cross-sectional	Hospital	Consecutive patients; unspecified age, gender and BMI	ISI≥15	N/R	AHI≥15 (sleep lab PSG)	≥3%	29.1%	N/R
Choi et al., 2015 [59]	Korea	117	Cross-sectional	Hospital	Consecutive patients; 87.2% male; mean age (range): 49.36 (20–75); mean BMI: 26.34; mean AHI: 32.19	ISI≥15	N/R	AHI≥5 (sleep lab PSG)	≥4%	27.4%	N/R
Choi et al., 2016 [60]	Korea	198	Cross-sectional	Hospital	Consecutive patients; 82.3% male; age range: (20–79); unspecified age, BMI and AHI	DSM-IV and ICSD-2	N/R	AHI≥5 (sleep lab PSG)	≥4%	24.7%	N/R
Bjorvatn et al., 2015 [51]	Norway	648	Cross-sectional	Hospital	Consecutive patients; 75% male; age range (17–83); unspecified age, BMI and AHI	DSM-IV	N/R	AHI≥5 (Type three portable monitor in home)	≥4%	73.8%	N/R
		323			Consecutive patients; 83.3% male; age range (17–83); unspecified age, BMI and AHI	DSM-IV	N/R	AHI≥15 (Type three portable monitor in home)	≥4%	72.1%	N/R
Nigro et al., 2018 [72]	Argentina	788	Cross-sectional	Hospital	Consecutive patients; 61.4% male; unspecified age, BMI, AHI	N/R	Questions designed by the investigators	AHI≥5 (sleep lab PSG)	unspecified	N/R	DFA (21.95%); DMS (20.3%)
Ambrogetti et al., 1991 [61]	Australia	66	Cross-sectional	Hospital	Consecutive patients; 66.7% male; mean age: 59.4; unspecified BMI and AHI	N/R	Questions designed by the investigators	AHI≥15 (sleep lab PSG)	unspecified	N/R	DFA (11.3%)
Krell et al., 2005 [73]	US	228	Cross-sectional	Hospital	Consecutive patients; age range (20–85); unspecified gender, BMI and AHI	N/R	Questions designed by the investigators	AHI≥10 (sleep lab PSG)	Did not use desaturation	N/R	Any insomnia complaints (51.8%); DFA (29.4%), DMS (36.4%); EMA (28.9%)
Wickwire et al., 2010 [74]	US	232	Baseline cross-sectional data of longitudinal design	Hospital	Consecutive patients; 56.5% male; mean age: 53.6; mean BMI: 34.4; mean AHI:41.8	N/R	Questions designed by the investigators	AHI≥5 (sleep lab PSG)	≥4%	N/R	Any insomnia complaints (37%); DFA (16.6%), DMS

(*continued on next page*)

Table 1 (*continued*)

Study	Country	OSA sample size	Study design	Recruitment setting	Sample	Insomnia Diagnosis criteria	Evaluation of insomnia symptoms	OSA criteria	Oxygen desaturation for hypopnea	Prevalence of insomnia	Prevalence rates of insomnia symptoms
											(23.7%), EMA (20.6%)
Subramanian et al., 2011 [75]	US	300	Cross-sectional	Hospital	Convenience sample; 50% male; mean Age: 49.42; mean BMI: 43.07; mean AHI: 46.79	N/R	Questions designed by the investigators	AHI>10 (sleep lab PSG)	Unspecified	N/R	DFA (57.3%); DMS (68%); EMA (48%)
Arnardottir et al., 2016 [52]	Iceland	164	Cross-sectional	Community	Recruited form general population; 60.4% male; mean age (range): 56.6 (40−65);;mean BMI: 29.4; mean AHI: 15.1	N/R	Questions derived from a valid questionnaire (BNSQ items)	AHI≥5 (Type three portable monitor)	≥4%	N/R	DFA (13%), DMS (36.9%), EMA (15.7%)
	Iceland	64	Cross-sectional	Community	Recruited form general population; 68.7% male; mean age (range): 57.49 (40−65); mean BMI: 30.08; mean AHI: 24.39	N/R	Questions derived from a valid questionnaire (BNSQ items)	AHI≥15 (Type 3 portable monitor)	≥4%	N/R	DFA (17%), DMS (38%), EMA (18.7%)
Björnsdóttir et al., 2016 [53]	Iceland	284	Cross-sectional	Hospital	Consecutive patients; 78.5% male; mean age: 53.9; mean BMI: 33.0; mean AHI: 33.1	N/R	Questions derived from a valid questionnaire (BNSQ items)	AHI≥15 (Type three portable monitor/ Embla 12 channel system/T3 device in sleep lab)	≥4%	N/R	DFA (18.5%), DMS (55.5%), EMA (28.0%)
Björnsdóttir et al., 2012 [24]	Iceland	824	Cross-sectional	Hospital	Consecutive patients; 81.2% male; mean age: 54.4; mean BMI: 33.53; unspecified AHI	N/R	Questions derived from a valid questionnaire (BNSQ items)	AHI≥15 (Type three portable monitor or an Embla 12 channel System in sleep lab)	≥4%	N/R	DFA (15.4%); DMS (53.6%)
Eysteinsdottir et al., 2017 [54]	Iceland	796	Baseline cross-sectional data of longitudinal design	Hospital	Consecutive patients; 80.9% male; mean age: 54.2; mean BMI: 33.5; mean AHI: 44.8	N/R	Questions derived from a valid questionnaire (BNSQ items)	AHI≥15 (Type three portable monitor or an Embla 12 channel System in sleep lab)	≥4%	N/R	EMA (27.7%)
Keenan et al., 2018 [49]	International (US, Australia, Germany, Brazil, and Taiwan)	757	Cross-sectional	Hospital	Recruited patients; 72.8% male; mean age: 50.9; mean BMI: 33.8; mean AHI: 46.6	N/R	Questions derived from a valid questionnaire (BNSQ items)	AHI≥15 (sleep lab PSG or home sleep test)	≥4%	N/R	DFA (33.0%), DMS (48.3%), EMA (39.2%)
	Iceland	215	Cross-sectional	Hospital	Recruited patients; 61.4% male; mean age: 55.3; mean BMI: 34.0; mean AHI: 29.8	N/R	Questions derived from a valid questionnaire (BNSQ items)	AHI≥15 (sleep lab PSG or home sleep test)	≥4%	N/R	DFA (40.9%), DMS (74.2%), EMA (43.5%)
Young et al., 1996 [76]	US	223	Baseline cross-sectional data of longitudinal design	Community	Recruited patients; 72.2% male; mean age (range): 47.25 (30−60); mean BMI: 33.36; unspecified AHI	N/R	Questions designed by the investigators	AHI≥5 (sleep lab PSG)	≥4%	N/R	DFA (18.46%), DMS (16.1%), EMA (15%)
		89	Baseline cross-sectional data of longitudinal design	Community	Recruited patients; 80.9% male; mean age (range): 47.21 (30−60); mean BMI: 34.85; unspecified AHI	N/R	Questions designed by the investigators	AHI≥15 (sleep lab PSG)	≥4%	N/R	DFA (18.57%), DMS (21.8%), EMA (19.74%)
Quintana-Gallegoet al., 2004 [55]	Spain	1166	Cross-sectional	Hospital	Consecutive patients; 83.2% male; mean age: 53.72; mean BMI: 33.17; unspecified AHI	N/R	Questions designed by the investigators	AHI≥10 (sleep lab PSG or home PG)	≥4%	N/R	Any insomnia complaints (17.3%)

