·Meta-Analysis·

# Retinal nerve fiber layer thickness changes in obstructive sleep apnea syndrome: a systematic review and Meta-analysis

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## Abstract

**• AIM: To evaluate the retinal nerve fiber layer (RNFL) thickness changes in patients with obstructive sleep apnoea syndrome (OSAS), and detect possible prevalence of glaucoma in this population.**

**• METHODS: Comprehensive studies were conducted on the Cochrane Library, PubMed and Embase through March, 2015. Only studies that fit the selection criteria about RNFL and OSAS would be included. For the measures, we calculated the 95% confidence interval (CI) and weighted mean differences (WMD). The systematic review and Meta-analysis was performed by RevMan 5.2 software.**

**• RESULTS: Nine case-control studies were analyzed containing a total of 1086 cases and 580 controls. Average RNFL thickness in OSAS was reduced significantly compared with healthy controls in random effects model (WMD=-2.56, 95% CI: -4.82 to -0.31, *P*=0.003, $I^2$=57%). A significant RNFL thickness reduction were found between the two groups in inferior quadrant (WMD=-3.11, 95% CI: -5.53 to -0.69, *P*=0.01), superior quadrant (WMD=-2.37, 95% CI: -4.7 to 0.04, *P*=0.05). In nasal quadrant (WMD=-2.54, 95% CI: -6.53 to 1.45, *P*=0.21) and temporal quadrant (WMD=-1.26, 95% CI: -2.19 to 0.47, *P*=0.15) there was no difference of RNFL thickness between the two groups.**

**• CONCLUSION: The results show that RNFL thickness is lower in patients with moderate or severe OSAS than in normal subjects or patients with mild OSAS according to the nine homogeneity studies.**

• **KEYWORDS:** retinal nerve fiber layer thickness; obstructive sleep apnea syndrome; Meta-analysis

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## INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a syndrome which is characterized by periodic incomplete or complete obstruction in the upper airway during sleep [1]. OSAS can be seen in both sexes and all races, ages, socioeconomic statuses, and ethnic groups, which is a common sleep disorder. Obstructive respiratory disturbances often lead to severe hypoxemia and consequent increases in vascular resistance which, in turn, may damage optic nerve head perfusion and oxygenation, eventually lead to glaucomatous optic neuropathy [2-4]. Frequently reported symptoms of OSAS are loud snoring, excessive daytime sleepiness, waking up in the morning tired, morning headache which is recommended by polysomnography. The prevalence of OSAS is more than 20% in United States [5]. When hypotension is happened in the disorder vascular of OSAS in sleeping, retinal nerve fiber layer (RNFL) damage and thinning might take place. As a result, optic nerve may become more sensitive to high intraocular pressure (IOP) or optic nerve damage may develop even with normal IOP [6-8]. OSAS has been implicated as a possible risk factor for the development of primary open angle glaucoma (POAG) and normal tension glaucoma (NTG). Several studies have shown that the prevalence of POAG and NTG in patients with OSAS ranges from 7% to 27% [6,8-10]. In 1982, Walsh and Montplaisir was first to report that 5 members of the same family had OSAS with glaucoma, which showed the combination of OSAS with glaucoma. People who suffer from optic neuropathy which is closely related to glaucoma tend to have enlarged optic nerve head cup/dish accomplied by thinner RNFL. RNFL thinning and characteristic visual field defects are one of the characteristic features of glaucoma, which is induced by ganglion cell death and its axonal loss [11]. The early detection of thinning in RNFL increases the chance of early diagnosis of glaucoma. A statistical analysis has been accomplished to respectively evaluate the thickness of RNFL of people who have OSAHS

and that of people from health-control group to figure that if OSAS would result in thinner RNFL.

## MATERIALS AND METHODS

**Study Selection** A comprehensive literature was searched, using the Cochrane Library，PubMed and Embase until to March, 2015. Key words included“retinal nerve fiber layer”, “retinal nerve fiber layer thickness”,“obstructive sleep apnea syndrome”, “OSAS”and “RNFL”. No specific language restriction was used on the publications. Two authors (Wang JS and Jia Y) independently browsed studies at the titles and/or abstracts of all the selected comprehensive studies. The full texts of the remaining studies were then carefully read to determine whether they met all inclusion criteria or not. In addition, their bibliographies of the included studies were also checked.

