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SLEEP BREATHING PHYSIOLOGY AND DISORDERS • REVIEW

The association between ophthalmologic diseases and obstructive sleep apnea: a systematic review and meta-analysis

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Abstract
Purpose The purpose of this study was to evaluate the association between obstructive sleep apnea (OSA) and ophthalmologic diseases, specifically glaucoma, nonarteritic anterior ischemic optic neuropathy (NAION), retinal vein occlusion (RVO), central serous chorioretinopathy (CSR), and floppy eyelid syndrome (FES), by performing a systematic review and meta-analysis of published studies.
Methods PubMed, Embase, and Scopus databases were searched for observational studies on OSA and its association with select ophthalmologic diseases. Data was pooled for random-effects modeling. The association between OSA and ophthalmologic diseases was summarized using an estimated pooled odds ratio with a 95 % confidence interval.
Results Relative to non-OSA subjects, OSA subjects have increased odds of diagnosis with glaucoma (pooled odds ratio (OR) = 1.242; $P < 0.001$) and floppy eyelids syndrome (pooled OR = 4.157; $P < 0.001$). In reverse, the overall pooled OR for OSA was 1.746 ($P = 0.002$) in the glaucoma group, 3.126 ($P = 0.000$) in the NAION group, and 2.019 ($P = 0.028$) in the CSR group. For RVO, one study with 5965 OSA patients and 29,669 controls demonstrated a 1.94-fold odds increase in OSA patients.
Conclusions Our results suggest significant associations between OSA and glaucoma, NAION, CSR, and FES. Screening for OSA should be considered in patients with glaucoma, NAION, CSR, or FES.

Keywords Obstructive sleep apnea · Glaucoma · Floppy eyelids · Nonarteritic anterior ischemic optic neuropathy · Central serous chorioretinopathy

Introduction

Obstructive sleep apnea (OSA) is characterized by recurrent episodes of partial or complete upper airway obstruction during sleep that is associated with desaturation and re-oxygenation sequences that can stress the cardiovascular system. It is hypothesized that the recurrent arousals and hypoxemia and re-oxygenation result in activation of the sympathetic nervous system, oxidative stress, acute increases in blood pressure, and activation of systemic inflammation [1]. Vascular changes associated with OSA have been well studied with regard to microvasculature [2], and abnormal vascular reactivity has been described in the cerebral circulation [3, 4]. Previous studies have suggested OSA increases the risk of cardiovascular and cerebrovascular events (hypertension [5, 6], coronary artery disease [7], stroke [8, 9], and death [8]) independent of known vascular and metabolic risk factors. OSA can have a similar effect on the eyes.

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The aim of this systematic review is to assess the association of OSA to the following ophthalmologic conditions: floppy eyelids syndrome, glaucoma (primary open-angle/normal tension), nonarteritic anterior ischemic optic neuropathy (NAION), retinal vein occlusion, and central serous chorioretinopathy. We chose these conditions a priori based on known vascular consequences of OSA.

Materials and methods

This review was conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Methods of the analysis and inclusion criteria were specified in advance and documented. This study is exempt from Stanford Investigational Review Board approval because all included studies are previously published and no new data is provided by this review. This review was not registered in a systematic review protocol registry.

Publication search

Online electronic database (PubMed, EMASE, and Scopus) was searched using the search terms: ("Obstructive sleep apnea/hypopnea syndrome" or OSAHS or "sleep apnea syndrome" or OSA or "obstructive sleep apnea") and the ophthalmologic disorders individually ("floppy eyelids syndrome," "glaucoma," "Nonarteritic anterior ischemic optic neuropathy," "retinal vein occlusion," "central serous chorioretinopathy"). The search was restricted to the English language and human participants.

Eligibility criteria

The following inclusion criteria were used: (1) The study should have evaluated the association between the OSA and risk of specific ophthalmologic disorders, (2) The study should have a case-control, cross-sectional, or cohort design, and (3) Sufficient data should have been provided to calculate odds ratio (OR) and 95 % confidence interval (CI). Case reports, case series, review articles, abstracts, commentaries, book chapters, and editorials were excluded. Only peer-reviewed articles were considered.

Data extraction

Information was extracted from all eligible studies by two independent investigators (LKH and SYL). Discrepancies between the two authors were settled by consensus. The recorded information for cross-sectional and case-control studies included the name of the first author, publication year, study design, participant selection, total number of cases and controls, methods for the diagnosis of OSA, adjustment for covariates, and the author's conclusions.