Gagnadoux et al., 2016 [56]	France	5983	Baseline cross-sectional data of longitudinal design	Hospital	Consecutive patients; 71.1% male; mean age (range): 60.1 (≥18); mean BMI: 31.7; mean AHI: 41	N/R	Questions designed by the investigators	AHI≥15 (PSG or overnight respiratory recording, unspecified performed in sleep or home)	>3%	N/R	Any insomnia complaints (23.5%)
Lee et al., 2014 [62]	Korea	655	Cross-sectional	Hospital	Consecutive patients; 86.9% male; mean age (range): 49.5 (18–83); mean BMI: 25.9; mean AHI: 28.5	N/R	Questions designed by the investigators	AHI≥5 (sleep lab PSG)	≥4%	N/R	Any insomnia complaints (35.5%), DFA (17.8%), DMS (28.8%), EMA (20.7%)
Nam et al., 2016 [63]	Korea	50	Cross-sectional	Hospital	Recruited patients; 90% male; mean age (range): 47.16 (≥20); mean AHI: 30.74; unspecified BMI	N/R	Questions designed by the investigators	AHI≥5 (sleep lab PSG)	≥4%	N/R	DFA (6%), DMS (48%)
Chung et al., 2005 [64]	China	157	Cross-sectional	Hospital	Consecutive patients; 93.0% male; mean age (range): 44.5 (20–72); mean BMI: 27.8; mean AHI: 37.8	N/R	Questions designed by the investigators	AHI≥5 (sleep lab PSG)	≥4%	N/R	Any insomnia complaints (42%), DFA (5.7%), DMS (25.5%), EMA (19.1%)
Luo et al., 2015 [65]	China	328	Cross-sectional	Hospital	Consecutive patients; 90.9% male; mean age (range): 45.6 (>18); unspecified BMI and AHI	N/R	Questions designed by the investigators	AHI≥5 (sleep lab PSG)	N/R	N/R	DFA (5.2%), EMA (1.52%),
		261	Cross-sectional	Hospital	Consecutive patients; 93.1% male; mean age (range): 45.26 (>18); unspecified BMI and AHI	N/R	Questions designed by the investigators	AHI≥15 (sleep lab PSG)	N/R	N/R	DFA (2.7%), EMA (0.77%)
Kapur et al., 2005 [77]	US	1115	Cross-sectional	Community	Community patients; 66.3% male; mean age (range): 64.79 (>40); mean BMI: 31.35; mean AHI: 29.97	N/R	Questions designed by the investigators	AHI≥15 (home PSG)	≥4%	N/R	DFA (13.4%), DMS (19.1%), EMA (17.4%)
Hasan et al., 2012 [69]	India	234	Case-control	Hospital	Consecutive patients; 79% male; mean age: 54; mean BMI: 36; mean AHI: 31.3	N/R	Questions designed by the investigators	AHI≥5 (sleep lab PSG)	≥4%	N/R	DMS (92%)
Basoglu et al., 2018 [57]	Turkey	2827	Cross-sectional	Hospital	Consecutive patients; 72.6% male; mean age (range): 51.96 (≥18); mean BMI: 33.03; unspecified AHI	Self-report	Questions designed by the investigators	AHI≥5 (sleep lab PSG)	Unspecified	N/R	Any insomnia complaints (25.9%)
Lang et al., 2017 [66]	Australia	370	Cross-sectional	Community	Community patients; 100% male; mean age (range): 60.44 (40–85); mean BMI: 29.1; unspecified AHI	N/R	Questions designed by the investigators	AHI≥10 (home PSG)	≥3%	N/R	Any insomnia complaints (12.7%)
Bianchi et al., 2013 [78]	US	185	Cross-sectional	Hospital	Consecutive patients; mean age (range): 53.44 (>18); 65.9% male; mean BMI: 32.16; mean AHI:19.15	N/R	Questions designed by the investigators	AHI>5 (sleep lab PSG)	NR	N/R	Any insomnia complaints (64.3%)
Kim et al., 2018 [67]	Korea	422	Cross-sectional	Community	Patients of population study; 68.5% male; mean age: 61.5; mean BMI: 26.2; mean AHI: 25.6	N/R	Questions derived from a valid questionnaire (BNSQ items)	AHI≥15 (home PSG)	≥4%	N/R	DFA (15.6%); DMS (16.6%); EMA (14.2%)
Gold et al., 2008 [79]	US	186	Cross-sectional	Hospital	Consecutive patient; unspecified male; age BMI; AHI	N/R	Questions designed by the investigators	AHI≥10 (sleep lab PSG)	NA	N/R	DFA (18.3%) DMS (65.1%)

(*continued on next page*)

Table 1 (*continued*)

Study	Country	OSA sample size	Study design	Recruitment setting	Sample	Insomnia Diagnosis criteria	Evaluation of insomnia symptoms	OSA criteria	Oxygen desaturation for hypopnea	Prevalence of insomnia	Prevalence rates of insomnia symptoms
Wahner-Roedler et al., 2007 [80]	US	406	Cross-sectional	Hospital	Consecutive patients; 65.8% male; mean age (range): 57 (18–76); unspecified BMI and AHI	N/R	Questions designed by the investigators	AHI≥5 (sleep lab PSG)	≥4%	N/R	DFA (26.8%); DMS (50.7%)
Tachikawa et al., 2017 [68]	Japan	57	Baseline cross-sectional data of longitudinal design	Hospital	Consecutive patients; 81% male; mean age (range): 60.98 (20–80); mean BMI: 27.85; mean AHI: 43.1	N/R	Questions derived from a valid questionnaire (PSQI items)	AHI>20 (sleep lab PSG)	≥3%	N/R	DFA (12.3%) Any insomnia complaints (38.6%)

AHI, Apnea-Hypopnea Index, events/h; BMI, Body Mass Index, kg/m^2; BNSQ, Basic Nordic Sleep Questionnaire; DFA, difficulty falling asleep; DMS, difficulty maintaining sleep; DSM, Diagnostic and Statistical Manual for Mental disorders; EMA, early morning awaking; ICSD, International Classification of Sleep Disorders; ISI, Insomnia Severity Index; N/R, not reported; OSA, Obstructive Sleep Apnea; PG, Polygraphy; PSG, Polysomnography; PSQI, Pittsburgh Sleep Quality Index.

($p < 0.01$, Table S18), but not with DMS and any insomnia complaints. In the evaluated studies, the reported co-occurrence prevalence rates for males compared to females, respectively, were 23.1% vs. 35.5% for any insomnia complaints, 17.9% vs. 27.9% for DFA, 33.9% vs. 41.8% for DMS, and 22.7% vs. 23.3% for EMA (Table S19).

Age was not significantly associated with the overall prevalence rates of insomnia symptoms in OSA patients ($p > 0.05$).

BMI was associated with overall prevalence rates of DFA, DMS and EMA in OSA patients ($p < 0.05$).

Effects of different AHI cutoffs to define OSA, OSA severity and oxygen desaturation threshold

The use of different AHI cutoffs (5 and 15) to define OSA was not statistically associated with the prevalence rates of insomnia, DFA, DMS and EMA in patients and OSA (Figs. S1–S5).

The potential associations of different oxygen desaturation thresholds (3% and 4%) with the prevalence rates of insomnia and insomnia symptoms in patients with OSA could not be examined because of limited data (Tables S12-S16).

Meta-regression analysis revealed that OSA severity (AHI value) was not associated with the pooled prevalence of insomnia, DFA and DMS ($p > 0.05$), but there was a small significant association with the pooled prevalence of EMA in patients with OSA (Table S18; point estimate = 0.037, $p = 0.006$).

Additional considerations

To assess potential effects of different methodologies, where possible, we also performed a meta-regression analysis to determine whether they had an exclusion criterion for co-occurrence of non-sleep conditions (Yes vs. No), different recruitment settings (community vs. hospital), whether they had an exclusion criteria for patients taking sleep medications (Yes vs. No), and whether the rates of OSA patients taking sleep medications influenced the pooled prevalence rates of co-occurrence (Table S18). We only found that recruitment setting was a significant source of heterogeneity for the pooled prevalence of DMS in patients with OSA ($p = 0.001$). The quality assessment of the included studies found no significant associations between percentage of "yes" answers with the pooled prevalence rates of insomnia/insomnia symptoms in patients with OSA ($p > 0.05$).

Publication bias

Fig. S6 shows the funnel plots of the meta-analyses for the prevalence of insomnia and insomnia symptoms in patients with OSA. No publication bias was found ($p > 0.05$).

OSA in insomnia

Study characteristics. In the studies reporting the prevalence of OSA in patients with insomnia, six studies (two overlapped with the seven studies reported insomnia in OSA) used PSG to diagnosis OSA and included a total of 2507 insomnia patients that met inclusion criteria (Table 2). Among the six eligible studies, two [81,82] were conducted in the European Region, three [60,83,84] were conducted in the Western Pacific Region, and one [71] was conducted in the Region of the Americas. Regarding OSA diagnosis, one study [60] used AHI≥5 to determine OSA, two studies [71,81] used AHI≥15, and three studies [82–84] used AHI≥5 and AHI≥15 as criteria. For oxygen desaturation for hypopnea, four studies [71,81,82,84] used ≥3%, and two studies [60,83] used ≥4%. For insomnia diagnosis, six studies [60,71,81–84] used DSM or ICSD

