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Original Article

Obstructive sleep apnea/hypopnea syndrome increases glaucoma risk: evidence from a meta-analysis

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Abstract: Associations between Obstructive sleep apnea/hypopnea syndrome (OSAHS) and risk of glaucoma remained controversial. Therefore, we performed this meta-analysis to investigate this association. We searched Pubmed, EMBASE, and Wangfang databases for studies before Oct. 10 2014. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to calculate the strength of association. A total of 12 studies with 36909 subjects on the association between OSAHS and glaucoma risk were included for this meta-analysis. OSAHS was associated with a significantly increased risk of glaucoma (OR = 1.65; 95% CI, 1.44-1.88; I^2 = 43%). In the race subgroup analysis, both Asians (OR = 1.78; 95% CI, 1.49-2.12; I^2 = 0%) and Caucasians (OR = 2.03; 95% CI, 1.12-3.69; I^2 = 57%) with OSAHS had increased glaucoma risk. In the subgroup analysis according to gender, both women and men were significantly associated with risk of glaucoma (OR = 1.81; 95% CI, 1.27-2.57; I^2 = 22% and OR = 1.62; 95% CI, 1.29-2.03; I^2 = 0%, respectively). In the subgroup analysis by glaucoma type, OSAHS patients showed increased primary open-angle glaucoma (POAG) risk (OR = 1.87; 95% CI, 1.54-2.33; I^2 = 0%) but not normal tension glaucoma (NTG) risk (OR = 3.57; 95% CI, 0.89-14.43; I^2 = 0%). In addition, severe OSAHS patients had an increased glaucoma risk (OR = 5.49; 95% CI, 1.04-33.83; I^2 = 0%), while mild and moderate OSAHS patients did not show significantly increased glaucoma risk. This meta-analysis suggested that the OSAHS may be a risk factor for glaucoma.

Keywords: OSAHS, glaucoma, meta-analysis, association

Introduction

Obstructive sleep apnea/hypopnea syndrome (OSAHS) is by far the most common respiratory disorder of sleep. OSAHS is caused by the loss of upper airway dilating muscle activity during sleep that is superimposed on a narrow upper airway, resulting in recurrent nocturnal asphyxia [1]. Termination of these events usually requires arousal from sleep to re-establish upper airway tone, eliminate obstruction and allow ventilation to resume. This sleep fragmentation and hypoxaemia lead to poor quality sleep, excessive daytime sleepiness, reduced vigilance, accidents, neurocognitive dysfunction, decreased work productivity, and reduced quality of life [2]. Furthermore, patients with untreated sleep apnoea are at increased risks of hypertension, stroke, heart failure and atrial fibrillation [3].

Glaucoma is a group of eye diseases characterized by a multifactorial progressive optic neuropathy that can result in irreversible vision loss and blindness [4]. The biological basis of glaucoma includes the degeneration of retinal ganglion cells resulting in characteristic cupping of the optic nerve with an accompanying pattern of visual field loss. A number of papers investigated the association between OSAHS and glaucoma risk. However, the results remained inconclusive [5-16]. Meta-analysis is a useful method for investigating associations between genetic factors and diseases, because a quantitative approach is used to combine the results from different studies on the same topic, thereby providing more reliable conclusions. Thus, we performed a meta-analysis to clarify the association of OSAHS and glaucoma risk. To our knowledge, this is the first meta-analysis of the association between OSAHS and glaucoma risk.

Methods

Publication search

Online electronic databases (PubMed, EMBASE, and Wanfang database) was searched using the search terms: ("Obstructive sleep apnea/