Level and quality of evidence assessments

We assessed the articles for both the level of evidence and the quality of each study. The 2011 Oxford Centre for Evidence-Based Medicine Levels of Evidence table was used to assess the level of evidence. Level 1 represents systematic reviews of randomized trials; level 2 represents a randomized trial; level 3 represents a non-randomized controlled cohort; level 4 represents a case series, case-control, or historically controlled study; and level 5 represents a mechanism-based reasoning study.

Statistical methods

In this study, the strength of association between OSA and odds of ophthalmologic comorbidity was assessed by calculating OR with 95 % CI. The summary of OR estimates from each study was calculated by a random-effects Mantel-Haenszel method. The meta-analysis was performed using Comprehensive Meta-Analysis (Version 3.3.070). P value <0.05 was considered to indicate statistical significance.

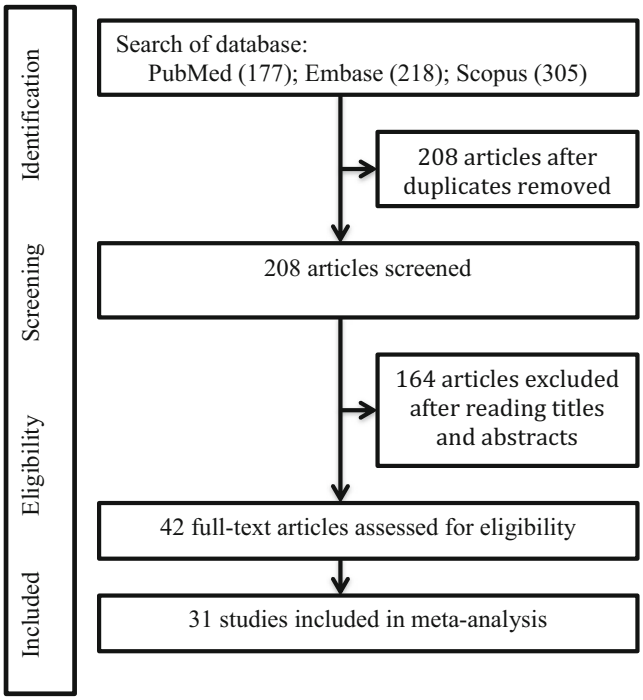

Fig. 1 PRISMA flow diagram for studies retrieved through the searching and selection processes

Table 1 Prevalence of OSA among patients diagnosed with specific ophthalmologic diseases