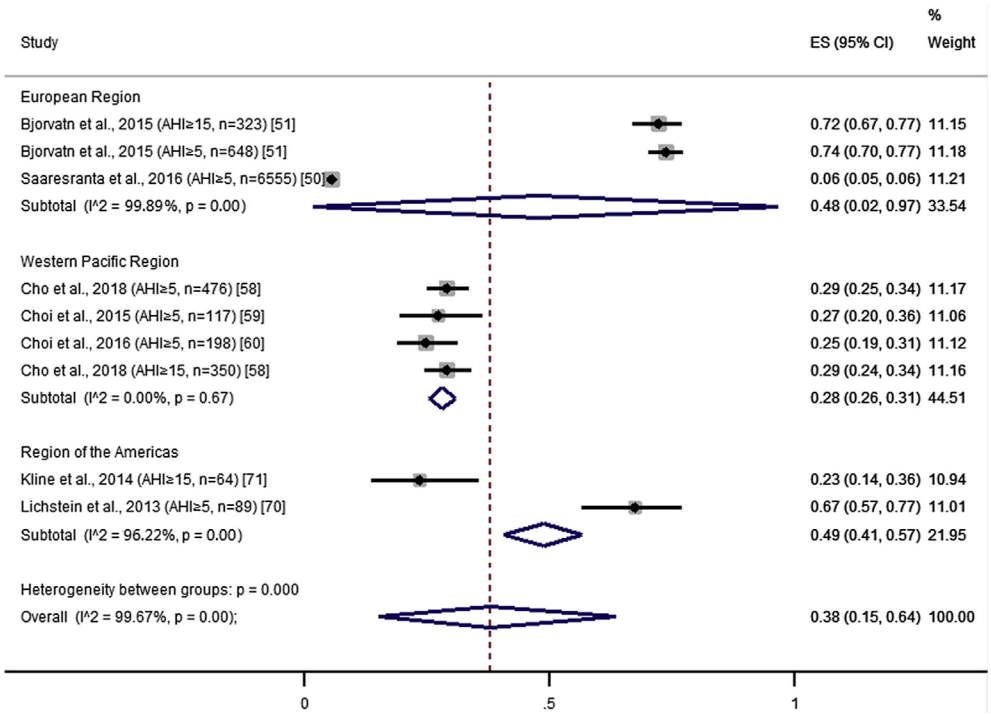

Fig. 2. Forest plot of the overall prevalence of insomnia in patients with OSA. The results are shown as prevalence and 95% confidence interval (CI). ES, effect size (prevalence rate).

criteria. The quality assessments of included studies are available in Table S11.

Prevalence of OSA in patients with insomnia

The prevalence rates of insomnia in OSA patients in the studies using AHI≥5 and studies using AHI≥15 were 35% (95%CI: 31–40%) and 29% (95%CI: 18–41%; Fig. 7), respectively. An analysis of the regional prevalence of insomnia was not performed because of insufficient data in each AHI group.

Effects of oxygen desaturation threshold

The potential associations of different oxygen desaturation thresholds (3% and 4%) with the prevalence of OSA in patients

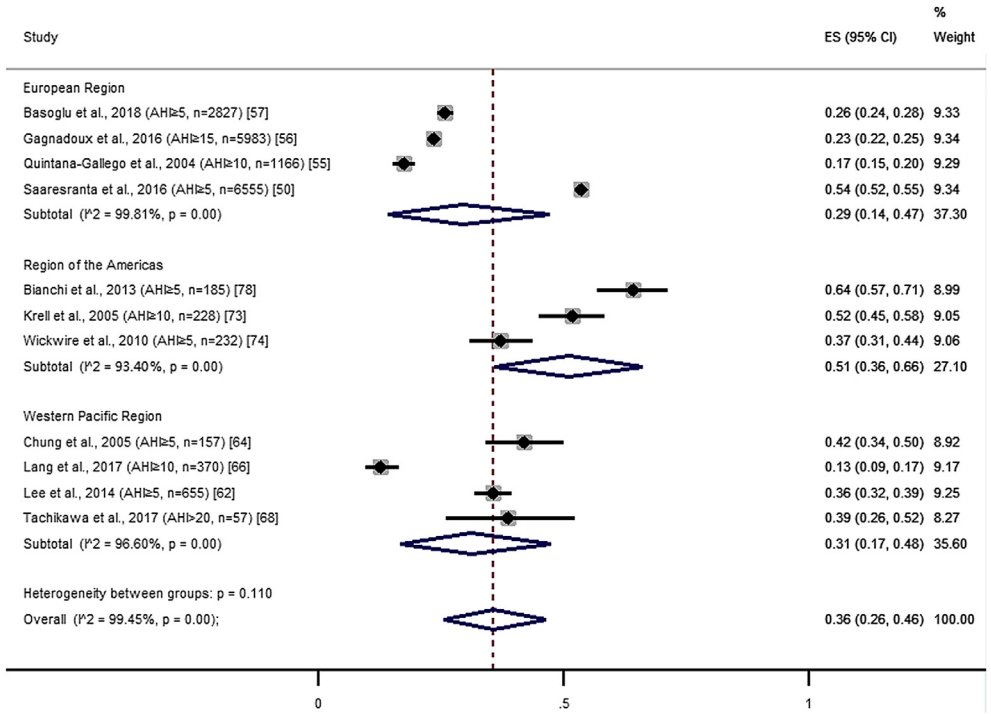

Fig. 3. Forest plot of the overall prevalence of any insomnia complaints in patients with OSA. The results are shown as prevalence and 95% confidence interval (CI). ES, effect size (prevalence rate).

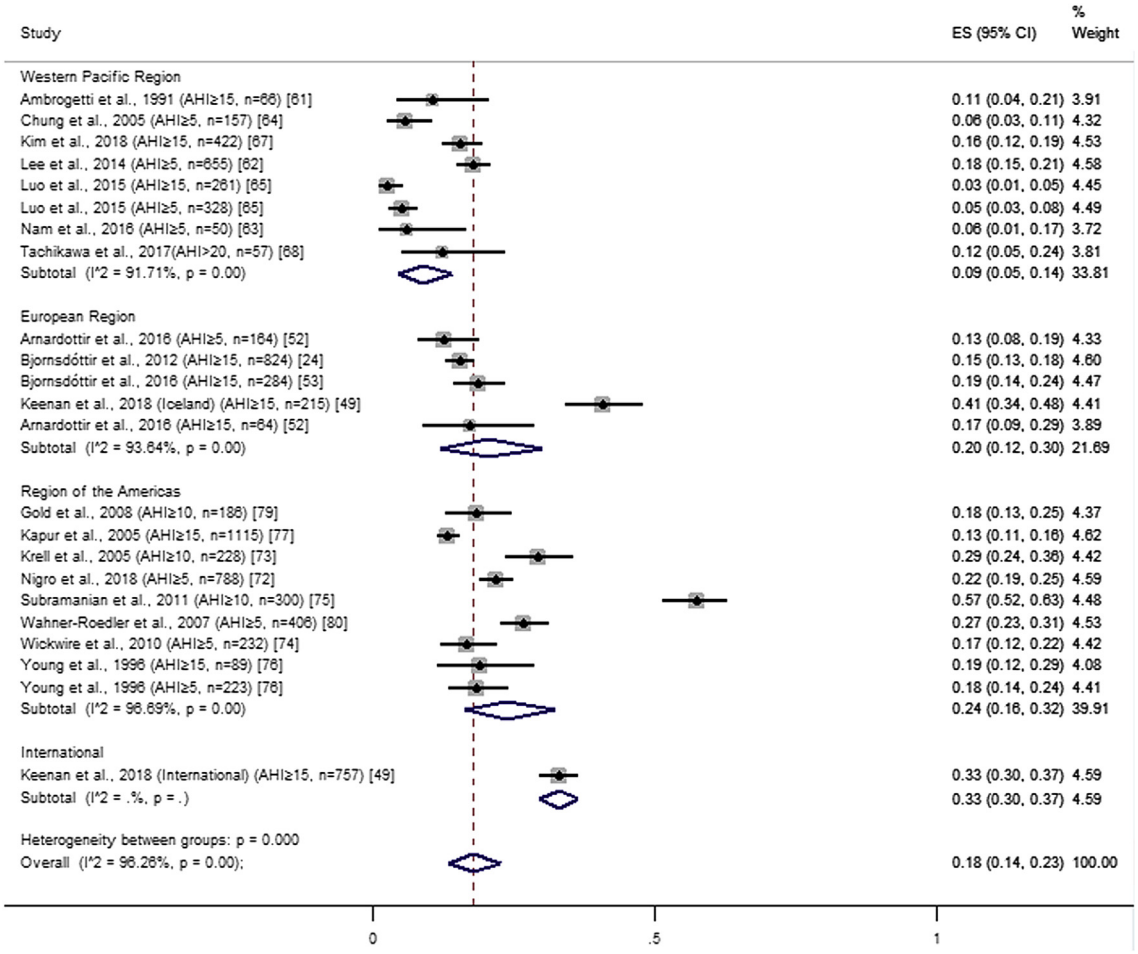

Fig. 4. Forest plot of the overall prevalence of difficulty falling asleep in patients with OSA. The results are shown as prevalence and 95% confidence interval (CI). ES, effect size (prevalence rate).

with insomnia determined by AHI cutoff are shown in Table S17.

