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COMMENT

Association between obstructive sleep apnea and erectile dysfunction: a systematic review and meta-analysis

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Abstract

The purpose of the present systematic review and meta-analysis was to assess the association between obstructive sleep apnea (OSA) and erectile dysfunction (ED). To address the focused question, "Is there an association between OSA and ED?" indexed databases were searched up to May 2017 without time or language restrictions using various key words including: obstructive sleep apnea, sleep apnea syndromes, erectile dysfunction, sleep-disordered breathing, snoring, sexual function, and impotence. Review articles, case-reports and case-series, commentaries, letters to the editor, interviews and updates, studies assessing the efficacy of OSA treatment in the improvement of ED, or studies evaluating the efficacy of ED treatment in the improvement of OSA were excluded. Twenty-eight observational studies were included for qualitative synthesis. Overall, 19 studies had a cross-sectional design, 7 studies were case–control, and 2 were cohort studies. The odds ratios (OR) with a 95% confidence interval were calculated from 10 studies. The combined OR was 0.45, with a 95% confidence interval of 0.18–0.71, indicating that in patients without OSA, the risk of ED is significantly lower compared with patients with OSA. The available evidence shows that OSA is associated with a higher risk of ED; however, further well-designed controlled clinical trials and longitudinal prospective studies are needed in this regard.

Introduction

Obstructive sleep apnea (OSA) is a chronic disorder characterized by sleep fragmentation and repetitive cessation of breathing during sleep due to the upper airway obstruction [1, 2]. OSA affects ~20% of the adult population in the United States [3], and the worldwide prevalence has been estimated between 9 and 38% [4]. OSA has been associated with poor quality of life, increased fatigue, excessive daytime sleepiness deterioration of personal relationships, and reduced sexual desire [5–7].

According The National Institutes of Health Consensus Conference, erectile dysfunction (ED) is defined as a "consistent inability to attain or maintain a penile erection, or both, sufficient for adequate sexual relations" [8]. It has been estimated that there are more than 18 million men in the United States affected by ED [9]. It has also been projected that there will be ~300 million men worldwide with ED by the year 2025 [10, 11]. Interestingly, clinical and epidemiological studies have suggested an association between OSA and ED [12–39]. Guilleminault et al. [40] in 1977 reported for first time an increased prevalence of ED among a population of patients diagnosed with OSA. Studies [13, 14, 19–21, 26–29, 32, 35, 36, 38, 39] conducted in sleep clinic populations have reported similar findings with an ED prevalence ranging between 41 and 80%. In a recent cross-sectional study, Chen et al. [18] reported that ED incidence was 9.44-fold higher in OSA patients compared with non-OSA patients. Moreover, studies [41, 42] have suggested that OSA treatment with continuous positive airway pressure (CPAP) or oral appliances improved ED. However, conflicting results have been reported. Schiavi

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et al. [33] evaluated 70 systemically healthy men and found no association between OSA and ED. Bozorgmehri et al. [15] performed a study on community dwelling men aged 67 years older and found that OSA was not associated with ED by 5-item International Index of Erectile Function (IIEF).

Since the association between OSA and ED remains debatable, the aim of the present systematic review and meta-analysis was to assess the association between OSA and ED.

Materials and methods

Focused question

The present study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [43]. The Participants, Exposure, Comparative, Outcome (PECO) format was used to formulate the focused question: "Is there an association between OSA and ED?"

Eligibility criteria

The inclusion criteria were as follows: (a) original observational studies (cohort, cross-sectional, or case–control) that evaluated the association between OSA and ED; (b) studies in which ED was assessed using validated instruments: physical examination, questionnaires, or clinical examination of erectile function; (c) studies in which OSA was diagnosed using polysomnography and/or questionnaires. The exclusion criteria were: (a) qualitative and/or quantitative reviews; (b) case-reports/case-series; (d) commentaries; (e) letters to the editor; (f) interviews and updates; (g) observational or interventional studies assessing the efficacy of OSA treatment (CPAP, surgical or oral appliances) in the improvement of ED, or studies evaluating the efficacy or ED treatment (pharmacological or surgical) in the improvement of OSA.

Literature search protocol and data extraction

To identify studies relevant to the focused question, a systematic and structured literature search without language or time restrictions was conducted by two authors (SVK and VRM) using PubMed (National Library of Medicine, Bethesda), Scopus, EMBASE, and Web of Science databases. The databases were searched up to and including May 2017 using different combinations of the following Medical Subject Headings (MeSH) terms: (1) OSA; (2) sleep apnea syndromes; and (3) ED. Other related non-MeSH terms were used in the search strategy to detect articles discussing the association between OSA and ED. These included: (4) sleep apnea; (5) sleep-disordered breathing; (6) snoring; (7) sexual function, and (8) impotence. These keywords were used with Boolean operators (OR, AND) to combine the key words mentioned above: 1 or 2 or 4 or 5 or 6 and 3 or 7 or 8.