Prevalence of OSA among patients diagnosed with glaucoma							
Studies	Study design	No of patients Glaucoma/non-glaucoma	% of diagnosed of OSA in glaucoma	% of diagnosed of OSA in non-glaucoma	Diagnostic tools	Level of evidence	Included/excluded for meta-analysis
Onen et al., 2000 [23]	Case-control	212/218	58/212 (27 %)	39/218 (17 %)	Sleep questionnaire	4	Included
Marcus et al., 2001 [24]	Case control	37/30	2/37 (5 %)	1/30 (3 %)	PSG	4	Included
Girkin et al., 2006 [25]	Database study	667/6667	7/667 (1 %)	32/6667 (0.4 %)	ICD-9	4	Included
Roberts et al., 2009 [26]	Case control	52/60	9/52 (17 %)	7/60 (11 %)	Oximetry monitoring, ODI > 20	4	Included
Khandgave et al., 2013 [27]	Case control	40/40	4/40 (10 %)	1/40 (2.5 %)	Sleep history, PSG	4	Included
Bilgin et al., 2014 [28]	Case control	24/24	10/24 (41 %)	3/24 (12 %)	PSG AHI > 20	4	Included
Prevalence of OSA among patients diagnosed with nonarteritic ischemic optic neuropathy (NAIOH)							
Studies	Study design	No of patients NAION/non-NAION	% of diagnosed of OSA in NAION	% of diagnosed of OSA in non-NAION	Diagnostic tools	Level of evidence	Included/excluded for meta-analysis
Mojon et al., 2002 [31]	Case control	17/17	12/17 (71 %)	3/17 (18 %)	PSG (RDI >10)	4	Included
Palombi et al., 2006 [32]	Prospective, cohort	27 NAION	24/27 (89 %)		PSG (AHI > 15)	4	Excluded
Li et al., 2007 [33]	Case control	73/73	22/73 (30.1 %)	13/73 (17.8 %)	SA-SDQ questionnaire	4	Included
Bilgin et al., 2013 [34]	Case control	27/27	15/27 (55.6 %)	6/27 (22.2 %)	PSG (AHI > 20)	4	Included
Arda et al., 2013 [35]	Case control	20/20	17/20 (85 %)	13/20 (65 %)	PSA (AHI > 5)	4	Included
Aptel et al., 2015 [36]	Prospective, cohort	89 NAION	67/89 (75 %)		PSG (AHI > 15)	4	Excluded
Prevalence of OSA among patients with floppy eyelids syndrome (FES)							
Studies	Study design	No of patients FEs/non-FES	% of diagnosed of OSA in FES	% of diagnosed of OSA in non-FES	Diagnostic tools	Level of evidence	Included/excluded for meta-analysis
McNab et al., 2007 [50]	Case series	27 FES	26/27 (96 %)		Sleep study	4	Excluded
Ezra et al., 2010 [47]	Case control	102/102	32/102 (31.3 %)	9/102 (8.8 %)	Epworth somnolence score	4	Excluded
Prevalence of OSA among patients with central serous chorioretinopathy (CSR)							
Studies	Study design	No of patients CSR/non-CSR	% of diagnosed of OSA in CSR	% of diagnosed of OSA in non-CSR	Diagnostic tools	Level of evidence	Included/excluded for meta-analysis
Leveque et al., 2007 [37]	Case control	29/29	22/29 (76 %)	9/29 (31 %)	Berlin questionnaire	4	Included
Kloos et al., 2008 [51]	Case series	36 CSR	8/36(22.2 %)		PSG and ESS	4	Excluded
Yavas et al., 2014 [52]	Case series	23 CSR	14/23(60.9 %)		PSG	4	Excluded
Brodie et al., 2015 [39]	Case control	49/49	22/49 (45.8 %)	21/49 (43.8 %)	Berlin questionnaire	4	Included
Prevalence of OSA among patients with retinal vein occlusion (RVO)							
Studies	Study design	No of patients RVO/non-RVO	% of diagnosed of OSA in RVO	% of diagnosed of OSA in non-RVO	Diagnostic tools	Level of evidence	Included/excluded for meta-analysis
Galecet-Bernard et al., 2010 [41]	Case series	63 RVO	23/63 (37 %)		PSG	4	Excluded
Kanai et al., 2012 [42]	Case series	40 RVO	15/40 (37 %)		PSG	4	Excluded