Additional considerations

As shown in Table S20, the use of an exclusion criteria for patients taking sleep medications (Yes vs. No), different recruitment setting (Hospital vs. Community), and whether they had an exclusion criterion for co-occurrence of non-sleep conditions (Yes vs. No) were not associated with prevalence of OSA in insomnia in studies using AHI≥5 or AHI≥15 as OSA criteria. The quality assessment of included studies found that the percentage of "yes" answers was a significant source of heterogeneity in the pooled prevalence of OSA in patients with insomnia in studies using AHI≥5 to determine OSA, as well as in studies using AHI≥15 to determine OSA. The prevalence of OSA in insomnia patients was increased with a decrease in percentage of "yes" answers.

Publication bias

Fig. S6 shows the funnel plots of the meta-analyses for the prevalence of OSA in patients with insomnia. No publication bias was found ($p > 0.05$).

Discussion

Summary of findings

We found that the overall pooled prevalence rates of insomnia, any insomnia complaints, DFA, DMS and EMA were 38%, 36%, 18%, 42%, and 21% in patients with OSA, respectively. The prevalence of OSA in patients with insomnia was 35% (AHI≥5) and 29% (AHI≥15), respectively. The prevalence of insomnia and insomnia symptoms varied across regions. Compared with the European Region and Region of the Americas, the rates of insomnia, DFA, DMA and EMA in OSA in the Western Pacific Region were relatively lower.

Co-occurrence of OSA and insomnia

Our meta-analysis revealed that insomnia/insomnia symptoms commonly co-occur with OSA. Given that insomnia and OSA are both associated with the presence and severity of cardiovascular diseases [85,86], their co-occurrence should be closely monitored. It should be noted that the pooled prevalence rate of DMS (42%) in patients with OSA was higher than that of DFA (18%) and of EMA (21%), indicating that the most common insomnia symptom in patients with OSA is DMS, whereas DFA is most common in patients with primary insomnia. This may be due to the fact that the clinical syndrome of sleep apnea associated with insomnia is characterized

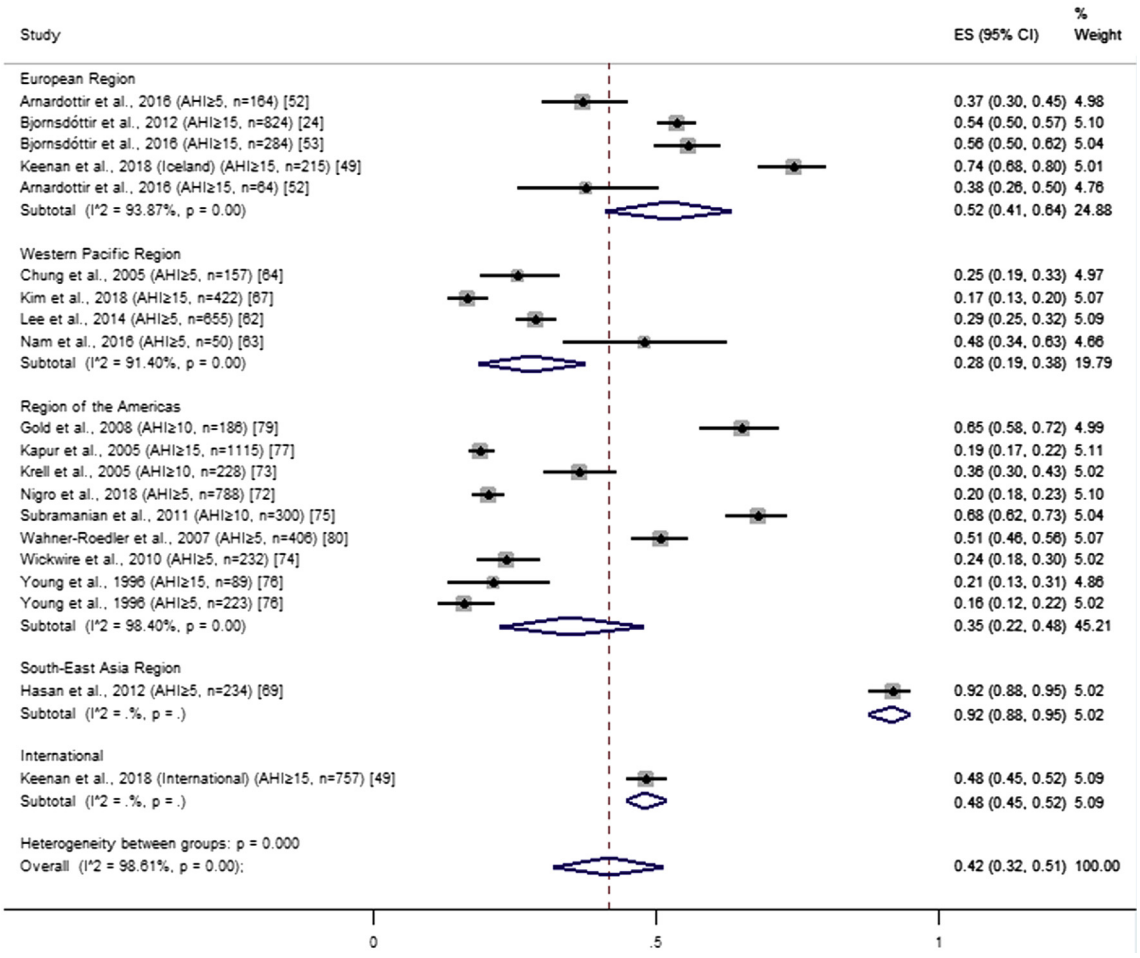

Fig. 5. Forest plot of the overall prevalence of difficulty maintaining sleep in patients with OSA. The results are shown as prevalence and 95% confidence interval (CI). ES, effect size (prevalence rate).

by repeated episodes of apnea during sleep and with respiration onset associated with general arousal and often complete awakening [15]. By comparison, the interactions between neurophysiological hyperarousal and psychological and behavioral processes contribute to the development of insomnia symptoms in patients with primary insomnia [87]. Interestingly, although Nguyên et al. reported that insomnia symptoms in OSA patients could significantly improve with the first-line treatment with CPAP [88], Bjornsdóttir et al. found that CPAP only significantly reduced DMS [26]. Other insomnia symptoms, including DFA and EMA, tended to persist regardless of CPAP treatment, and DFA even negatively impacted CPAP adherence [26]. These results highlight the importance of assessing different insomnia symptoms in the management of OSA [89]. Analyzing the prevalence rates of co-occurrence of each insomnia symptom with OSA has the potential to better support healthcare professionals and policy-makers in making evidence-based decisions that effectively target and address disease burden issues, both now and in the future.

The co-occurrence of insomnia and OSA may also be attributed to their shared pathological physiology and clinical manifestations [17,18]. The sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis play important roles in the development of OSA [90,91], as well as in insomnia [85,92]. Beneto et al. proposed that metabolic factors and activation of the HPA axis could be a link between insomnia and OSA [19].

OSA facilitates the development of insomnia via a psychophysiological conditioning process in which responses to repeated awakenings in sleep lead to a dysfunction in sleep behaviors [19]. In turn, insomnia could worsen OSA symptoms through unknown mechanisms that alter upper airway muscle tone induced by sleep fragmentation and by greater exposure to a less stable, lighter stage of non-rapid eye movement sleep (stage 1) [19,23].

Regional difference and its contributors

These meta-analytic findings provide a general profile of the co-occurrence of OSA and insomnia around the world, and indicate that the prevalence rates of insomnia, DFA, DMS and EMA in patients with OSA in the Western Pacific Region were lower than in other WHO regions. These results might have implications for the prevention and clinical management of the co-occurrence of OSA and insomnia among healthcare providers and policy makers. In the European Region and the Region of Americas, additional effort promoting screening for DFA, DMS and EMA in OSA patients, and of monitoring the associations of different insomnia symptoms with CPAP treatment, could be helpful for improving clinical outcomes.