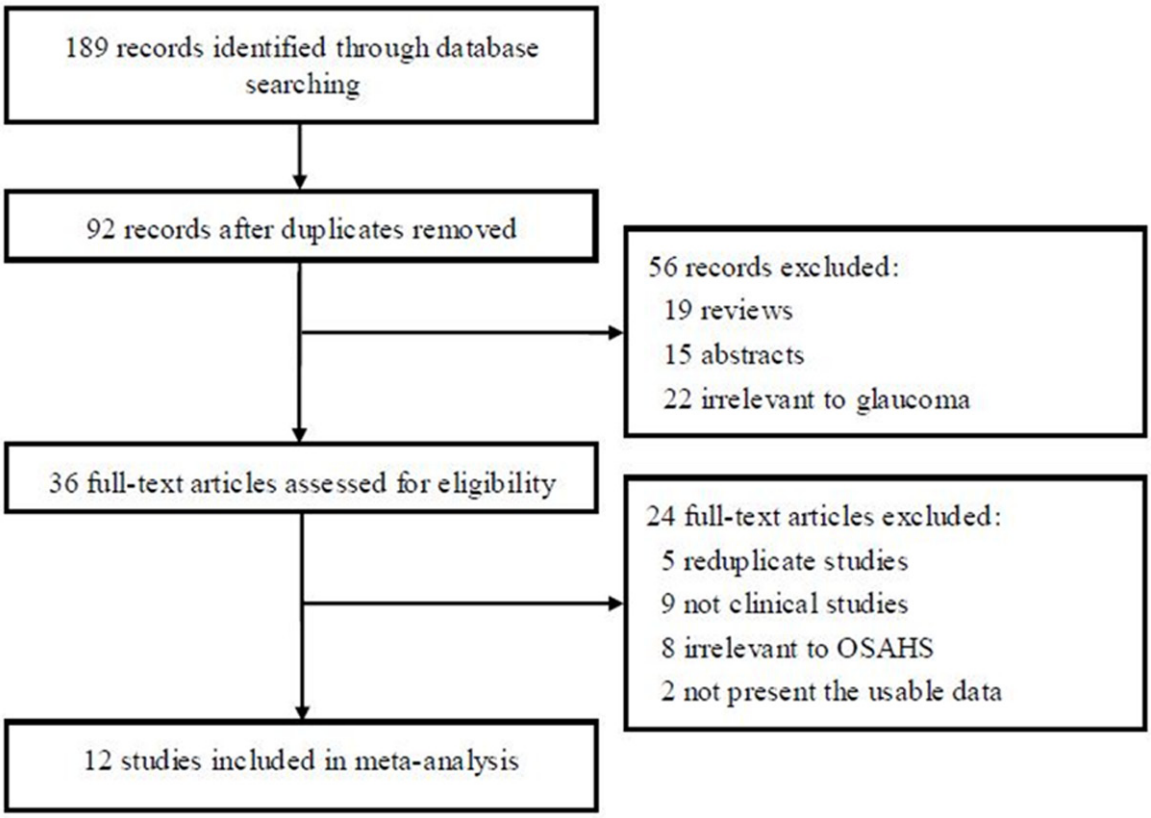

Figure 1. Flow of study identification, inclusion, and exclusion.

Table 1. Characteristics of the studies included in meta-analysis

First author	Year	Country	Ethnicity	Age	Gender	Diagnose of OSAHS	Glaucoma type	Total number (n)
Onen	2000	France	Caucasian	65	Mixed	NA	POAG	430
Girkin	2006	USA	Mixed	69	Mixed	ICD-9 CM	Mixed	7334
Sergi	2007	Italy	Caucasian	64	Mixed	AHI ≥ 10	NTG	91
Karakucuk	2008	Turkey	Caucasian	52	Mixed	AHI ≥ 5	POAG, NTG	56
Kadyan	2010	UK	Caucasian	55	Mixed	NA	NA	115
Lin PW	2011	China	Asian	42	Mixed	AHI ≥ 5	NTG	247
Nowak	2011	Poland	Caucasian	51	Mixed	AHI ≥ 5	POAG, NTG	86
Lin CC	2013	China	Asian	56	Mixed	ICD-9 CM	POAG	6072
Moghimi	2013	Iran	Caucasian	47	Mixed	AHI ≥ 5	POAG, NTG	106
Aptel	2014	France	Caucasian	63	Mixed	AHI ≥ 15	NA	9580
Chen	2014	China	Asian	45	Mixed	ICD-9 CM	NA	12640
Muniesa	2014	Spain	Caucasian	54	Mixed	AHI ≥ 10	POAG, NTG	152

OSAHS, obstructive sleep apnea/hypopnea syndrome; RDI, respiratory disturbance index; AHI, apnea-hypopnea index; POAG, primary open-angle glaucoma; NTG, normal tension glaucoma; NA, not available.

hypopnea syndrome" or OSAHS or "sleep apnoea syndrome" or OSA or "Obstructive Sleep Apnea") and glaucoma. Additional studies were identified by a hand search from reference of original studies or review articles on this topic. There was no language restriction.