Table 2 Prevalence of ophthalmologic consequences among patients with OSA

Prevalence of Glaucoma among patients diagnosed with OSA							
Studies	Study design	No of patients OSA/non-OSA	% of diagnosed of glaucoma in OSA	% of diagnosed of glaucoma in non-OSA	Diagnostic tools	Level of evidence	Included/excluded for meta-analysis
Lin et al., 2013 [53]	Cohort study	1012/6072	11.2 % (114/1012)	6.7 % (410/6072)	ICD-9 code	4	Included
Sergi et al., 2007 [54]	Cross-sectional	51/40	5.8 % (3/51)	0 % (0/40)	Eye examination	4	Included
Boonyaleephan et al., 2008 [55]	Cross-sectional	44/42	13.6 % (6/44)	7.1 % (3/42)	Eye examination	4	Included
Karakucuk et al., 2008 [56]	Cross-sectional	31/25	12.9 % (4/31)	0 % (0/25)	Eye examination	4	Included
Kadyan et al., 2010 [57]	Cross-sectional	89/26	3.3 % (3/89)	3.8 % (1/26)	Eye examination	4	Included
Lin et al., 2011 [58]	Cross-sectional	209/38	5.7 % (12/209)	0 % (0/38)	Eye examination	4	Included
Boyle-Walker et al. 2011 [59]	Cross-sectional	2725/69,235	8.3 % (228/2725)	4.9 % (3410/68,235)	Eye examination	4	Included
Stein et al., 2011 [10]	Cross-sectional	151,633/2,030,682	4557/151,633	50,533/2,030,682	Billing records	4	Included
Muniesa et al., 2014 [44]	Cross-sectional	202/25	16/202	0/25	Eye examination	4	Included
Aptel et al., 2014 [60]	Cross-sectional	6754/2826	240/6754	89/2826	Eye examination	4	Included
Moghimi et al., 2013 [17]	Case control	51/54	2/51	0/54	Eye examination	4	Included
Nowak et al., 2011 [61]	Case control	34/18	2/34	0/18	Eye examination	4	Included
Prevalence of nonarteritic ischemic optic neuropathy (NAIOH) among patients diagnosed with OSA							
Studies	Study design	No of patients	Findings:				
Stein et al., 2011 [10]	Cohort study	2 million billing records	Incidence of NAION in OSA 0.09 vs. 0.05 % in non-OSA	Billing records	4	Excluded	
Prevalence of retinal vein occlusion (RVO) among patients diagnosed with OSA							
Studies	Study design	No of patients OSA/non-OSA	% of diagnosed of RVO in OSA	% of diagnosed of RVO in non-OSA			
Chou et al., 2012 [11]	Databases	5965/29,699	0.22 % (13/5965)	0.13 % (39/29,699)	ICD-9	4	Excluded
Prevalence of floppy eyelids syndrome (FES) among patients diagnosed with OSA							
Studies	Study design	No of patients OSA/non-OSA	% of diagnosed of FES in OSA	% of diagnosed of FES in non-OSA			
Mojon et al., 1999 [62]	Cross-sectional	44/28	29.9 % (13/44)	3.6 % (1/28)	Eyelid distraction distance	4	Included
Karger et al., 2006 [46]	Cross-sectional	44/15	4.5 % (2/44)	0 % (0/15)	Eyelid laxity measurement	4	Included
Kadyan et al., 2010 [57]	Cross-sectional	89/26	31.5 % (28/89)	3.8 % (1/26)	Easily eversion lids with presence of conjunctivitis and irritation ocular symptoms	4	Included
Beis et al., 2012 [49]	Cross-sectional	81/54	34 % (28/81)	16 % (9/54)	Eversion of upper lid easily Grading in two stages of severity	4	Included
Chambe et al., 2012 [48]	Cross-sectional	89/38	25.8 % (23/89)	15.8 % (6/38)	Grading of horizontal laxity of the upper eyelid in five groups of severity	4	Included
Acar et al., 2013 [63]	Cross-sectional	254/26	41.7 % mild OSA (25/60) 66.7 % mod. OSA (48/72) 74.6 % severe OSA (91/122)	23.1 % (6/26)	Grading in three groups of the severity of upper eyelid eversion on lifting the upper lid skin	4	Included
Muniesa et at, 2013 [44]	Cross-sectional	89/25	16 % (54/89)	8 % (2/25)	Eyelid laxity measurement	4	Included

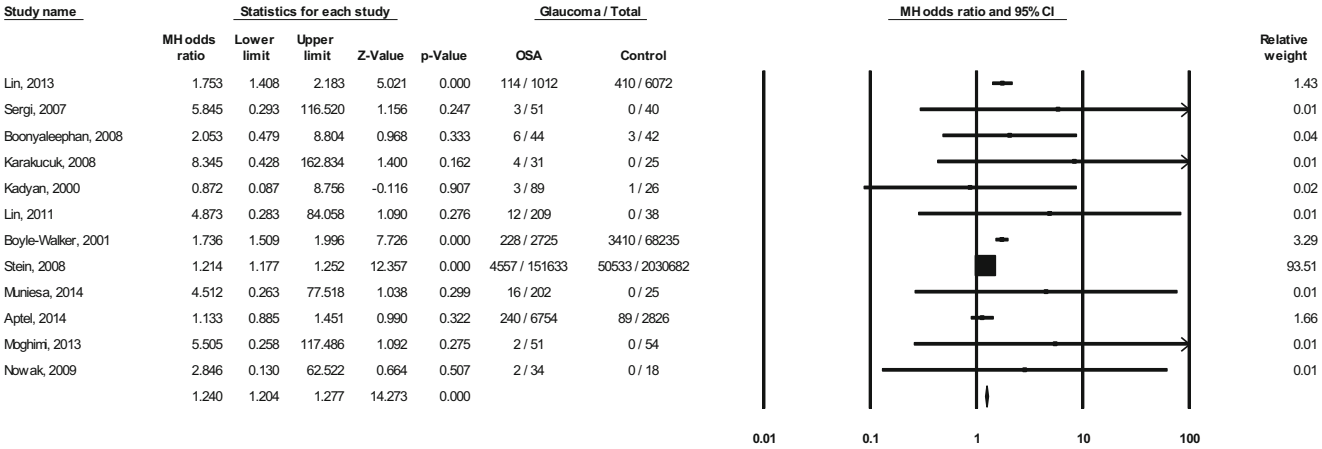

Fig. 2 Forest plots of meta-analysis of the included studies showing the odds ratios of glaucoma for subjects with and without OSA

Results

Both investigators agreed on the results of study selection (inclusion/exclusion). The strategy for study identification and study selection is shown in Fig. 1. The characteristics of each study are presented in Table 1 and Table 2.