**Inclusion and Exclusion Criteria** Studies were considered for inclusion if they met the following criteria: 1) case-control study, cohort, cross-sectional, randomized controlled trials and retrospective study; 2) compared OSAS with healthy controls; 3) studies should provide the data of peripapillary RNFL thickness (mean±SD); 4) the diagnostic criteria were met apnea-hypopnea index (AHI)>5 considered to have OSAS. Patients with OSAS were evaluated in 3 groups according AHI scores: 5-15 score was mild, 16-30 score was moderate and over 30 score was classified as severe OSAS. Exclusion criteria as following: 1) duplicate publications; 2) data can't be used.

**Data Extraction** Information from eligible studies was carefully collected by two independent investigators (Wang JS and Xie HT) according to the inclusion criteria listed above into a standardized form. The following basic information was collected from the included articles, such as: authors, year of publication, number of eyes, country or region, age and gender. Number of eyes restriction were not defined. Parameters used to access the the RNFL thickness include the avarage thickness (360° unit circle), the temporal quadrant thickness (316°-45°unit circle), the nasal quadrant thickness (136° -225° unit circle), the supirior quadrant thickness (46° -135° unit circle) and inferior quadrant thickness (226°-315° unit circle). Scrupulous discussion with another author (Zhang MC) was held to clarify and settle disagreements between reviewers.

**Quality Assessment** Newcastle-Ottawa Scale (NOS) using a start-rating system for quality of case-control studies in Meta-analysis was adopted to evaluate the methodologic quality of studies involved [12]. The judgment was made according to three dimensions, namely, selection, comparability and exposure, of which the highest grade were 4 stars, 2 stars and 3 stars respectively. The maximum NOS score is 9 stars when the 3 dimensions all get the highest score. Studies scored higher than 6 stars were regarded as being of comparatively high quality. Through this way the two reviewers (Wang JS and Xie HT) assess the studies independently. Also disagreements were settled after discussion.

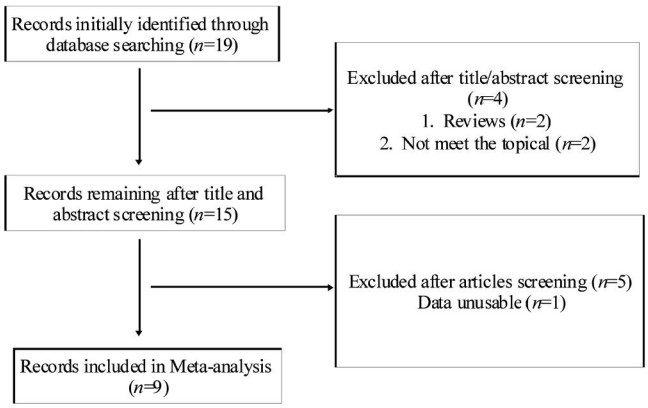


**Figure 1 Search and study selection process.**

**Statistical Analysis** As much original data as possible was managed to be obtained from those articles and that couldn't be obtained was to be calculated when necessary. The three groups were further analysed and divided into subgroups based on AHI score. To complete statistical analysis, RevMan software (version 5.2, Cochrane Collaboration, Oxford, UK) was employed. Summary estimation was done and 95% confidence intervals (CIs) were calculated as well. Then for further estimation, means and standard deviations were adopted to calculate the weighted mean difference (WMD). Mean while heterogeneity was evaluated using Chi-square test, tau$^2$ and Higgins $I^2$ [13]. $I^2$ test is a method for quantifying inconsistency during studies and describing the percentage of variability in effect estimation which is caused by heterogeneity. If $I^2$ is lower than 25%, which suggests that there is minor heterogeneity or homogeneity, the fixed-effect model would be selected to analyses [14]. Fixed- effects model is used when heterogeneity doesn't existed across studies ($P$>0.1, $I^2$<50%). Otherwise what is used should be the random-effects model. If $P$ value lower than 0.05, there was regarded statistically significant. A funnel plot was employed to detect potential publication bias. As a result, publication bias was proved to be existed by the discovery of a strong correlation between sample size and summary estimation.