To minimize the potential for reviewer bias, titles and abstracts of studies identified using the above-described protocol were independently screened by 2 authors (SVK and VRM) and checked for agreement. Full-texts of studies judged by title and abstract to be relevant were read and independently evaluated for the stated eligibility criteria. After initial electronic search, references of the identified studies were hand-searched to identify further potentially relevant studies. Any disagreements in the study selection were resolved via discussion and consensus between the authors (SVK and VRM). Cohen's kappa value (κ) was used to determine the inter-reviewer reliability [44]. Data were extracted using standardized evaluation forms: first author's last name, country of study, year of publication, study design, population size, age (range and mean), body mass index, methods to assess ED, methods to assess OSA, exclusion criteria, prevalence of ED or OSA, variables adjusted, and main outcomes. Authors of the studies included were contacted via electronic mail in case data was missing or additional information regarding their studies was required. The reviewers (SVK and VRM) crosschecked all extracted data. Any disagreement was resolved by discussion.

Quality assessment

Methodological Quality Assessment of each cross-sectional [12–14, 16–18, 20, 22, 24, 26–28, 30–34, 37, 39] or cohort [15, 23] study include in the present systematic review and meta-analysis was performed using the Critical Appraisal Skills Program (CASP) Cohort Study Checklist [45]. A systematic approach based on 12 specific criteria was used, which were: 1) Study issue is clearly focused; 2) Cohort is recruited in an acceptable way; 3) Exposure is accurately measured; 4) Outcome is accurately measured. 5) Confounding factors are addressed; 6) Follow-up is long and complete; 7) Results are clear; 8) Results are precise; 9) Results are credible; 10) Results can be applied to the local population; 11) Results fit with available evidence; and 12) There are important clinical implications. Each criterion was given a response of either "Yes", "No", or "cannot tell". Each study could have a maximum score of 12.

The Newcastle-Ottawa Scale [46] (NOS) was used to grade the methodological quality of case–control studies

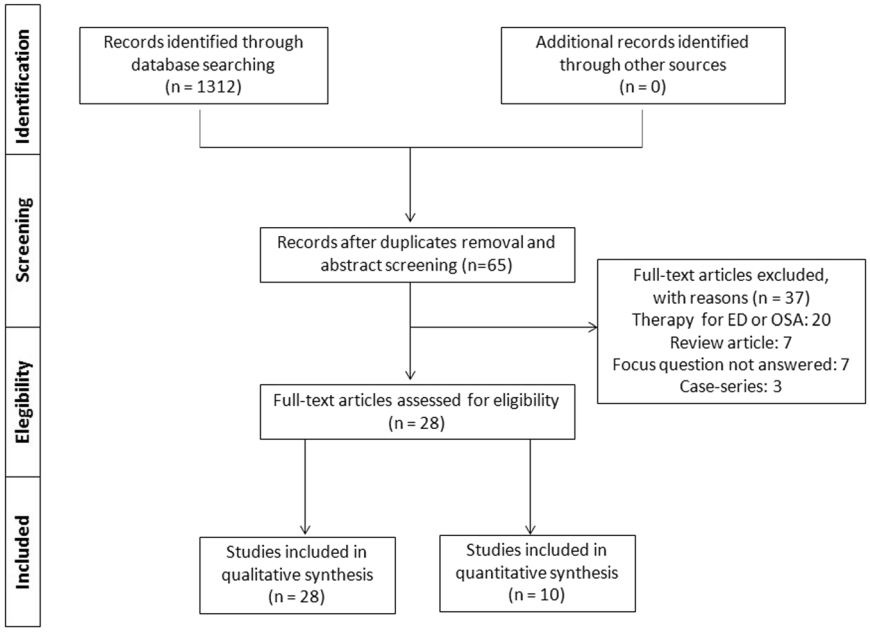

Fig. 1 Article selection flow chart for the systematic review according to PRISMA guidelines

[19, 21, 25, 29, 35, 36, 38] included in the present review. In summary, the NOS scale uses a systematic approach based on three specific criteria: Selection (S), Comparability (C) and Exposure (E), which are subdivided in 9 criteria: S1) Adequate case definition; S2) Representativeness of the cases; S3) Selection of control; S4) Definition of control; C1) Comparability of cases; C2) Controls on the basis of the analysis; E1) Ascertainment of exposure; E2) Same method of ascertainment for cases and controls; E3) Non-response rate. Each criterion was given a response of either "Yes", "No", or "cannot tell,". Each study could have a maximum score of 9. Quality assessment of all studies [12–39] included was conducted independently by two authors (VRM and SVK) using the above-described tools, and checked for disagreement via discussion among the authors.