Results of meta-analysis

Glaucoma

The association between OSA and glaucoma odds is summarized in Fig. 2 and Fig. 3. The results of the meta-analysis of 12 studies showed that relative to non-OSA subjects, patients with OSA have increased odds of glaucoma (pooled OR of 1.242; $P < 0.001$) (Fig. 2). Of the six case-control studies, which involved 1122 glaucoma patients and 7122 controls, the overall pooled OR for OSA was 1.746 ($P = 0.002$) in the glaucoma group (Fig. 3).

Nonarteritic ischemic optic neuropathy (NAIOH)

Since we could only find one cohort study, meta-analysis was not performed for the risk of NAION in OSA patients [10]. Of the four case-control studies, which involved 137 NAION patients and 137 controls, the overall pooled OR for OSA was 3.126 ($P < 0.001$) in the NAION group. (Fig. 4).

Central serous chorioretinopathy (CSR)

Of the two case-control studies, one showed a positive association between OSA and CSR, while the other showed no association. The pooled analysis showed a significant pooled OR for OS in the CSR group (pooled OR = 2.019; $P = 0.028$) (Fig. 5).

Retinal vein occlusion (RVO)

The study by Chou et al. [11] identified 5965 OSA patients and 29,669 controls; this study was a retrospective non-

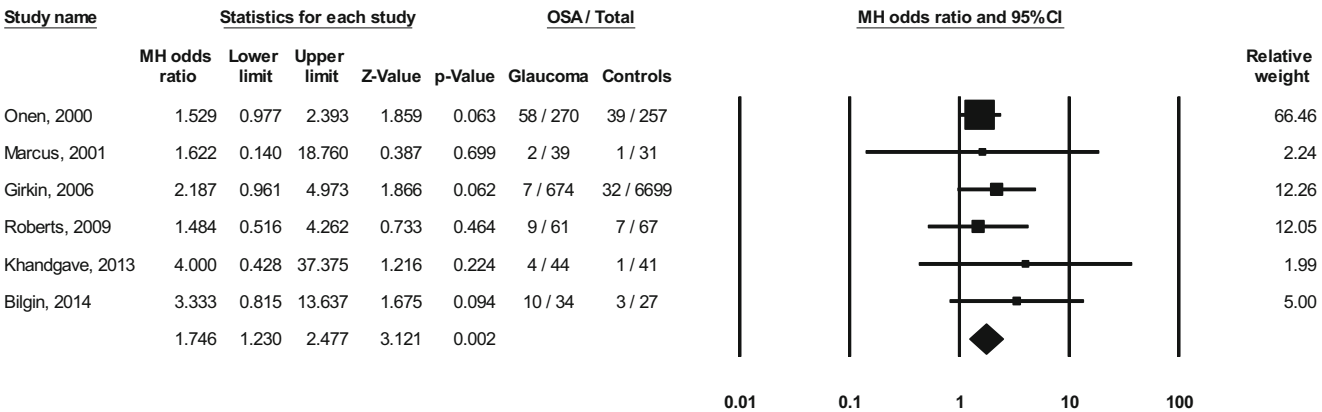

Fig. 3 Forest plots of meta-analysis of the included studies showing the odds ratios of OSA for subjects with and without glaucoma