## RESULTS

**Characteristics of Included Studies** Figure 1 shows the summary of selection of studies. Among 19 articles that were chosen initially, 2 were unrelated, 2 were review articles, so 15 articles were valid for further evaluation. Nevertheless, among the 15 remained articles, data in 6 articles was unuseful for analysis, which means that the 6 articles could not be included for the inclusion criteria of Meta-analysis. Eventually, a total of 9 articles about case-control studies which were in correspondence with our inclusion criteria were adopted for final Meta-analysis[15-23]. Overall, 1086 cases and 580 controls were included from 9 selected studies. The

**Table 1 Demographics of the patients**

| Author year | Country | No. of eyes | | Mean age (a) | | Gender (M/F) | | NOS | | | Totle score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | OSAS | HC | OSAS | HC | OSAS | HC | Selection | Comparability | Expose | |
| Adam 2013[15] | Turkey | 43 | 40 | 48.4 | 52.9 | 34/9 | 27/13 | 3 | 1 | 2 | 6 |
| Sagiv 2014[16] | Israel | 108 | 108 | 51.9 | 51.1 | 76/32 | 82/26 | 4 | 1 | 2 | 7 |
| Zengin 2014[17] | Turkey | 44 | 35 | 52.6 | 51.2 | 27/17 | 23/12 | 3 | 1 | 2 | 6 |
| Lin 2011[18] | Taiwan, China | 210 | 44 | NR | NR | 54/28 | 15/7 | 3 | 2 | 2 | 7 |
| Casas 2013[19] | Spain | 96 | 64 | 50.9 | 49.1 | 41/9 | 19/14 | 3 | 2 | 2 | 7 |
| Huseyinoglu 2014[20] | Turkey | 202 | 40 | 52.4 | 49.3 | 55/46 | 11/9 | 3 | 2 | 2 | 7 |
| Xin 2015[21] | China | 91 | 28 | NR | 55.4 | NR | 16/12 | 3 | 1 | 2 | 6 |
| Bayhan 2015[22] | Turkey | 92 | 32 | NR | 47.3 | NR | 17/15 | 3 | 2 | 2 | 7 |
| Ferrandez 2014[23] | Spain | 80 | 111 | 48.8 | 50.8 | NR | NR | 3 | 2 | 2 | 7 |

OSAS: Obstructive sleep apnea syndrome; HC: Healthy controls; RNFL: Retinal nerve fiber layer; NOS: Newcastle-Ottawa scale; NR: Not reported.