Inclusion and exclusion criteria

The following inclusion criteria were used: (1) the study should have evaluated the association between the OSAHS and glaucoma risk; (2) the study should have a case-control or cohort

Table 2. Results of meta-analysis and subgroup analyses

	No. of studies	Test of association			Model	Heterogeneity		
		OR (95% CI)	*Z*	*P* Value		χ^2	*P* Value	I^2 (%)
Overall	12	1.65 (1.44-1.88)	7.40	< 0.00001	R	19.15	0.06	43
Race								
Asian	3	1.78 (1.49-2.12)	6.35	< 0.00001	F	0.91	0.63	0
Caucasian	8	2.03 (1.12-3.69)	2.33	0.02	R	16.46	0.02	57
Gender								
Male	2	1.62 (1.29-2.03)	4.15	< 0.0001	F	0.64	0.42	0
Female	2	1.81 (1.27-2.57)	3.30	0.001	F	1.28	0.26	22
Glaucoma type								
POAG	6	1.87 (1.54-2.33)	6.09	< 0.00001	F	3.79	0.58	0
NTG	5	3.57 (0.89-14.43)	1.79	0.07	F	0.49	0.97	0
Severity of OSAHS								
Mild	3	2.60 (0.27-25.40)	0.82	0.41	F	0.04	0.85	0
Moderate	2	5.44 (0.27-108.60)	1.11	0.27	F	0.54	0.76	0
Severe	4	5.49 (1.04-33.83)	2.01	0.04	F	0.20	0.91	0

POAG, primary open-angle glaucoma; NTG, normal tension glaucoma; OSAHS, obstructive sleep apnea/hypopnea syndrome; R, random-effects model; F, fixed-effects model.