Statistical analysis

In the meta-analysis, we combined results from ten studies [14, 15, 21, 25, 26, 34, 35, 37–39] to obtain an overall odds ratio (OR). For each study, we can only retract the estimated OR and 95% confidence interval (CI). We used the method proposed by Chinn [47] to convert the OR to effect sizes. A random effect model was used to estimate the overall effect size (and standard deviation) from the studies included in the present meta-analysis. The estimated effect size was converted to the OR using the methods proposed by Chinn [47]. The statistical analysis was implemented with SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Study selection

Through the initial search, 1312 articles were identified. After the initial screening of titles and abstracts, 1247 publications were excluded because did not answer the PECO question or were duplicates. A total of 65 manuscripts were selected for full-text reading. In the second step of evaluation, 37 articles were further excluded (Appendix A). After the final stage of selection, 28 studies [12–39] for qualitative synthesis and 10 studies [14, 15, 21, 25, 26, 34, 35, 37–39] for quantitative analysis were included. The κ score for inter-reviewer agreement at full-text eligibility was 0.84. Overall, 19 studies [12–14, 16–18, 20, 22, 24, 26–28, 30–34, 37, 39] presented a cross-sectional design, 7 studies [19, 21, 25, 29, 35, 36, 38] were case–control, and 2 were cohort studies [15, 23]. Twenty-seven studies [12–19, 21–39] were published in English and 1 study [20] in Spanish. Figure 1 shows the study identification flow chart according to PRISMA guidelines with the reasons for exclusion of articles after full-text reading.

Studies reporting prevalence of ED in sleep clinic populations

General characteristics

A total of 14 studies [13, 14, 19–21, 26–29, 32, 35, 36, 38, 39] reported the prevalence of ED in sleep clinic populations, out of which 8 studies [13, 14, 20, 26–28, 32, 39]

Table 1 General characteristics of the studies included reporting the prevalence of ED in a sleep clinic population

Authors, year (region of study)	Study design	Population (non-OSA/ OSA)	Mean age in years (range)	Mean BMI (kg/m^2)	ED diagnostic methods	OSA diagnostic methods	Exclusion criteria	ED prevalence (%)
Fanfulla et al. [19], 2000 (Italy)	Case–control	50 (25/25)	48 ± 11.9	39.8 ± 9.9	Self-reported Electrophysiologic Test of sacral Segment function	PSG (AHI ≥ 10)	History or treatment for ED, DM, CVD, cancer, systemic disorders, alcoholism	72
Margel et al. [27], 2004 (Israel)	Cross-sectional	209 (23/186)	AHI <5: 43.95 ± 11.8 (21–70) AHI >5 to <20: 44.31 ± 11.8 (21–70) AHI >20 to <40: 49.88 ± 9.56 (28-66) AHI >40: 50.19 ± 8.36 (34–67)	AHI <5: 25.72 ± 2.86 AHI >5 to <20: 26.97 ± 3.31 AHI >20 to <40: 28.55 ± 3.52 AHI >40: 30.7 ± 3.59	IIEF-5	PSG (AHI ≥ 5)	History or treatment for ED, HBP, DM, hyperlipidemia	NR
Teloken et al. [39], 2006 (USA)	Cross-sectional	50 (20/30)	48 ± 10	NR	IIEF-5	ESS > 10	History or treatment for ED	80
Shin et al. [35], 2008 (South Korea)	Case–control	59 (27/32)	Control: 42.9 ± 9.9 Cases: 44.6 ± 9.8 (20–60)	Control: 26.8 ± 2.5 Cases: 25.0 ± 2.5	KIIEF-5	PSG (AHI ≥ 10) SAQLI ESS	Psychiatric disorders, HBP, DM, DVT non-OSA sleep disorders, history or treatment for ED	59.3
Budweiser et al.[14]. 2009 (Germany)	Cross-sectional	401 (32/369)	ED: 61.7 (53.7–69.6) No-ED: 49.9 (42.0–55.4)	ED: 32.2 (29.1–36.7) No-ED: 31.7 (27.7–35.6)	IIEF-15	PSG (AHI ≥ 5) ESS > 10	Psychiatric disorders, treatment for ED, alcohol and lung disease	69
Stannek et al. [36], 2009 (Switzerland)	Case–control	186 (55/131)	Control: 46.6 ± 13.7 Cases: 51.1 ± 11.4	Control: 28.4 ± 5.2 Cases: 29.6 ± 4.2	Modified IIEF	PSG (AHI ≥ 5) ESS	Participation in other clinical study in the past 6 months	NR
Petersen et al. [29], 2010 (Denmark)	Case–control	1493 (1185/ 308)	50.6 ± 10.3 (30–69)	31.5 ± 6.3	Fugl-Meyer Life Satisfaction Checklist Brief Sexual Function Inventory	PSG ESS > 11	NR	NR
Giner et al. [20], 2011 (Spain)	Cross-sectional	142	53 ± 11	32.1 ± 4.4	IIEF-5	PSG (AHI ≥ 5) ESS > 12	Treatment for OSA, sexual inactivity in the past 6 months, COPD, penile disorders	69
Gurbuz et al. [21], 2011 (Turkey)	Case–control	39 (15/24)	Control: 42.3 ± 7.9 Cases: 41.0 ± 8.8	Control: 28.0 ± 3.7 Cases: 30.0 ± 4.0	IIEF-5 Urologist evaluation	PSG (AHI > 10) ESS	CVD, HBP, DVT, hyperlipidemia, DM, history or treatment for ED	54.2
Santos et al. [32], 2012 (Portugal)	Cross-sectional	62	52.16	29.69	IIEF-5	Polygraphic cardiorespiratory sleep study (AHI ≥ 5)	History of ED	64.4
Bouloukaki et al. [13], 2014 (Greece)	Cross-sectional	404	42.6 ± 9.3 (18–65)	33.3 ± 5.05	IIEF-5	PSG ESS (>10)	OSA treatment, BMI > 40, DM, CVD, HBP, dyslipidemias, drug and alcohol abuse, Cushing syndrome, DVT, depression, narcolepsy, history or treatment for ED	40.9