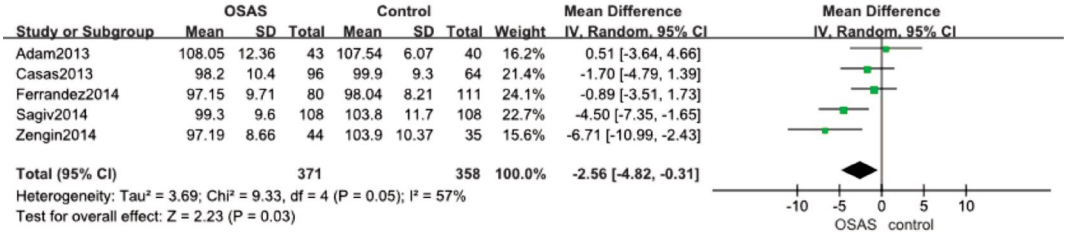


**Figure 2 Meta-analysis of average RNFL thickness between OSAS patients and healthy controls.**

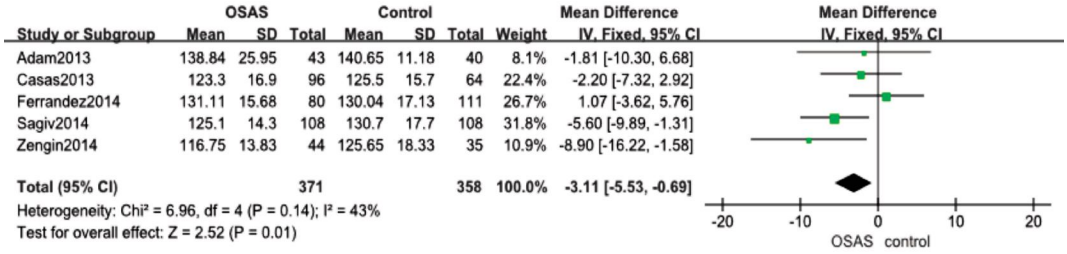


**Figure 3 Meta-analysis of inferior RNFL thickness between OSAS patients and healthy controls.**

RNFL analyses were performed using optical coherence tomography (OCT) with the fast RNFL scan protocol and only high-quality images were included by the same investigator in all studies of our Meta-analysis: 4 with Stratus OCT (Carl Zeiss Meditec, Inc., Dublin, CA, USA)[15-16,18-19], 2 with 3D-OCT (Topcon Corp., Tokyo, Japan)[17,21], 2 with spectral domain-OCT (RTVue; Optovue, USA)[21-22] and 1 with spectral domain-OCT (Cirrus HD, Carl Zeiss Meditec, Dublin, CA, USA)[23]. Patients who had a history of glaucoma were excluded from their study in eight articles [15-20,22-23], only one article reported that OSAS had a high prevalence of POAG [21]. The information of authors, publication year, national sources, sample size and the NOS score of each study were listed in Table 1.

**Quality Assessment Results** Scores of the 9 studies ranged from 6 to 7, with 6.67 being the median, showing that the case-control studies were of high quality (≥6). As for the three dimensions, the median scores of selection, comparability and exposure were respectively 3.1, 1.5 and 2.0.

**Pooled-analysis Results** It was found in analysis of average RNFL thickness in the 9 studies in OSAS patients and in healthy control group that heterogeneity was significant ($I^2 \geqslant 57\%$) among articles, therefore the data was pooled through the random effects model. It's indicated by the Meta-analysis of these data that the average RNFL thickness in patients with OSAS was significantly thinner than that of heath control group (WMD=-2.56, 95% CI: -4.82 to -0.31, $P$=0.03; Figure 2). At the same time, data of RNFL thickness in each quadrant between patient with OSAHS and health control group was included for comparison in Meta-analysis and it was suggested that compared with the health control group, the thickness was significantly reduced in patients with OSAS in inferior quadrant (WMD=-3.11, 95% CI: -5.53 to -0.69, $P$=0.01; Figure 3) and in superior quadrant (WMD=-2.37, 95% CI: -4.7 to -0.04, $P$=0.05; Figure 4). However, no significant difference was found between the two groups in RNFL thickness in nasal quadrant (WMD=-2.54, 95% CI: -6.53 to 1.45, $P$=0.21; Figure 5) and temporal quadrant (WMD=-1.26, 95% CI: -2.99 to 0.47, $P$=0.15; Figure 6).