Age, sex and BMI might be important contributors to the regional differences in co-occurrence of OSA and insomnia. Due to the limited variations of mean age (range from 44.5 to 64.79 y) across studies, we did not find significant associations between the overall prevalence rates of insomnia symptoms (DFA, DMS and EMA) and age in OSA patients within our meta-regression analysis. The mean age of OSA patients in the Western Pacific Region was relatively younger compared to those in almost all the included

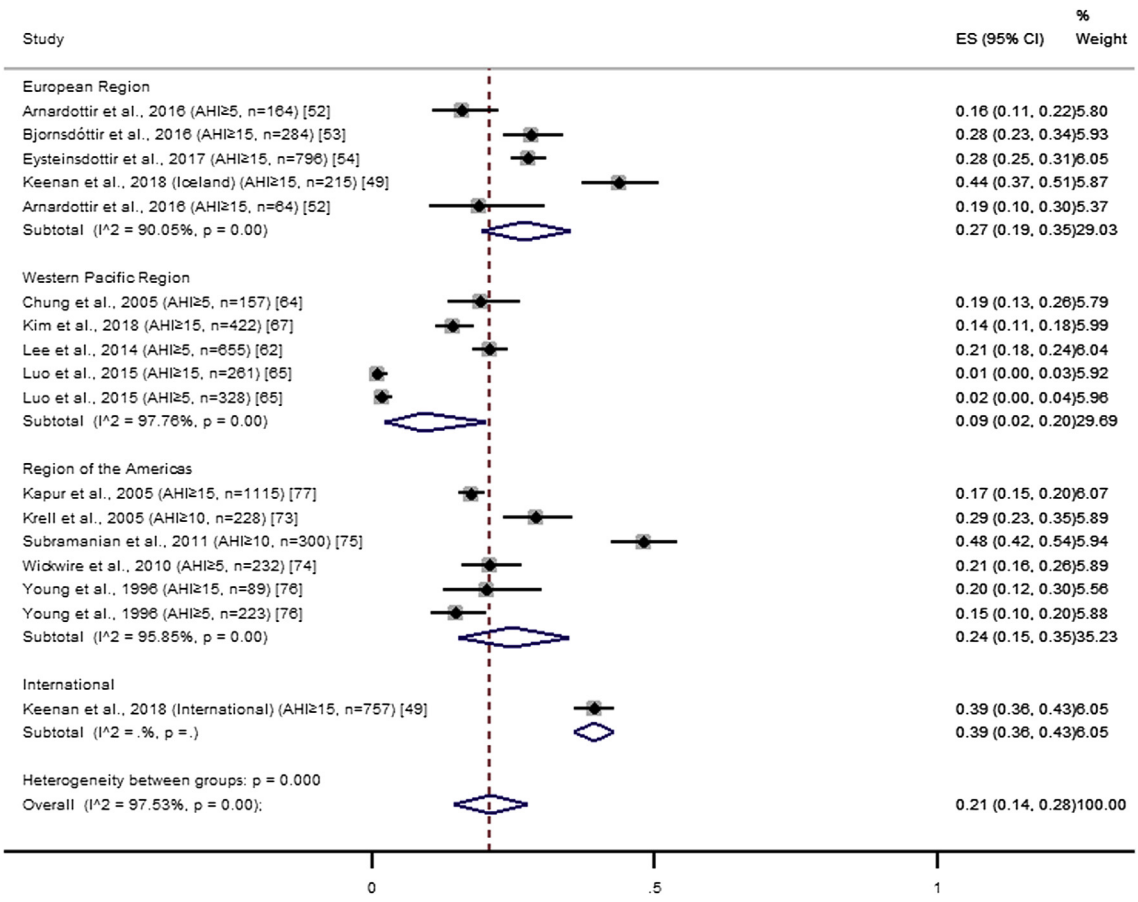

Fig. 6. Forest plot of the overall prevalence of early morning awaking in patients with OSA. The results are shown as prevalence and 95% confidence interval (CI). ES, effect size (prevalence rate).

studies from other regions in our study (Table 1). This result is consistent with our previous findings that OSA patients in the Western Pacific Region have younger ages relative to countries in Europe, North America, and South America [93]. Moreover, a progressively increased risk ratio of insomnia in elderly subjects compared to that in young adults has been reported for the general population in previous studies [29]. Thus, that the rates of insomnia and insomnia symptoms in OSA patients in the Western Pacific Region were lower than those in other regions may partially be explained by differences in age.

The results of the present study indicated that female patients with OSA are more likely to have insomnia symptoms, in particular, DFA and EMA. This finding was similar to that of a previous meta-analysis showing that the risk ratio of insomnia was 1.41 (95% CI: 1.28–1.55) for females compared with males in the general population [29]. Differences between females and males in the action of sex hormones, stress responses in sleep mechanisms, social patterning of behaviors that affect sleep, circadian clock genes, and in respiratory control [94–96] may contribute to sex differences in insomnia symptoms in OSA patients. The regional differences we observed may also relate to the fact that studies in the Western Pacific Region provided data on fewer females (0–33%) than did those from other regions (19.1–100%). It should be noted that there was no sex difference in the prevalence of DMS in OSA patients. This may be due to the fact that the effects of repeated episodes of apnea during sleep on the development of DMS are similar in male and female patients with OSA.

Our meta-regression analysis also found a significant association between BMI and overall prevalence rates of insomnia symptoms in OSA patients, which is accordant with a recent meta-analysis by Chan et al. [97]. They found a significant cross-sectional correlation between insomnia and BMI which supported the hypothesis that insomnia and obesity has an impact on the maintenance of each other [97]. For instance, in a study by Lallukka et al. [98], women with obesity had greater odds of having persistent insomnia at a 5.5 y follow-up than did those without obesity. BMI is a strong determinant of persistent and increasing insomnia symptoms [98]. Therefore, the regional differences we observed may also involve differences in BMI found in the Western Pacific Region (25.56–29.10 kg/m^2) compared to other regions (29.4–43.07 kg/m^2).

Roles of different definitions of OSA and insomnia

It should be noted that the AHI cutoff used to define OSA as well as the oxygen desaturation threshold used to define hypopnea varied across studies in this review. Using different oxygen desaturation thresholds and AHI cutoffs can affect severities of OSA even within the same sex- and age-specific subgroup [99], and thus probably affect the pooled rate of occurrence of insomnia and OSA. To test this possibility, we conducted a meta-regression analysis to explore the effect of AHI on insomnia and insomnia symptoms. However, non-significant relationships were found between AHI and insomnia, DFA, and DMS, and only a small, significant correlation was established between AHI and EMA (point estimate = 0.037, $p = 0.006$). These findings suggest that insomnia and most insomnia symptoms in OSA are not explained by different severities of sleep apnea, as suggested by a previous study [68]. With respect to the pooled rate of OSA in insomnia, a subgroup

Table 2
Summary of included studies reporting the prevalence OSA in patients with insomnia used in the meta-analysis (for more information please see Table S10).

Study	Country	Insomnia sample size	Study design	Recruitment setting	Sample	Insomnia diagnosis criteria	OSA criteria	Oxygen desaturation for hypopnea	Prevalence of OSA in insomnia
Wong et al., 2015 [83]	Singapore	106	Cross-sectional	Hospital	Consecutive patients; 58.5% male; mean age (range): 44.8 (19–81); mean BMI: 23.90; mean AHI:13.87	DSM-IV	AHI≥5	≥4%	42.5%
							AHI>15 (sleep lab PSG)	≥4%	29.2%
Li et al., 2015 [84]	China	860	Cross-sectional	Hospital	Consecutive patients; 47.6% male; mean age (range): 43.0 (18–81); mean BMI: 22.99; mean AHI: 6.58	DSM-IV	AHI≥5 (sleep lab PSG)	≥3%	30.2%
						DSM-IV	AHI≥15 (sleep lab PSG)	≥3%	13.6%
Kline et al., 2014 [71]	US	48	Baseline cross-sectional data of longitudinal design	Community	Recruited patients; 100% female; mean age: 52.4; mean BMI: 34.1	DSM-IV	AHI≥15 (home PSG)	≥3%	31.3%
Choi et al., 2016 [60]	Korea	118	Cross-sectional	Hospital	Consecutive patients; 44.9% male; unspecified age, BMI and AHI	DSM-IV and ICSD	AHI≥5 (sleep lab PSG)	≥4%	41.5%
Hein et al., 2017 [82]	Belgium	1311	Cross-sectional	Hospital	Recruited patients; 47.2% male; mean age (range): 45.09 (>18); mean BMI: 26.92	DSM-IV	AHI≥5	≥3%	34.5%
							AHI≥15 (sleep lab PSG)	≥3%	13.9%
Kinugawa et al., 2012 [81]	France	64	Cross-sectional	Hospital	Aged 60 and older among consecutive patients; 37.5% male; mean age: 72; unspecified BMI and AHI	ICSD	AHI≥15 (sleep lab PSG)	≥3%	68.75%

AHI, Apnea-Hypopnea Index; BMI, Body Mass Index; DSM, Diagnostic and Statistical Manual for Mental disorders; ICSD, International Classification of Sleep Disorders; OSA, Obstructive Sleep Apnea; PSG, Polysomnography.