Table 1 (continued)

Authors, year (region of study)	Study design	Population (non-OSA/OSA)	Mean age in years (range)	Mean BMI (kg/m^2)	ED diagnostic methods	OSA diagnostic methods	Exclusion criteria	ED prevalence (%)
Jeon et al. [26], 2015 (South Korea)	Cross-sectional	713 (50/663)	44.8 ± 12.4	AHI < 5: 23.6 ± 2.2 AHI >5 to < 15: 24.8 ± 2.6 AHI > 15 to <30: 25.4 ± 3.0 AHI >30: 26.6 ± 3.0	KIIEF-5	PSG (AHI ≥ 5) ESS SAQLI	Psychiatric disorders, treatment for OSA, limb movement disorder, endocrinological and pulmonary dysfunctions, HBP, CVD, non-OSA sleep disorders, story or treatment for ED	44.49
Popp et al. [28], 2015 (Germany)	Cross-sectional	381	ED: 60.7 ± 11.2 No-ED: 49.0 ± 9.4	ED: 33.4 ± 6.2 No-ED: 31.9 ± 5.4	IIEF-15	PSG (AHI ≥ 5) ESS > 10 VIGIL-S1	Psychiatric and neurological disorders, lung disease, hypogonadism, treatment for ED	65
Taken et al. [38], 2016 (Turkey)	Case–control	55 (17/38)	43.09 ± 11.48	28.97 ± 4.17	IIEF-15	PSG (AHI ≥ 5)	Smoking, CVD, hypogonadism, lung disease, treatment for ED	63.2

OSA obstructive sleep apnea, *BMI* body mass index, *ED* erectile dysfunction, *PSG* polysomnography, *AHI* Apnea–hypopnea Index, *DM* diabetes mellitus, *CVD* cardiovascular diseases, *IIEF* The International Index of Erectile Function, *HBP* high blood pressure, *NR* not reported, *ESS* Epworth Sleepiness Scale, *DVT* deep vein thrombosis, *SAQLI* Calgary Sleep Apnea Quality of Life Index, *COPD* chronic obstructive pulmonary disease, *VIGIL-S1* test Vigil-vigilance, *KIIEF* Korean version of the IIEF

presented a cross-sectional design and 6 studies [19, 21, 29, 35, 36, 38] were case–control. These primary studies were conducted in the following countries: Denmark, Germany, Greece, Israel, Italy, Portugal, South Korea, Spain, Switzerland, Turkey and United States of America (USA). The number of study participants ranged between 39 and 1493 individuals with age ranging between 20 years and 85 years, and a median age ranging between 41.0 ± 8.8 years and 61.7 years.

Main outcomes

The prevalence of ED among patients with OSA was reported in 11 studies [13, 14, 19–21, 26, 28, 32, 35, 38, 39] ranging from 40.9 to 80%. In three studies [27, 29, 36], the prevalence of ED among patients with OSA remained unclear. Fanfulla et al. [19] showed that OSA severity, in terms of Apnea–Hypopnea Index (AHI) and oxygen saturation <90% during sleep, was associated with altered bulbocavernosus reflex. Seven studies [14, 21, 26, 32, 35, 36, 38] reported that OSA severity (AHI) was not associated with ED. Three studies [13, 20, 27] reported that patients with higher AHI presented higher ED severity. One study [26] suggested that ED was independently associated with results from Sleep Apnea Quality of Life Index and depressive symptoms. Giner et al. [20] reported that ED was positively associated with persistent waketime sleepiness; whereas, Budweiser et al. [14] did not find an association between ED and waketime sleepiness. In one study [28], impaired vigilance was associated with higher prevalence of ED (Table 1).