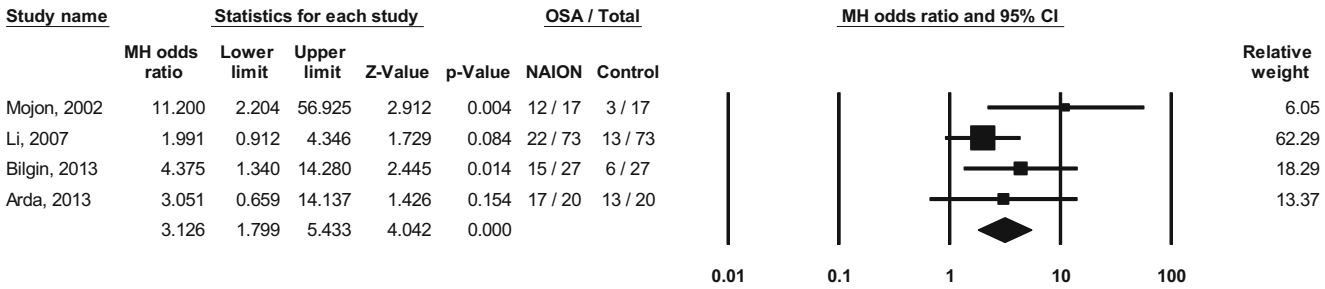

Fig. 4 Forest plots of meta-analysis of the included studies showing the odds ratios of OSA for subjects with and without nonarteritic ischemic optic neuropathy (NAIOH)

randomized, matched-control cohort study, which demonstrated a 1.94-fold increase in the incidence of RVO in OSA patients. No meta-analysis for the association of RVO and OSA was performed as only one article met study criteria.

Floppy eyelid syndrome (FES)

Of the seven cross-sectional studies, FES was present in 312 of 690 patients with OSA and 25 of 212 patients without OSA. The overall pooled OR for FES was 3.126 ($P < 0.001$) in the OSA group versus the non-OSA group. (Fig. 6).

Confounding factors

There are limited numbers of studies that had data available to adjust for confounding factors of OSA and ophthalmologic diseases. The reported pooled estimates for this meta-analysis are based on unadjusted OR.

Discussion

To our knowledge, this is the largest systematic review and meta-analysis describing the association between OSA and select ophthalmologic diseases vulnerable vascular abnormality. The results of our meta-analysis show that relative to non-OSA individuals, those with OSA have increased odds in concurrent diagnosis of glaucoma and floppy eyelids syndrome. In patients with NAIOH and CSR, there are increased odds of OSA diagnosis. Our meta-analysis does not prove causation, but does confirm a statistically significant association between OSA and several ophthalmologic diseases.

The retina has the greatest oxygen demand as part of the central nervous system [12]. Thus, it is sensitive to hypoxia [13]. Hypoxia and hypercapnia from apneic events in OSA patients may result in direct and indirect functional impairment of the retina and choroid. Meanwhile, hypoperfusion and ischemia may lead to fluctuations in blood pressure and activation of the sympathetic nervous system, thus aggravating vascular endothelial dysfunction of the retina [14]. Large fluctuations in vascular oxygen and carbon dioxide resulting in oxidative stress and systemic inflammation may alter the auto-regulatory capacity of vascular regulation of the optic nerve and retina [14–16]. OSA patients were reported to have higher intraocular pressure, worse visual field indices, and lower RNFL parameters compared with the control group [17]. Using optical coherence tomography (OCT), a new and noninvasive diagnostic tool to diagnose axonal damage, high-resolution imaging of the retinal nerve fiber layer, and optic nerve head topography has been studied. Several studies report unique retinal neurodegeneration

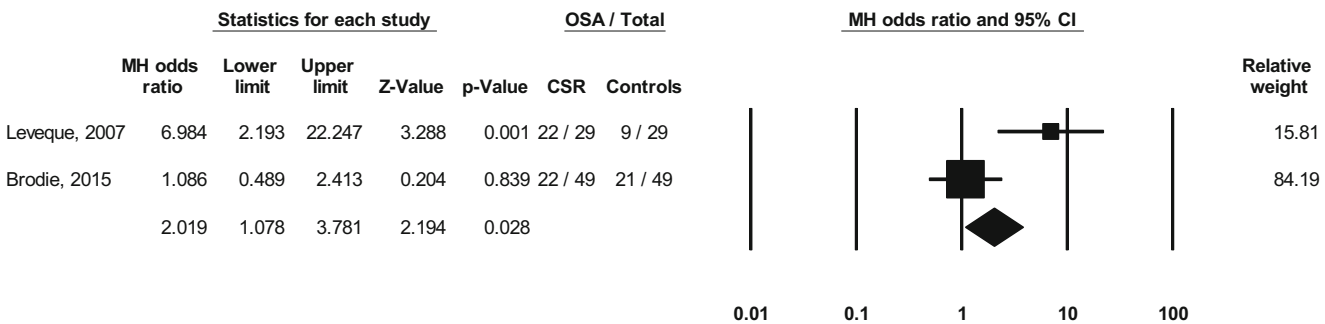

Fig. 5 Forest plots of meta-analysis of the included studies showing the odds ratios of OSA for subjects with and without central serous chorioretinopathy (CSR)