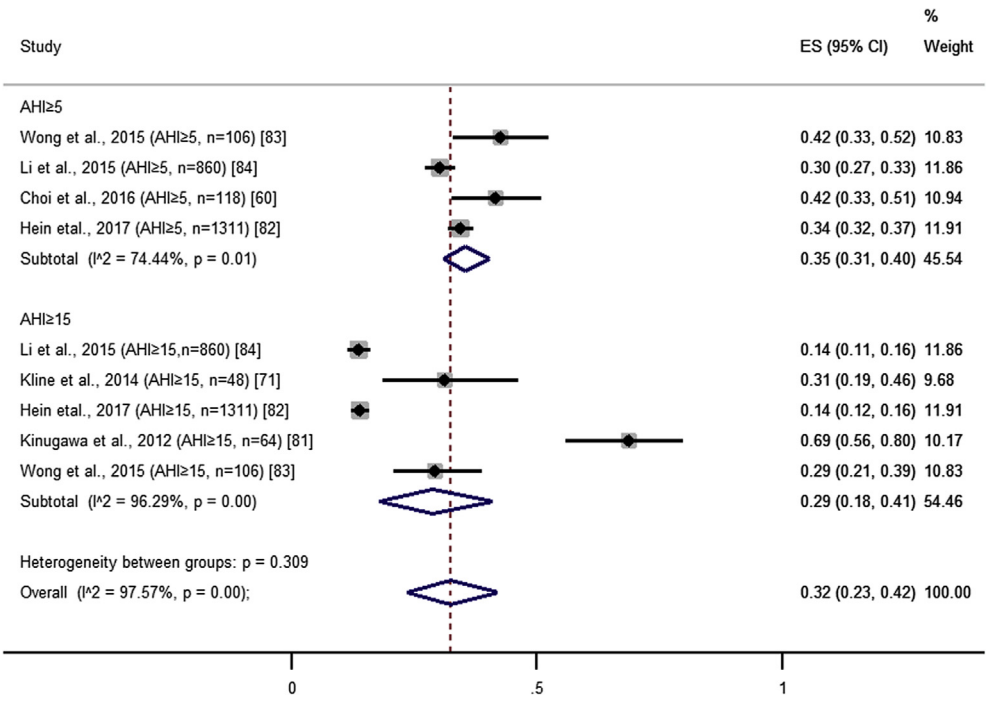

Fig. 7. Forest plot of the overall prevalence of OSA in patients with insomnia. The results are shown as prevalence and 95% confidence interval (CI). AHI, apnea hypopnea index; ES, effect size (prevalence rate).

analysis was performed to explore the effects of oxygen desaturation threshold and different AHI cutoffs (Table S17). However, the limited data in the subgroups prevented definite conclusions, and suggests that this question should be examined in future studies.

A subgroup analysis revealed that the different insomnia definitions (DSM/ICSD, ISI≥15 or physician diagnosed) were a significant source of heterogeneity in the overall pooled prevalence of insomnia in OSA patients, indicating that different definitions of insomnia diagnosis could impact assessments of the prevalence of insomnia in OSA patients. The rating scales, such as ISI, were often informant-based, patient−informant association and informants' expectation of normal behavior may have influenced insomnia diagnoses. Therefore, we used random effects modeling, which accounts for random variations between studies by including both within-study and between-study variance in the calculated effect size [100], to analyze the regional prevalence of insomnia. We found that the rate of insomnia in patients with OSA in the Western Pacific Region was relatively lower than in the Regions of Americas ($p < 0.001$). Although random effects modeling was used, we acknowledge that the lower prevalence of insomnia in OSA patients in the Western Pacific Region may be biased by different definitions of insomnia. Furthermore, the fact that the limited studies in each region could impact estimates of the regional differences in the prevalence of insomnia in OSA indicates that the results should be interpreted with caution.

The results of regional differences were mainly derived from the analysis for insomnia symptoms, including DFA, DMS and EMA. Indeed, the assessment of each insomnia symptom was based on very similar questions across the included studies, only the query mode of the sleep question varied across studies. The potential effect of differences in “query mode” could not be analyzed in our study, because the differences cannot be formulated as a categorical or continuous variable of the type needed to perform a subgroup or meta-regression analysis. There also are no published studies indicating whether different query modes for a sleep question could bias the rates of insomnia symptoms. Thus, we also used random effects modeling to perform the analysis.

Limitations

The present study has limitations. First, although Egger's test found no publication bias, it should be noted that the overall pooled prevalence rates of insomnia/insomnia symptoms in OSA patients or OSA in insomnia patients were mainly sourced from the Region of the Americas, the European Region and the Western Pacific Region. This was due to the fact that so few studies have been conducted in the African Region, the South-East Asia Region and the Eastern Mediterranean Region. Furthermore, assessments of publication bias within each region were not performed because of limited data. Thus, more studies in these regions are warranted. Second, there were insufficient data to allow exploring the effects of oxygen desaturation of hypopnea on the pooled prevalence measures. Therefore, the results of the prevalence rates of insomnia and/or insomnia symptoms with OSA may be biased and should be verified in future studies. Third, the low number of included studies that have documented the prevalence of insomnia in OSA and the prevalence of OSA in insomnia to date resulted in a limited total number of participants for review. Thus, more well-designed studies with quality control and larger sample sizes are needed. Fourth, none of our included studies provided control groups which would have enabled comparisons of the prevalence of insomnia in patients with and without OSA, and of the prevalence of OSA in patients with and without insomnia. Such comparisons are needed in order to place these prevalence data in the context of occurrences within the general population.

Conclusion

In conclusion, insomnia and insomnia symptoms are commonly seen in patients with OSA, and DMS is the most common insomnia

symptom in patients with OSA. Regional differences of the prevalence rates of insomnia, DFA, DMS and EMA in patients with OSA were found, and these were lower in the Western Pacific Region than in the European Region and the Region of the Americas. Co-occurrence of OSA in patients with insomnia is also a common condition, but there are insufficient current data to allow exploring regional differences. The findings of this review therefore highlight the need to undertake systematic and routine screening and comprehensive assessment of co-occurring OSA and insomnia.

Practice points

1) Patients with obstructive sleep apnea may be vulnerable to insomnia, and patients with insomnia may be vulnerable to obstructive sleep apnea.
2) The rates of insomnia, difficulty falling asleep, difficulty maintaining sleep and early morning awakening in the Western Pacific Region were lower than in the European Region and Region of the Americas for patients with obstructive sleep apnea.
3) Difficulty maintaining sleep is the most common insomnia symptom in patients with obstructive sleep apnea.
4) Female patients with obstructive sleep apnea are more likely to complain of difficulty falling asleep and early morning awakening compared with male patients with obstructive sleep apnea.

Research agenda

1) Investigate the prevalence of co-occurrence of obstructive sleep apnea and insomnia in the African Region, the Eastern Mediterranean Region and South-East Asia Region.
2) Investigate the contributions of sex, age and body mass index on the regional differences of prevalence rates of insomnia and insomnia symptoms with obstructive sleep apnea.
3) Develop effective measures for treatment and management to improve clinical outcomes and quality of life in patients with obstructive sleep apnea and insomnia.
4) Explore the mechanisms that underlie the relationship between obstructive sleep apnea and insomnia.

Conflicts of interest

None.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2019.01.004.