Studies reporting prevalence of OSA in an ED population

General characteristics

A total of five studies [16, 24, 25, 30, 34] reported the prevalence of OSA in an ED population, out of which four studies [16, 24, 30, 34] presented a cross-sectional design and one was a case–control study [25]. All the studies [16, 24, 25, 30, 34] were conducted in USA. The number of study participants ranged between 31 and 1025 individuals with age ranging between 20 years and 85 years, and a median age ranging between 50 ± 9.0 and 58 ± 9.8 years.

Main outcomes

All studies [16, 24, 25, 30, 34] reported the prevalence of OSA among patients with ED ranging from 28 to 78.92%. Hirshkowitz et al. [25] reported that patients with ED and high blood pressure (treated or untreated) presented higher AHI compared to hypertensive patients without

Table 2 General characteristics of the studies included reporting the prevalence of OSA in an ED population

Authors, year (region of study)	Study design	Population	Mean age in years (range)	Mean BMI (kg/m^2)	ED diagnostic methods	OSA diagnostic methods	Exclusion criteria	Prevalence (%)
Pressman et al. [30], 1986 (USA)	Cross-sectional	31	58.4 ± 6.8	NR	NPT	PSG (AHI ≥ 5)	History of sleep disorders	32.25
Hirshkowitz et al. [25], 1989 (USA)	Case–control	275 Control: 71 Cases: 204	(50 ± 9.0–58 ± 9.8)	NR	NPT	PSG (AHI ≥ 5)	History of sleep disorders	78.92
Hirshkowitz et al. [24], 1990 (USA)	Cross-sectional	1025	54 (20-82)	NR	NPT	PSG (AHI ≥ 5)	NR	43.80
Chediak et al. [16], 1996 (USA)	Cross-sectional	37	52.2 ± 14	26.5 ± 3.8	NPT	PSG (AHI ≥ 10)	Alcohol	49
Seftel et al. [34], 2002 (USA)	Cross-sectional	285 Control: 117 Cases: 168	53 ± 13 (16-81)	27 ± 5	Medical History Depression Inventory	Cleveland Sleep Habits Questionnaire	NR	28

OSA obstructive sleep apnea, *BMI* body mass index, *ED* erectile dysfunction, *PSG* polysomnography, *AHI* Apnea–hypopnea Index, *NR* not reported, *NPT* nocturnal penile tumescence

ED. One study [24] showed a positive association between OSA severity and increased age in patients with ED. According to results by Seftel et al. [34], ED is not associated with persistent waketime sleepiness or fatigue (Table 2).

Population studies assessing the association between OSA and ED

General characteristics

Nine studies [12, 15, 17, 18, 22, 23, 31, 33, 37] assessed the association between ED and OSA in the general population, out of which seven studies [12, 17, 18, 22, 31, 33, 37] presented a cross-sectional design and two studies [15, 23] a cohort design. These primary studies [12, 15, 17, 18, 22, 23, 31, 33, 37] were conducted in the following countries: Brazil, Israel, Poland, Taiwan, and USA. The number of study participants ranged between 70 and 149,885 individuals with age ranging between 20 years and 85 years, and a median age ranging between 36.1 ± 6.8 and 76.2 ± 5.5 years.

Main outcomes

Two studies [23, 33] reported no association between ED and OSA; whereas, in one study [15], the association between OSA and ED was no statistically significant after cofounders adjustment (OR = 1.39, 95% CI: 1.00–1.92). Szymanski et al. [37] reported that OSA patients with history of S-T segment elevation myocardial infarction (STEMI) presented higher prevalence of ED compared with STEMI without OSA. Hanak et al. [23] reported a positive association between severe OSA and low sexual satisfaction. Studies [17, 18] by Chen et al. in 2015 and 2016, showed that OSA was an independent risk factor for developing ED (HR = 2.0, 95% CI: 1.5–2.7) and that ED incidence was 9.44-fold higher in OSA patients, respectively (Table 3).

Quality assessment

The total quality score for cross-sectional [12–14, 16–18, 20, 22, 24, 26–28, 30–34, 37, 39] and cohort [15, 23] studies according to the CASP ranged from 7 to 11 (maximum score of 12). On average, the quality of cross-sectional and cohort included studies was good. The most common shortcoming among these primary studies was the short term, incomplete follow-up of the groups, and omission of confounding variables assessment. Table 4 summarizes the CASP quality assessment of the individual cross-sectional and cohort studies.