**Subgroup Analysis** To explore whether the RNFL thicknesses between the patients with OSAS and the health

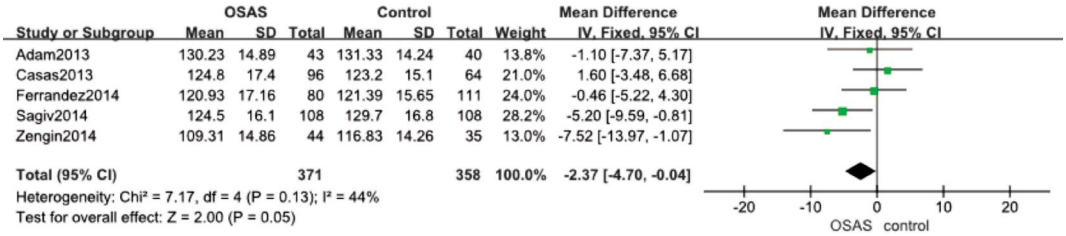


**Figure 4 Meta-analysis of superior RNFL thickness between OSAS patients and healthy controls.**

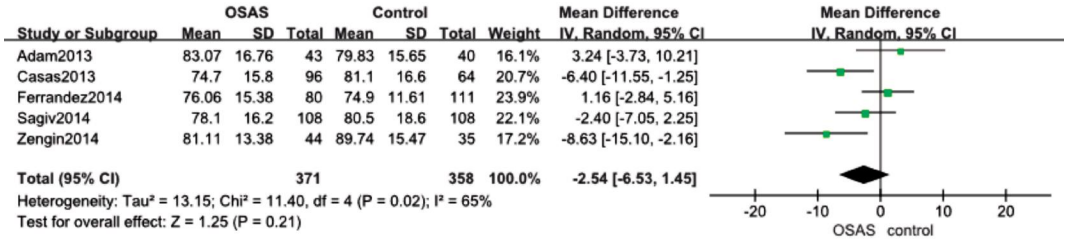


**Figure 5 Meta-analysis of nasal RNFL thickness between OSAS patients and healthy controls.**

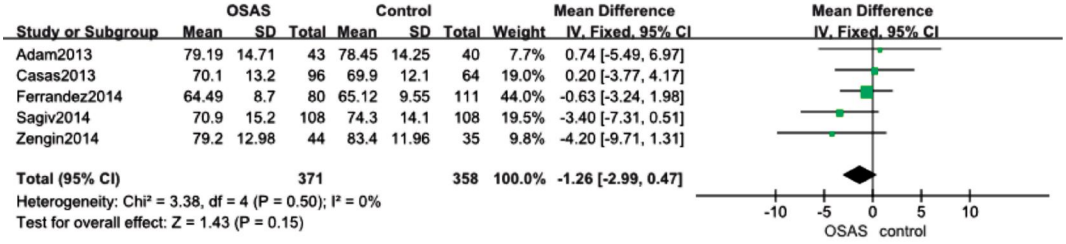


**Figure 6 Meta-analysis of temporal RNFL thickness between OSAS patients and healthy controls.**

control group were difference, subgroup analysis was used according to AHI scores. It was indicated by results that differences of RNFL thickness were statistically significant between OSAS patients and the health control group in average quadrant no matter how serious OSAS is. As for temporal quadrant, RNFL thickness in the other four quadrants in OSAS patients reduced significantly compared with that in health control group on condition that AHI was higher than 30. It was indicated that when AHI scores rise, RNFL thickness gets continuously thinner with temporal quadrant being excluded (Table 2).

**Publication Bias** There was no correlation between study sample as well as any other evidence of publication bias from the funnel plot (Figure 7).

## DISCUSSION

Obstructive sleep apnea, which is a risk factor for cardiovascular, neurologic, and endocrine disease and other complications and accidents. Seriously it's a potentially deadly sleep respiratory diseases [24-29]. During sleep, repeated episodes of apnea, consequently appeared hypoxemia, hypercapnia, haemodynamic, humoral, and neuroendocrine responses finally affect the circulation of the optic nerve with loss of ganglion cells [2]. Deterioration of auto regulation in blood flow to the optic nerve was due to recurrent apneas[30]. This vascular phenomenon may compromise optic nerve perfusion and oxygenation, ultimately leading to optic neuropathy. In a study [31] where ophthalmic artery resistance and central artery resistance were examined in patients with OSAS by Doppler ultrasonography, no statistically significant difference was found between vascular resistance as well as IOP. However, the positive correlation observed between IOP and AHI suggests that increased IOP values may reflect the severity of OSAS. Erdem *et al* [32] reported that they