References

[1] Pretto JJ, Gyulay SG, Hensley MJ. Trends in anthropometry and severity of sleep-disordered breathing over two decades of diagnostic sleep studies in an Australian adult sleep laboratory. Med J Aust 2010;193(4):213–6.
[2] Punjabi NM, Caffo BS, Goodwin JL, Gottlieb DJ, Newman AB, O'Connor GT, et al. Sleep-disordered breathing and mortality: a prospective cohort study. PLoS Med 2009;6(8):e1000132.
[3] Park JG, Ramar K, Olson EJ. Updates on definition, consequences, and management of obstructive sleep apnea. Mayo Clin Proc 2011;86(6):549–54. quiz 54-5.
[4] Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC, et al. Prevalence of obstructive sleep apnea in the general population: a systematic review. Sleep Med Rev 2017;34:70–81.
[5] Theorell-Haglow J, Miller CB, Bartlett DJ, Yee BJ, Openshaw HD, Grunstein RR. Gender differences in obstructive sleep apnoea, insomnia and restless legs syndrome in adults - what do we know? A clinical update. Sleep Med Rev 2018;38:28–38.
[6] Mai E, Buysse DJ. Insomnia: prevalence, impact, pathogenesis, differential diagnosis, and evaluation. Sleep Med Clin 2008;3(2):167–74.
[7] Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. Sleep Med Rev 2002;6(2):97–111.
[8] Roth T. Insomnia: definition, prevalence, etiology, and consequences. J Clin Sleep Med 2007;3(5 Suppl):S7–10.
[9] Ren R, Li Y, Zhang J, Zhou J, Sun Y, Tan L, et al. Obstructive sleep apnea with objective daytime sleepiness is associated with hypertension. Hypertension 2016;68(5):1264–70.
[10] Li Y, Vgontzas AN, Fernandez-Mendoza J, Bixler EO, Sun Y, Zhou J, et al. Insomnia with physiological hyperarousal is associated with hypertension. Hypertension 2015;65(3):644–50.
[11] Reutrakul S, Mokhlesi B. Obstructive sleep apnea and diabetes: a state of the art review. Chest 2017;152(5):1070–86.
[12] Anothaisintawee T, Reutrakul S, Van Cauter E, Thakkinstian A. Sleep disturbances compared to traditional risk factors for diabetes development: systematic review and meta-analysis. Sleep Med Rev 2016;30:11–24.
[13] Kapur V, Blough DK, Sandblom RE, Hert R, de Maine JB, Sullivan SD, et al. The medical cost of undiagnosed sleep apnea. Sleep 1999;22(6):749–55.
[14] Walsh JK, Engelhardt CL. The direct economic costs of insomnia in the United States for 1995. Sleep 1999;22(Suppl 2):S386–93.
[15] Guilleminault C, Eldridge FL, Dement WC. Insomnia with sleep apnea: a new syndrome. Science 1973;181:856–8.
[16] Wickwire EM, Collop NA. Insomnia and sleep-related breathing disorders. Chest 2010;137(6):1449–63.
*[17] Luyster FS, Buysse DJ, Strollo Jr PJ. Comorbid insomnia and obstructive sleep apnea: challenges for clinical practice and research. J Clin Sleep Med 2010;6(2):196–204.
*[18] Sweetman AM, Lack LC, Catcheside PG, Antic NA, Chai-Coetzer CL, Smith SS, et al. Developing a successful treatment for co-morbid insomnia and sleep apnoea. Sleep Med Rev 2017;33:28–38.
*[19] Beneto A, Gomez-Siurana E, Rubio-Sanchez P. Comorbidity between sleep apnea and insomnia. Sleep Med Rev 2009;13(4):287–93.
[20] Ong JC, Crawford MR. Insomnia and obstructive sleep apnea. Sleep Med Clin 2013;8(3):389–98.
[21] Zhang J, Lamers F, Hickie IB, He JP, Feig E, Merikangas KR. Differentiating nonrestorative sleep from nocturnal insomnia symptoms: demographic, clinical, inflammatory, and functional correlates. Sleep 2013;36(5):671–9.
[22] Smith S, Sullivan K, Hopkins W, Douglas J. Frequency of insomnia report in patients with obstructive sleep apnoea hypopnea syndrome (OSAHS). Sleep Med 2004;5(5):449–56.
*[23] Krakow B, Melendrez D, Ferreira E, Clark J, Warner TD, Sisley B, et al. Prevalence of insomnia symptoms in patients with sleep-disordered breathing. Chest 2001;120(6):1923–9.
[24] Bjornsdottir E, Janson C, Gislason T, Sigurdsson JF, Pack AI, Gehrman P, et al. Insomnia in untreated sleep apnea patients compared to controls. J Sleep Res 2012;21(2):131–8.
[25] Morin CM, Benca R. Chronic insomnia. Lancet 2012;379(9821):1129–41.
*[26] Bjornsdottir E, Janson C, Sigurdsson JF, Gehrman P, Perlis M, Juliusson S, et al. Symptoms of insomnia among patients with obstructive sleep apnea before and after two years of positive airway pressure treatment. Sleep 2013;36(12):1901–9.

* The most important references are denoted by an asterisk.

[27] https://en.wikipedia.org/wiki/WHO_regions.
[28] http://www.who.int/.
[29] Zhang B, Wing YK. Sex differences in insomnia: a meta-analysis. Sleep 2006;29(1):85–93.
[30] Smagula SF, Stone KL, Fabio A, Cauley JA. Risk factors for sleep disturbances in older adults: evidence from prospective studies. Sleep Med Rev 2016;25:21–30.
[31] Ong CW, O'Driscoll DM, Truby H, Naughton MT, Hamilton GS. The reciprocal interaction between obesity and obstructive sleep apnoea. Sleep Med Rev 2013;17(2):123–31.
[32] Tuomilehto H, Seppa J, Uusitupa M. Obesity and obstructive sleep apnea–clinical significance of weight loss. Sleep Med Rev 2013;17(5):321–9.
*[33] Hnin K, Mukherjee S, Antic NA, Catcheside P, Chai-Coetzer CL, McEvoy D, et al. The impact of ethnicity on the prevalence and severity of obstructive sleep apnea. Sleep Med Rev 2018;41:78–86.
[34] Rosenthal R, DiMatteo MR. Meta-analysis: recent developments in quantitative methods for literature reviews. Annu Rev Psychol 2001;52:59–82.
[35] Stanley TD. Wheat from chaff: meta-analysis as quantitative literature review. J Econ Perspect 2001;15(3):131–50.
[36] Rapoport DM. POINT: is the apnea-hypopnea index the best way to quantify the severity of sleep-disordered breathing? Yes. Chest 2016;149(1):14–6.
[37] American Psychology Association. Diagnostic and statistical manual of mental disorders. Washington, DC: American Psychiatric Association; 1994.
[38] American Academy of Sleep Medicine. International classification of sleep disorders: diagnostic & coding manual. 2nd ed. Westchester, IL: American Academy of Sleep Medicine; 2005.
[39] Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med 2001;2(4):297–307.
[40] Smith S, Trinder J. Detecting insomnia: comparison of four self-report measures of sleep in a young adult population. J Sleep Res 2001;10(3):229–35.
[41] Sinha SS. Trauma-induced insomnia: a novel model for trauma and sleep research. Sleep Med Rev 2016;25:74–83.
[42] Hughes JM, Ulmer CS, Gierisch JM, Nicole Hastings S, Howard MO. Insomnia in United States military veterans: an integrated theoretical model. Clin Psychol Rev 2018;59:118–25.
[43] Krakow BJ, Ulibarri VA, Moore BA, McIver ND. Posttraumatic stress disorder and sleep-disordered breathing: a review of comorbidity research. Sleep Med Rev 2015;24:37–45.
[44] Aloia MS. Understanding the problem of poor CPAP adherence. Sleep Med Rev 2011;15(6):341–2.
[45] Mason M, Cates CJ, Smith I. Effects of opioid, hypnotic and sedating medications on sleep-disordered breathing in adults with obstructive sleep apnoea. Cochrane Database Syst Rev 2015;7:CD011090.
[46] Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. Int J Evid Based Healthc 2015;13(3):147–53.
[47] Munn Z, Moola S, Riitano D, Lisy K. The development of a critical appraisal tool for use in systematic reviews addressing questions of prevalence. Int J Health Policy Manag 2014;3(3):123–8.
[48] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315(7109):629–34.
[49] Keenan BT, Kim J, Singh B, Bittencourt L, Chen NH, Cistulli PA, et al. Recognizable clinical subtypes of OSA across a worldwide sleep center population: a cluster Analysis. Sleep 2018;41(3):zsx214.
*[50] Saaresranta T, Hedner J, Bonsignore MR, Riha RL, McNicholas WT, Penzel T, et al. Clinical phenotypes and comorbidity in european sleep apnoea patients. PLoS One 2016;11(10):e0163439.
[51] Bjorvatn B, Lehmann S, Gulati S, Aurlien H, Pallesen S, Saxvig IW. Prevalence of excessive sleepiness is higher whereas insomnia is lower with greater severity of obstructive sleep apnea. Sleep Breath 2015;19(4):1387–93.
[52] Arnardottir ES, Bjornsdottir E, Olafsdottir KA, Benediktsdottir B, Gislason T. Obstructive sleep apnoea in the general population: highly prevalent but minimal symptoms. Eur Respir J 2016;47(1):194–202.
[53] Bjornsdottir E, Benediktsdottir B, Pack AI, Arnardottir ES, Kuna ST, Gislason T, et al. The prevalence of depression among untreated obstructive sleep apnea patients using a standardized psychiatric interview. J Clin Sleep Med 2016;12(1):105–12.
[54] Eysteinsdottir B, Gislason T, Pack AI, Benediktsdottir B, Arnardottir ES, Kuna ST, et al. Insomnia complaints in lean patients with obstructive sleep apnea negatively affect positive airway pressure treatment adherence. J Sleep Res 2017;26(2):159–65.
[55] Quintana-Gallego E, Carmona-Bernal C, Capote F, Sanchez-Armengol A, Botebol-Benhamou G, Polo-Padillo J, et al. Gender differences in obstructive sleep apnea syndrome: a clinical study of 1166 patients. Respir Med 2004;98(10):984–9.
*[56] Gagnadoux F, Le Vaillant M, Paris A, Pigeanne T, Leclair-Visonneau L, Bizieux-Thaminy A, et al. Relationship between OSA clinical phenotypes and CPAP treatment outcomes. Chest 2016;149(1):288–90.
[57] Basoglu OK, Tasbakan MS. Gender differences in clinical and polysomnographic features of obstructive sleep apnea: a clinical study of 2827 patients. Sleep Breath 2018;22(1):241–9.
[58] Cho YW, Kim KT, Moon HJ, Korostyshevskiy VR, Motamedi GK, Yang KI. Comorbid insomnia with obstructive sleep apnea: clinical characteristics and risk factors. J Clin Sleep Med 2018;14(3):409–17.
[59] Choi SJ, Joo EY, Lee YJ, Hong SB. Suicidal ideation and insomnia symptoms in subjects with obstructive sleep apnea syndrome. Sleep Med 2015;16(9):1146–50.
[60] Choi SJ, Suh S, Ong J, Joo EY. Sleep misperception in chronic insomnia patients with obstructive sleep apnea syndrome: implications for clinical assessment. J Clin Sleep Med 2016;12(11):1517–25.
[61] Ambrogetti A, Olson LG, Saunders NA. Differences in the symptoms of men and women with obstructive sleep apnoea. Aust N Z J Med 1991;21(6):863–6.
[62] Lee MH, Lee SA, Lee GH, Ryu HS, Chung S, Chung YS, et al. Gender differences in the effect of comorbid insomnia symptom on depression, anxiety, fatigue, and daytime sleepiness in patients with obstructive sleep apnea. Sleep Breath 2014;18(1):111–7.
[63] Nam H, Lim JS, Kim JS, Lee KJ, Koo DL, Lee C. Sleep perception in obstructive sleep apnea: a study using polysomnography and the multiple sleep latency test. J Clin Neurol 2016;12(2):230–5.
[64] Chung KF. Insomnia subtypes and their relationships to daytime sleepiness in patients with obstructive sleep apnea. Respiration 2005;72(5):460–5.
[65] Luo M, Zheng HY, Zhang Y, Feng Y, Li DQ, Li XL, et al. A nomogram for predicting the likelihood of obstructive sleep apnea to reduce the unnecessary polysomnography examinations. Chin Med J (Engl) 2015;128(16):2134–40.
[66] Lang CJ, Appleton SL, Vakulin A, McEvoy RD, Wittert GA, Martin SA, et al. Co-morbid OSA and insomnia increases depression prevalence and severity in men. Respirology 2017;22(7):1407–15.
[67] Kim J, Keenan BT, Lim DC, Lee SK, Pack AI, Shin C. Symptom-Based subgroups of koreans with obstructive sleep apnea. J Clin Sleep Med 2018;14(3):437–43.
[68] Tachikawa R, Minami T, Matsumoto T, Murase K, Tanizawa K, Inouchi M, et al. Changes in habitual sleep duration after continuous positive airway pressure for obstructive sleep apnea. Ann Am Thorac Soc 2017;14(6):986–93.
[69] Hasan A, Uzma N, Swamy TL, Shoba A, Kumar BS. Correlation of clinical profiles with obstructive sleep apnea and metabolic syndrome. Sleep Breath 2012;16(1):111–6.
[70] Lichstein KL, Justin Thomas S, Woosley JA, Geyer JD. Co-occurring insomnia and obstructive sleep apnea. Sleep Med 2013;14(9):824–9.
[71] Kline CE, Irish LA, Buysse DJ, Kravitz HM, Okun ML, Owens JF, et al. Sleep hygiene behaviors among midlife women with insomnia or sleep-disordered breathing: the SWAN sleep study. J Womens Health (Larchmt) 2014;23(11):894–903.
[72] Nigro CA, Dibur E, Borsini E, Malnis S, Ernst G, Bledel I, et al. The influence of gender on symptoms associated with obstructive sleep apnea. Sleep Breath 2018;22(3):683–93.
[73] Krell SB, Kapur VK. Insomnia complaints in patients evaluated for obstructive sleep apnea. Sleep Breath 2005;9(3):104–10.
[74] Wickwire EM, Smith MT, Birnbaum S, Collop NA. Sleep maintenance insomnia complaints predict poor CPAP adherence: a clinical case series. Sleep Med 2010;11(8):772–6.
[75] Subramanian S, Guntupalli B, Murugan T, Bopparaju S, Chanamolu S, Casturi L, et al. Gender and ethnic differences in prevalence of self-reported insomnia among patients with obstructive sleep apnea. Sleep Breath 2011;15(4):711–5.
[76] Young T, Hutton R, Finn L, Badr S, Palta M. The gender bias in sleep apnea diagnosis. Are women missed because they have different symptoms? Arch Intern Med 1996;156(21):2445–51.
[77] Kapur VK, Baldwin CM, Resnick HE, Gottlieb DJ, Nieto FJ. Sleepiness in patients with moderate to severe sleep-disordered breathing. Sleep 2005;28(4):472–7.
[78] Bianchi MT, Williams KL, McKinney S, Ellenbogen JM. The subjective-objective mismatch in sleep perception among those with insomnia and sleep apnea. J Sleep Res 2013;22(5):557–68.
[79] Gold AR, Gold MS, Harris KW, Espeleta VJ, Amin MM, Broderick JE. Hypersomnolence, insomnia and the pathophysiology of upper airway resistance syndrome. Sleep Med 2008;9(6):675–83.
[80] Wahner-Roedler DL, Olson EJ, Narayanan S, Sood R, Hanson AC, Loehrer LL, et al. Gender-specific differences in a patient population with obstructive sleep apnea-hypopnea syndrome. Gend Med 2007;4(4):329–38.
[81] Kinugawa K, Doulazmi M, Sebban C, Schumm S, Mariani J, Nguyen-Michel VH. Sleep apnea in elderly adults with chronic insomnia. J Am Geriatr Soc 2012;60(12):2366–8.
[82] Hein M, Lanquart JP, Loas G, Hubain P, Linkowski P. Prevalence and risk factors of excessive daytime sleepiness in insomnia sufferers: a study with 1311 individuals. J Psychosom Res 2017;103:63–9.
[83] Wong SH, Ng BY. Review of sleep studies of patients with chronic insomnia at a sleep disorder unit. Singap Med J 2015;56(6):317–23.
[84] Li Z, Li Y, Yang L, Li T, Lei F, Vgontzas AN, et al. Characterization of obstructive sleep apnea in patients with insomnia across gender and age. Sleep Breath 2015;19(2):723–7.
[85] Javaheri S, Redline S. Insomnia and risk of cardiovascular disease. Chest 2017;152(2):435–44.