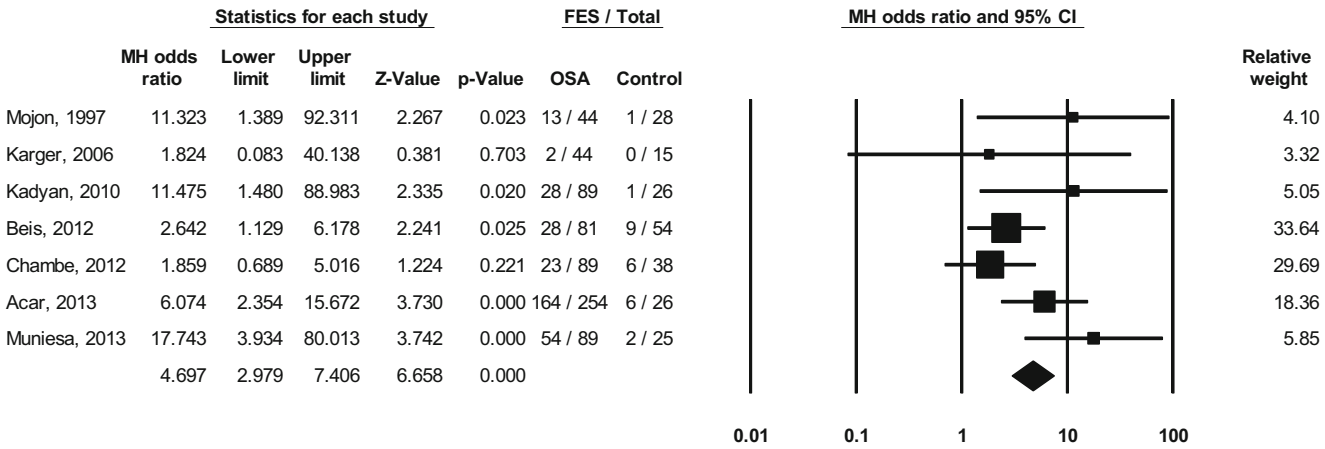

Fig. 6 Forest plots of meta-analysis of the included studies showing the odds ratios of FES for subjects with and without OSA

with decreased retinal nerve fiber layer thickness due to hypoxia in OSA patients [18–22].

Determining the association between OSA and ophthalmologic diseases is important from a public health standpoint, as they are common medical disorders. The association between OSA and ophthalmologic diseases are further described as below:

Glaucoma

Glaucoma is characterized by increased size of the optic disk and thinning of the peripapillary retinal nerve fiber layer, resulting in progressive optic neuropathy that may cause irreversible vision loss. High prevalence of glaucomatous neuropathy has been reported in OSA patients, including both primary open-angle glaucoma and normal tension glaucoma [23–28]. Girkin et al. reported the largest case-controlled study with 667 glaucoma patients and 6667 controls [25]. After adjusting for confounding factors, there was no association found between glaucoma and OSA. For our meta-analysis, there were six case-controlled studies that examined the prevalence of OSA among patients with glaucoma, and 10 cross-sectional and 2 case-controlled studies examined the prevalence of glaucoma among patients with OSA. Our results showed that relative to non-OSA patients, individuals with OSA have increased odds of being diagnosed with glaucoma (pooled OR of 1.242; $P < 0.001$), while the overall pooled OR for OSA was 1.746 ($P = 0.002$) in the glaucoma group.

Nonarteritic ischemic optic neuropathy (NAIOH)

Ischemic optic neuropathy (ION) is the result of vascular insufficiency and considered to be equivalent to a "stroke of the optic nerve." Ninety percent of ION cases are anterior ION, also known as nonarteritic (not related to vasculitis, most often giant-cell arteritis). Classically, NAIOH presents with sudden and painless visual loss upon awakening. The majority of NAION patients are older than 50 years of age and Caucasian [29, 30]. NAION is frequently associated with diseases that increase risk of hypoperfusion and ischemia of the optic nerve, including hypertension, diabetes mellitus, stroke, ischemic heart disease, and sleep apnea. The mechanism by which OSA may cause NAION is unknown. It is hypothesized that acute surges in blood pressure, increased intracranial pressure, and nocturnal hypoxemia from apneic events may result in hypoperfusion and ischemia of the optic nerve head. Several studies reveal higher incidence of OSA in patients with NAION (35 to 89 %) [31–36]. In our study, the meta-analysis from four case-controlled studies with 137 subjects showed that OSA was significantly associated with odds of NAION, with pooled OR for NAION 3.126 ($P < 0.001$) in the OSA group. Stein et al. [10] reported 0.09 % of NAION in an OSA cohort. They found that after adjusting for confounding factors, OSA patients without CPAP treatment show a 16 % increase in the prevalence of NAION. There is no established effective treatment for NAION. Thus, it is important to detect and control vascular risk factors such as OSA in cases of NAION.