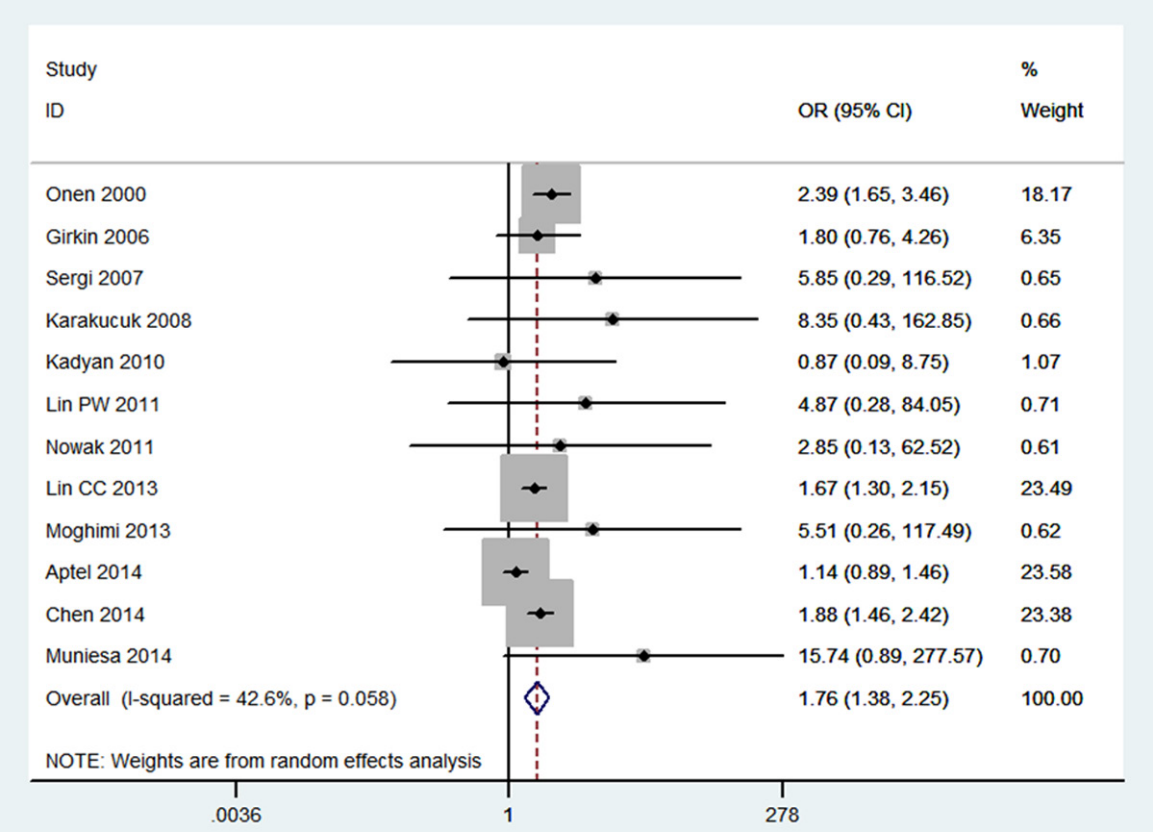

Figure 2. Meta-analysis for the association between OSAHS and glaucoma risk.

design; (3) sufficient data should have been provided in order to calculate odds ratios (OR) and 95% confidence interval (CI). Studies were excluded if any of the following conditions

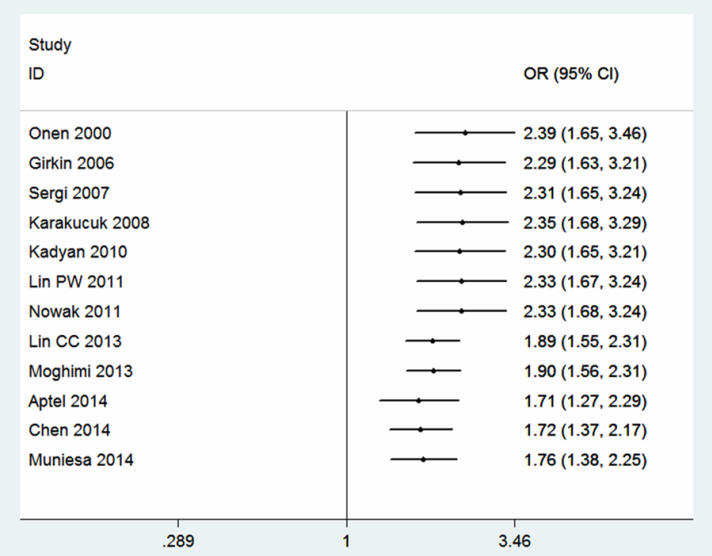

Figure 3. Cumulative meta-analysis for the association between OSAHS and glaucoma risk.

applied: (1) only abstracts or reviews were available, without sufficient data; (2) animal studies; (3) studies were repeated or publications overlapped.

Data extraction

The following data were recorded from each article: first author, years of publication, country, ethnicity of participants, gender, age, diagnose of OSAHS, type of glaucoma, numbers of subjects. The data were extracted by two of the authors independently. Discrepancies between these two authors were resolved by discussion.

Statistical analysis

The strength of association between the OSAHS and glaucoma risk was assessed by calculating OR with 95% CI. A statistical test for heterogeneity was performed based on the Q statistic. The $P > 0.10$ of the Q-test indicated a lack of heterogeneity among studies. The summary OR estimate of each study was calculated by the random-effects model or fixed-effects model. Stratified analysis was performed by race, gender, glaucoma type, and severity of OSAHS. Potential publication bias was examined by funnel plot and Egger's test [17]. Cumulative meta-analysis and sensitivity analysis were performed. All statistical tests were performed with the software STATA version 11.0 (Stata Corporation, College station, TX, USA). A P value < 0.05 was considered statistically significant.

Results

Study characteristics

A total of 12 studies (**Figure 1**) with 36909 subjects on the association between OSAHS and glaucoma risk were included for this meta-analysis [5-16]. There were 3 studies of Asian population and 8 studies of Caucasian population. Diagnose of OSAHS was based on apnea-hypopnea index (AHI) or ICD-9CM. The characteristics of each study are presented in **Table 1**.