The total quality score for case–control studies [19, 21, 25, 29, 35, 36, 38] according to NOS ranged between 6 and 9 out of a maximum score of 9. The most common shortcoming among all studies was the inadequate control selection. Quality assessment of the case–control studies is summarized in Table 5. The κ score for inter-reviewer agreement at quality assessment was 0.76.

Statistical analysis

From the literature reviewed, the OR with a 95% CI was calculated from 10 studies (Table 6). The combined OR was 0.45, with a 95% confidence interval of 0.18–0.71, indicating that patients without OSA, the risk of ED is significantly lower compared with patients with OSA (Fig. 2).

Discussion

Based upon the outcomes of the present systematic review and meta-analysis, an association between ED and OSA seems to exist. An explanation for these findings is that

Table 3 General characteristics of population studies included assessing the association between ED and OSA

Authors (region of study)	Study design	*n*	Mean age (range)	BMI (kg/m^2)	ED diagnostic methods	OSA diagnostic methods	Exclusion criteria	Main outcome
Schiavi et al. [33], 1991 (USA)	Cross-sectional	70	(45–75)	NR	NPT psychosexual interview	Partial PSG (AHI ≥ 5)	Sexual inactivity, educational attainment, medical conditions, drug intake, obesity, psychiatric disorders	No association between OSA and ED
Heruti et al. [22], 2005 (Israel)	Cross-sectional	3363	36.1 ± 6.8	26.8 ± 4.2	SHIM Questionnaire	SQQ	NR	Significant association between ED and OSA. OSA severity associated with ED severity
Hanak et al. [23], 2008 (USA)	Cohort	827	64 (51–90)	NR	Brief Male Sexual Function Inventory	Questionnaire (self-reported)	Medical conditions associated with urinary function	No association between OSA and ED. Severe OSA was associated with lower sexual satisfaction
Andersen et al. [12], 2010 (Brazil)	Cross-sectional	467	(20–80)	NR	Questionnaire	PSG (AHI ≥ 5)	NR	OSA and AHI > 15 were associated with ED
Szymanski et al. [37], 2011 (Poland)	Cross-sectional	90 STEMI	Non-OSA: 54.5 ± 8.3 OSA: 53.7 ± 5.3	Non-OSA: 27.3 ± 3.5 OSA: 32 ± 4.5	IIEF-5	Berlin Questionnaire ESS > 10	Post-cardiac arrest	Patients with OSA and STEMI presented higher prevalence of ED compared with STEMI patients without OSA
Chen et al. [17], 2015 (Taiwan)	Cross-sectional	60326	46.4 ± 13.1	NR	Ambulatory claim database	ICD-9-CM PSG	<18 y/o and >90 y/o ED diagnosis before OSA diagnosis	OSA was an independent risk factor for developing ED
Chen et al. [18], 2016 (Taiwan)	Cross-sectional	53335	Non-OSA: 53.8 ± 16.6 OSA: 48.2 ± 14.4	NR	ICD-9-CM	ICD-9-CM	<20 y/o Sleep disorders history prior diagnosis	Patients with OSA presented higher ED incidence. Higher risk of ED in OSA patients aged <40 years
Chung et al. [31], 2016 (Taiwan)	Cross-sectional	6180	47.8 ± 13	NR	ICD-9-CM	ICD-9-CM PSG	NR	Patients with OSA presented a higher ED prevalence compared with patients without OSA
Bozorgmehri et al. [15], 2017 (USA)	Cohort	2857	76.2 ± 5.5	NR	IIEF-5 MMAS	PSG (AHI ≥ 5)	NR	Association between OSA and ED was no significant after adjustment of cofounders

OSA obstructive sleep apnea, *BMI* body mass index, *ED* erectile dysfunction, *PSG* polysomnography, *AHI* Apnea–hypopnea Index, *IIEF* The International Index of Erectile Function, *NR* not reported, *NPT* nocturnal penile tumescence, *MMAS* Massachusetts Male Aging Study Scale, *SQQ* Sleep Quality Questionnaire, *SHIM* Sexual Health Inventory for Men, *STEMI* S-T segment elevation myocardial infarction, *ICD-9-CM* The International Classification of Diseases, Ninth Revision, Clinical Modification

Table 4 Assessment of study quality with Newcastle-Ottawa Scale for case–control studies