[86] Ayas NT, Taylor CM, Laher I. Cardiovascular consequences of obstructive sleep apnea. Curr Opin Cardiol 2016;31(6):599–605.
[87] Levenson JC, Kay DB, Buysse DJ. The pathophysiology of insomnia. Chest 2015;147(4):1179–92.
*[88] Nguyên XL, Rakotonanahary D, Chaskalovic J, Fleury B. Insomnia related to sleep apnoea: effect of long-term auto-adjusting positive airway pressure treatment. Eur Respir J 2013;41(3):593–600.
*[89] Ye L, Pien GW, Ratcliffe SJ, Bjornsdottir E, Arnardottir ES, Pack AI, et al. The different clinical faces of obstructive sleep apnoea: a cluster analysis. Eur Respir J 2014;44(6):1600–7.
[90] Wszedybyl-Winklewska M, Wolf J, Szarmach A, Winklewski PJ, Szurowska E, Narkiewicz K. Central sympathetic nervous system reinforcement in obstructive sleep apnoea. Sleep Med Rev 2018;39:143–54.
[91] Kritikou I, Basta M, Vgontzas AN, Pejovic S, Fernandez-Mendoza J, Liao D, et al. Sleep apnoea and the hypothalamic-pituitary-adrenal axis in men and women: effects of continuous positive airway pressure. Eur Respir J 2016;47(2):531–40.
[92] Vgontzas AN, Fernandez-Mendoza J, Liao D, Bixler EO. Insomnia with objective short sleep duration: the most biologically severe phenotype of the disorder. Sleep Med Rev 2013;17(4):241–54.
[93] Li Z, Du L, Li Y, Huang L, Lei F, Yang L, et al. Characterization of primary symptoms leading to Chinese patients presenting at hospital with suspected obstructive sleep apnea. J Thorac Dis 2014;6(5):444–51.
[94] Mong JA, Cusmano DM. Sex differences in sleep: impact of biological sex and sex steroids. Philos Trans R Soc Lond B Biol Sci 2016;371(1688):20150110.
[95] Mollayeva T, Thurairajah P, Burton K, Mollayeva S, Shapiro CM, Colantonio A. The Pittsburgh sleep quality index as a screening tool for sleep dysfunction in clinical and non-clinical samples: a systematic review and meta-analysis. Sleep Med Rev 2016;25:52–73.
[96] Tang J, Liao Y, Kelly BC, Xie L, Xiang YT, Qi C, et al. Gender and regional differences in sleep quality and insomnia: a general population-based study in hunan province of China. Sci Rep 2017;7:43690.
[97] Chan WS, Levsen MP, McCrae CS. A meta-analysis of associations between obesity and insomnia diagnosis and symptoms. Sleep Med Rev 2018;40:170–82.
[98] Lallukka T, Haario P, Lahelma E, Rahkonen O. Associations of relative weight with subsequent changes over time in insomnia symptoms: a follow-up study among middle-aged women and men. Sleep Med 2012;13(10):1271–9.
[99] Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. Lancet Respir Med 2015;3(4):310–8.
[100] Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods 2010;1(2):97–111.