Results of meta-analysis

The evaluations of the association between OSAHS and glaucoma risk are summarized in **Table 2**. OSAHS was associated with a significantly increased risk of glaucoma (OR = 1.65; 95% CI, 1.44-1.88; I^2 = 43%; **Figure 2**). In the race subgroup analysis, both Asians (OR = 1.78; 95% CI, 1.49-2.12; I^2 = 0%) and Caucasians (OR = 2.03; 95% CI, 1.12-3.69; I^2 = 57%) with OSAHS had increased glaucoma risk. In the subgroup analysis according to gender, both women and men were significantly associated with risk of glaucoma (OR = 1.81; 95% CI, 1.27-2.57; I^2 = 22% and OR = 1.62; 95% CI, 1.29-2.03; I^2 = 0%, respectively). In the subgroup analysis by glaucoma type, OSAHS patients showed increased primary open-angle glaucoma (POAG) risk (OR = 1.87; 95% CI, 1.54-2.33; I^2 = 0%) but not normal tension glaucoma (NTG) risk (OR = 3.57; 95% CI, 0.89-14.43; I^2 = 0%). In addition, severe OSAHS patients had an increased glaucoma risk (OR = 5.49; 95% CI, 1.04-33.83; I^2 = 0%), while mild and moderate OSAHS patients did not show significantly increased glaucoma risk.

As shown in **Figure 3**, significant associations were evident with each addition of more data over time. The results showed that the pooled ORs tended to be stable. A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled ORs, and the corresponding pooled ORs were not materially altered (**Figure 4**). The