Study	Selection				Compar-ability		Exposure			Number of stars
	S1	S2	S3	S4	C1	C2	E1	E2	E3	
Hirshkowitz et al. [25]	*	*	*	*	*	*	*	*	*	9
Fanfulla et al. [19]	*	*	*	*	*	*	*	*	*	9
Shin et al. [35]	*	*	*	*	*	*	*	*	*	9
Stannek et al. [36]	*	*		*		*		*	*	6
Petersen et al. [29]	*	*			*	*	*		*	6
Gurbuz et al. [21]	*	*	*	*	*	*	*	*	*	9
Taken et al. [38]	*	*	*	*	*	*	*	*	*	9

S1—Adequate case definition, S2—representativeness of the cases, S3—selection of control, S4—definition of control, C1—comparability of cases, C2—controls on the basis of the analysis, E1—ascertainment of exposure, E2—same method of ascertainment for cases and controls, E3—non-response rate

Table 5 CASP quality assessment of studies with a cohort or cross-sectional design

Authors	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Total quality score
Pressman et al. [30]	Yes	Cannot tell	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	9
Hirshkowitz et al. [24]	Yes	Cannot tell	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	9
Schiavi et al. [33]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	10
Chediak et al. [16]	Yes	Cannot tell	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	9
Seftel et al. [34]	Yes	Cannot tell	Cannot tell	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	7
Margel et al. [27]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	11
Heruti et al. [22]	Yes	Yes	Cannot tell	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	9
Teloken et al. [39]	Yes	Yes	Cannot tell	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	9
Hanak et al. [23]	Yes	Yes	Cannot tell	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	10
Budweiser et al. [14]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	11
Andersen et al. [12]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	10
Giner et al. [20]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	11
Szymanski et al. [37].	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	11
Santos et al. [32]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	10
Bouloukaki et al. [13]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	11
Chen et al. [17]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Jeon et al. [26]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	11
Popp et al. [28]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	11
Chen et al. [18]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Chung et al. [31]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Bozorgmehri et al. [15]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	10

Item 1—study issue is clearly focused, item 2—cohort is recruited in an acceptable way, item 3—exposure is accurately measured, item 4—outcome is accurately measured, item 5—confounding factors are addressed, item 6—follow-up is long and complete, item 7—results are clear, item 8—results are precise, item 9—results are credible, item 10—results can be applied to the local population, item 11—results fit with available evidence, item 12—there are important clinical implications

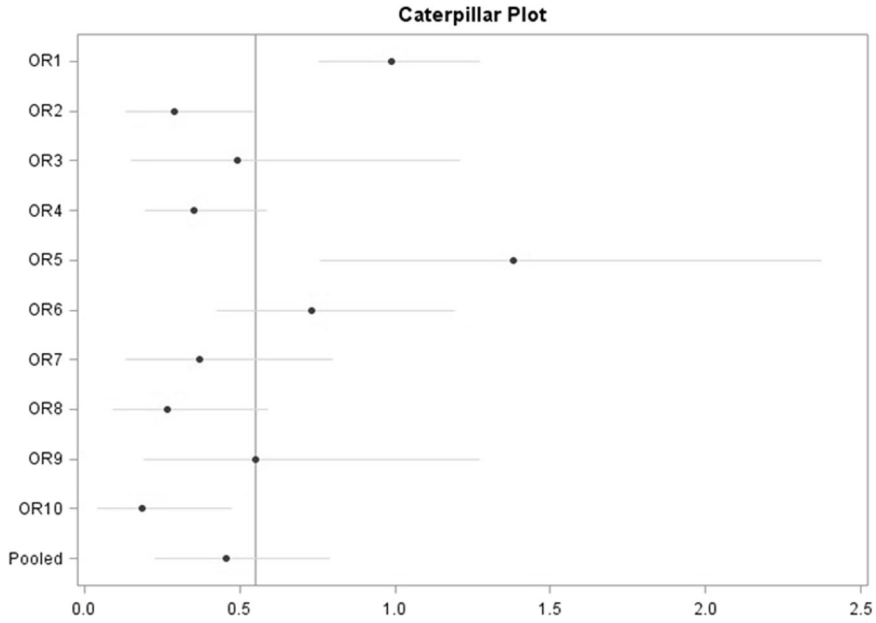

Fig. 2 Forest plot of articles included in the meta-analysis

Table 6 Odds ratios and 95% confidence interval of the studies included in the meta-analysis