Central serous chorioretinopathy (CSR)

CSR is characterized by idiopathic serous detachment of neurosensory retina, which presents with visual distortion, darkening, and/or image magnification. Several possible pathophysiologic mechanisms between OSA and CSR have been reported. Both OSA and CSR patients have increased sympathetic drive, which can cause endothelial dysfunction of the blood-retinal barrier. Leveque et al. reported 58.6 % of patients with CSR to be at increased odds for OSA compared with the control group (31 %) [37]. Jain et al. also reported an OSA patient with bilateral CSR who demonstrated rapid

resolution of the central retinal serous detachment after treatment with continuous positive airway pressure [38]. However, Brodie et al. reported that patients with CSR did not have higher rates of OSA (45 %), when compared with matched controls (43 %) [39]. The result of the meta-analysis from these two studies indicate that CSR is associated with increased odds of OSA (pooled OR = 2.019 (P = 0.028)). It supports a growing pool of evidence that diagnosis and treatment of OSA might be important in CSR patients. CSR is typically resolved within 6 months after recognizing and removing contributing risk factors such as OSA.

Retinal vein occlusion (RVO)

Retinal vein occlusion is the second most common cause of blindness from retinal vascular diseases after diabetic retinopathy. RVO is diagnosed according to the degree of retinal capillary ischemia seen by the ophthalmologist on fluorescein angiography. Leroux-les jardins et al. first reported possible association between RVO and OSA [40]. Galecte-Bernard et al. reported higher incidence of OSA in a series of patients with RVO (77 %), when compared to those without RVO (37 %) [41]. A large population-based study also showed that OSA increased the odds of RVO (1.94-fold, P = 0.041), and the odds were independent of age, gender, and comorbidities [42]. No meta-analysis for the association of RVO and OSA was performed because of insufficient data from published studies.

Floppy eyelid syndrome (FES)

Culbertson and Ostler first described FES in 1981 in patients with easily everted upper eyelids under minimal lateral traction and papillary conjunctivitis [43]. Age, BMI, and gender are confounding factors in the association of FES and OSA. FES in OSA patients may manifest due to repeat ischemia-reperfusion injury, and the sleeping posture and pressure on the eyes. The prevalence of FES in OSA patients ranged from 4.5 to 31.5 %, when compared to those without OSA [43–49]. The pooled OR of developing FES in OSA subjects in this meta-analysis was 4.157 (P = 0.000).

It is important to be aware of the association between OSA and select ophthalmologic diseases for early recognition, diagnosis, and treatment. Prospective studies that take into consideration potential confounders that occur in patients with both groups should include BMI, hypertension, and diabetes. The role of CPAP treatment in the prevention of ophthalmologic diseases in patients with OSA remains unclear.

There are limitations to this meta-analysis. First, confounding factors such as age, gender, and other medical comorbidities could not be examined by meta-regression analysis in this study. Second, selection bias may still exist since most of the included studies were case series or case-controlled studies. Third, the severity of disease could not be evaluated. Thus, the effect of increasing severity of OSA patients and the effect on the odds for concurrent ophthalmologic disease could not be assessed.

Conclusions

This systematical review and meta-analysis study show a statistically significant association between OSA and glaucoma, NAION, CSR, and FES. OSA screening should be considered in patients being seen for these ophthalmologic diagnoses.

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Compliance with ethical standards

Funding No funding was received for this research.

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Comments

This meta-analysis emphasize the association of sleep disordered breathing and ophthalmologic disorders caused or propagated by variable pathologic mechanism; therefore, clinicians should consider this evidence a reason to pay more attention in their clinical practices of ophthalmology and consider screening patients for sleep disorders or referring patients to sleep disorders evaluation when clinically appropriate.

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