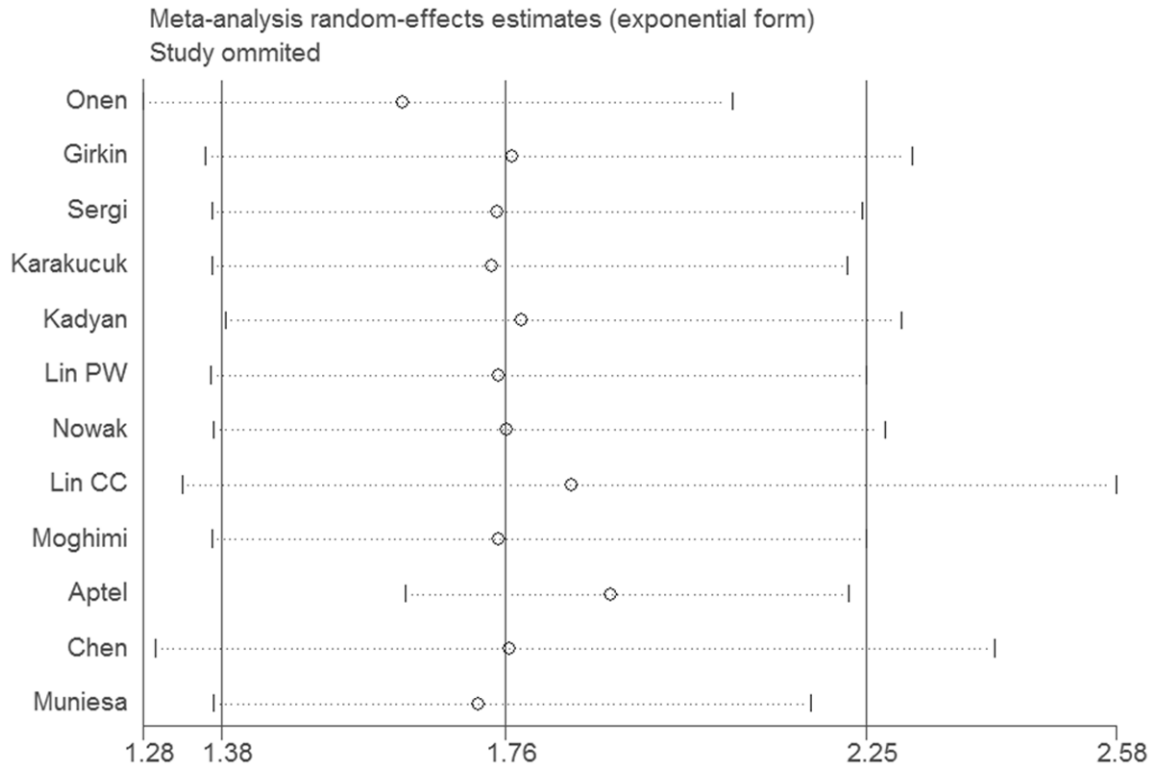

Figure 4. Sensitivity meta-analysis for the association between OSAHS and glaucoma risk.

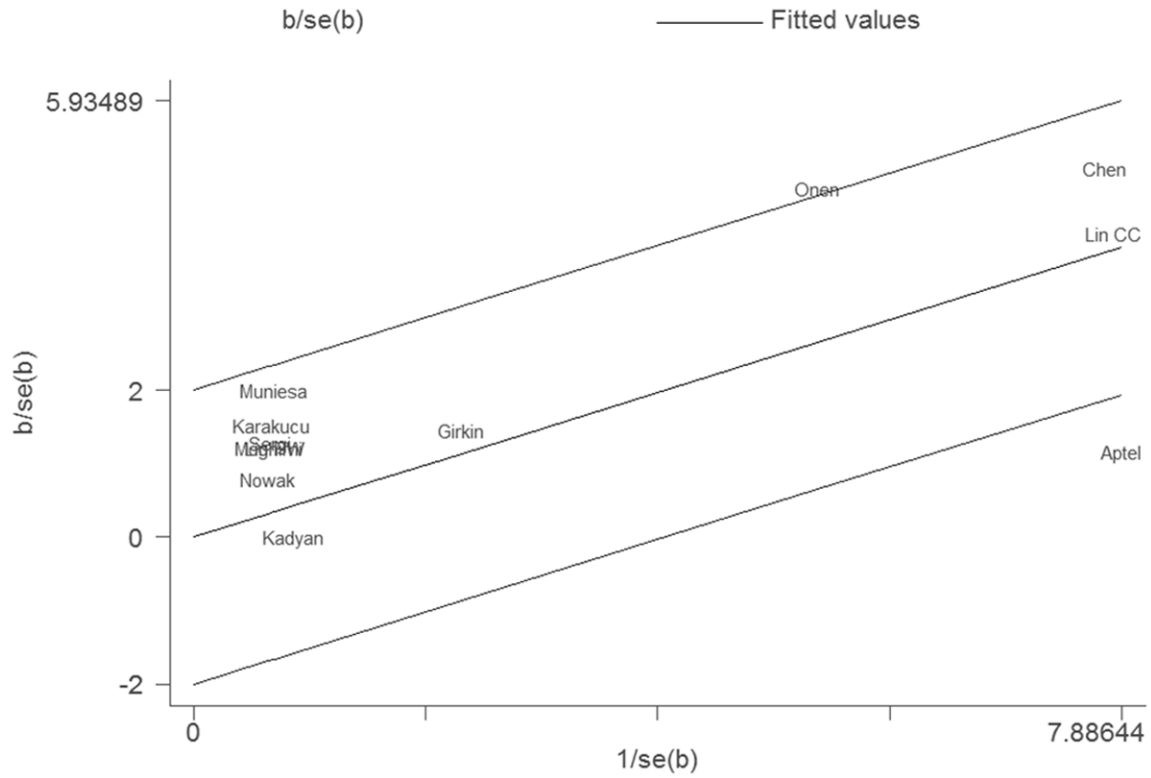

Figure 5. Galbraith plot of OSAHS and glaucoma risk.