	Study	Odds ratio	95% Confidence interval	
OR1	Bozorgmehri et al. [15]	0.9868	0.7446	1.2546
OR2	Budweiser et al. [14]	0.2899	0.1129	0.4971
OR3	Gurbuz et al. [21]	0.4934	0.1025	1.0306
OR4	Hirshkowitz et al. [25]	0.3528	0.171	0.5458
OR5	Jeon et al. [26]	1.3818	0.6951	2.238
OR6	Seftel et al. [34]	0.7309	0.3859	1.1343
OR7	Shin et al. [35]	0.3698	0.0917	0.7203
OR8	Szymanski et al. [37]	0.2679	0.0625	0.5216
OR9	Taken et al. [38]	0.5507	0.1208	1.0981
OR10	Teloken et al. [39]	0.1841	0.0189	0.4045
	Pooled	0.4550	0.1874	0.7193

sleep disruption and impaired ventilation function associated with frequent hypoxic events, triggers a cascade of vascular and inflammatory events, including release of oxygen radicals, vascular endothelial dysfunction, and downregulation of circulating nitric oxide (NO) levels [48–50]. NO has a key role in the physiology of the erection, by stimulating vasodilatation, increasing blood flow to the corpora cavernosa, and promoting smooth muscle relaxation [51, 52]. Moreover, hypoxia has been linked to increased levels of endothelins, vasoconstrictor peptides that cause contraction of smooth muscles cells of the corpora cavernosa [53, 54]. Furthermore, other non-vascular mechanisms have been proposed to explain the role of OSA as underlying cause of ED, such as hormonal changes [55–57] (decreased testosterone levels and deregulation of hypothalamic–gonadal axis), neural mechanisms [19, 58] (increased circulating norepinephrine and neural dysfunction) and psychological mechanisms [48, 59] (decreased libido and excessive fatigue). Therefore, it is tempting to speculate that individuals with OSA are at increased risk on developing ED as compared to individuals without OSA. However, it is pertinent to mention that a variety of factors may have biased these results. Firstly, in nearly 70% of the studies [12, 14, 15, 19–23, 26–29, 32, 34–39] included in the present study, the diagnosis of ED was self-reported or based on standardized questionnaires (such as IIEF-5). Although these questionnaires are considered a validated tool to evaluate ED [60], vasculogenic ED diagnosis should include a comprehensive medical, sexual, and psychological examination, including underlying cardiovascular risk factors assessment and current medication, and other diagnostic tests to assess erectile function including nocturnal penile rigidity and Doppler ultrasound [11, 61]. Moreover, studies [62, 63] have suggested that IIEF scores may be an unsuitable tool for the assessment of ED in susceptible populations, and cannot be used as a tool for differential diagnosis of vasculogenic ED. Therefore, it is feasible that they might have been patients with ED in the control group and vice versa. In this regard, the conclusions of the studies included in the present systematic review should be interpreted with caution.

It is well known that tobacco smoking, alcohol consumption, and low testosterone levels are significant risk factors for OSA as well as ED [56, 64–66]. Results from ~93% of the studies [13, 14, 16–39] remained unadjusted

for testosterone levels (total or free testosterone concentration), ~72% of the studies [12–14, 16–19, 21, 24–27, 29–31, 33–35, 37, 39] the results were not adjusted for smoking and 67% of the studies [12, 17, 18, 21–23, 25–31, 33–35, 37–39] remained unadjusted for alcohol consumption. Moreover, none of the included studies [12–39] assessed levels of circulating oxidative stress. It is therefore hypothesized that besides OSA, other risk factor such as raised systemic levels of pro-inflammatory cytokines and overall oxidative stress levels may have significantly contributed in aggravating ED. Furthermore, it is pertinent to mention that ~97% of the studies [13–39] included were conducted in developed countries in Europe, Asia, and North America. Woods et al. [67] reported that individuals from developed countries present an overall greater prevalence and severity of OSA, mainly associated with a higher prevalence of comorbidities (such as cardiovascular diseases and diabetes), obesity, alcohol, and tobacco. Therefore, we believe that is hard to extrapolate these findings to the whole population. Hence, additional prospective studies including larger samples and incorporating different ethnicities, habits, races, beliefs, and cultures are needed. Moreover, interventional studies [41, 42] have suggested that OSA treatment might improve erectile function. Therefore, future research should focus and emphasize in the effectiveness of OSA therapeutics such as CPAP and oral appliances in the improvement of ED.

It is important to note that besides offering treatment for ED, it is mandatory for physicians to evaluate the possible underlying causes of ED including OSA. It is also recommended that patients referring high respiratory distress index, fatigue or waketime sleepiness should be consulted regarding their sexual function and referred to the urologist for evaluation. Likewise, dentists can also have an important role in the recognition and initial diagnosis of patients with OSA. Dentists detecting OSA should refer the patient to a sleep medicine specialist for further evaluation and treatment. The authors of the present systematic review and meta-analysis also suggest that routine community-based programs should be conducted to educate people about the significance of OSA and its influence on the overall health and quality of life.

Conclusion

Although the causal or casual association between OSA and ED are yet to be determined, overall the evidence supports that OSA is associated with a higher risk of ED. Further well-designed controlled clinical trials and longitudinal prospective studies are needed to determine the causal association.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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