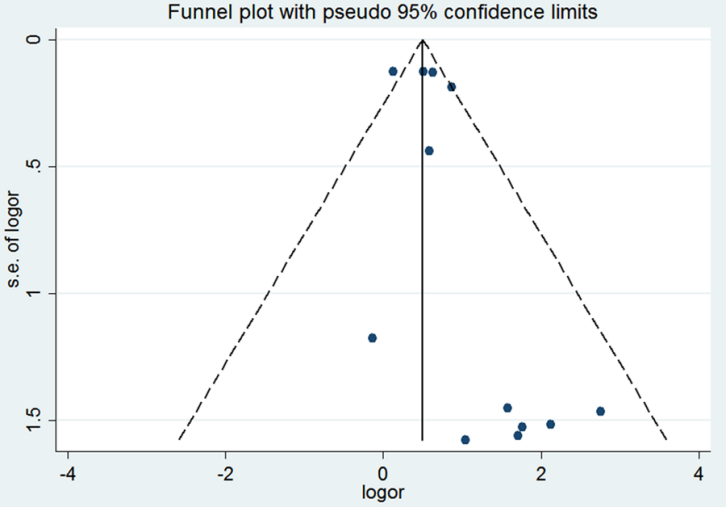

Figure 6. Funnel plot for the association between OSAHS and glaucoma risk.

Galbraith plot was used to find the source of the heterogeneity. As shown in **Figure 5**, two studies were the outliers. After excluding these studies, the between-study heterogeneity effectively decreased and there was no obvious heterogeneity among the twenty-four remaining studies (I^2 = 0%, P = 0.77). Besides, the result was still statistically significant (OR = 1.81; 95% CI, 1.52-2.15).

Funnel plot was performed to assess the publication bias of literatures. The shape of the funnel plot showed symmetry (**Figure 6**). Egger's test found no evidence of publication bias (P = 0.335).

Discussion

In this meta-analysis, we investigated the association between the OSAHS and glaucoma risk including 36909 subjects. We found that individuals with OSAHS showed an increased risk of glaucoma in the overall population. The result from our meta-analysis suggested that OSAHS patients had a 65% increased glaucoma risk compared to those normal individuals. In the stratified analysis by ethnicity, the significant association was observed in Asians and Caucasians. Only three studies conducted in Asians population were searched in our meta-analysis. Thus, more studies with Asians and other ethnic groups are still needed to address the role of OSAHS on glaucoma risk. In the subgroup analysis by gender, we found that OSAHS exhibited increased glaucoma risk in men and women. This result indicated that the role of glaucoma was not selective by gender. The subgroup analysis based on glaucoma type found that OSAHS showed increased POAG risk but not NTG risk. This meta-analysis included only 5 studies using NTG patients, the positive association between OSAHS and NTG could not be ruled out because studies with small sample size may have insufficient statistical power to detect a slight effect. In the future, more studies should be performed focusing on NTG patients with OSAHS. When subgroup analysis was performed according to severity of OSAHS, a significant association was showed in severe OSAHS patients. Since the number of studies included in this subgroup analysis was small, the results lacked sufficient reliability to confirm or refute an association in a definitive manner. In the future, more studies should be designed to analyze these associations.

The pathogenesis of ocular complications in OSAHS is likely to have a multifactorial origin, in which both vascular and mechanical factors may be present. Among the vascular factors, it has been postulated that there may be insufficient blood supply to nourish the retinal nerve fiber layer (RNFL) and/or optic nerve [8]. Repetitive or prolonged episodes of hypoxia may cause direct damage to the optic nerve [18]. Besides, the repetitive prolonged upper airway obstruction followed by arousal produces transient hypoxemia and hypercapnia, as well as increased sympathetic tone, which activates the renin-angiotensin system [19] and can lead to an increase in blood pressure and vascular resistance [20].

Results from one-way sensitivity analysis and cumulative meta-analysis suggested high stability and reliability of our results. Besides, we had to mention the importance of heterogeneity and publication bias, which might influence the results of meta-analysis. In our study, significant heterogeneity was observed. We used Galbraith plots to explore the sources of heterogeneity. We found that I^2 value was decreased after excluding the outliers. The results suggested that the 2 outlying studies might be

the major source of the heterogeneity. However, heterogeneity did not seem to influence the results, because the significance of the result was not altered after excluding the outliers. Additionally, funnel plots and Egger's tests were used to find potential publication bias. The results indicated that there was no significant publication bias.

In conclusion, this meta-analysis suggested that OSAHS may be associated with the risk of glaucoma.

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Disclosure of conflict of interest

None.

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