**Table 2 Subgroup analysis according to AHI scores**

| Subgroups | No. of studies | WMD (95% CI) of RNFL thickness | *P* |
|---|---|---|---|
| Mild OSAS *vs* Control | | | |
| Average | 5 | -2.10 (-4.06, -0.13) | 0.04 |
| Superior | 4 | -2.20 (-5.54, 1.13) | 0.2 |
| Nasal | 4 | -2.30 (-8.65, 4.05) | 0.48 |
| Inferior | 4 | -2.90 (-9.20, 3.39) | 0.37 |
| Temporal | 4 | 1.42 (-2.41, 5.25) | 0.47 |
| Moderate OSAS *vs* Control | | | |
| Average | 5 | -3.87 (-5.80, -1.93) | <0.0001 |
| Superior | 4 | -2.75 (-5.78, 0.29) | 0.08 |
| Nasal | 4 | -5.18 (-10.50, 0.13) | 0.06 |
| Inferior | 4 | -9.52 (-16.53, -2.51) | 0.008 |
| Temporal | 4 | -2.40 (-5.60, 0.79) | 0.14 |
| Severe OSAS *vs* Control | | | |
| Average | 6 | -6.19 (-9.72, -2.66) | 0.0006 |
| Superior | 5 | -6.29 (-11.24, -1.34) | 0.01 |
| Nasal | 5 | -6.99 (-11.10, -2.87) | 0.0009 |
| Inferior | 5 | -5.52 (-8.67, -2.17) | 0.001 |
| Temporal | 5 | 0.01 (-2.74, 2.76) | 0.99 |

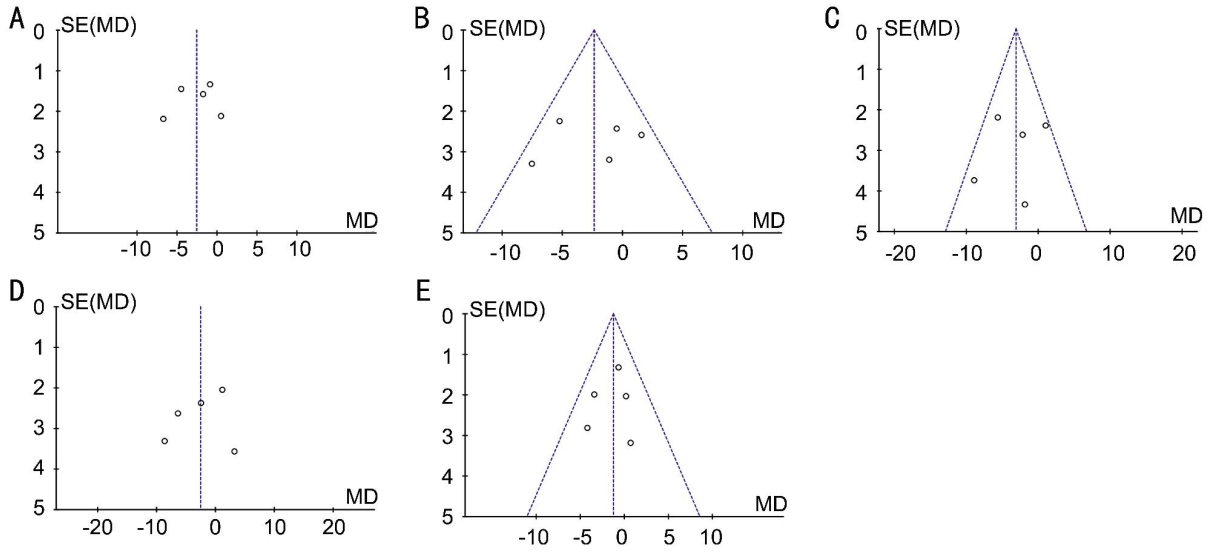


**Figure 7 A funnel plot for evaluating the publication bias** A: Average; B: Superior; C: Inferior; D: Nasal; E: Temporal.

measured postsystolic and enddiastolic volumes by Doppler ultrasonography in patients with severe OSAS. Blood flow velocities were higher in most measured vessels in patients with OSAS than they were in the control subjects. The blood flow was significantly increased in ophthalmic artery, central retinal artery, and posterior ciliary artery, whereas in patients of mild OSAS the blood flow increased only in posterior ciliary artery. This increase may be a compensatory response occurring against chronic hypoxia. Leung *et al* [33] reported that almost all of the quadrants of RNFL were thinner in patients with OSAS, indicating that there is a diffuse loss of axons entering the neuroretinal rim as expected in glaucoma, especially the thickness of the superior quadrant and inferior quadrant is affected earlier in glaucoma.

Significant reduction in average circumpapillary RNFL in OSAS patients was indicated in Meta-analysis compared with the health control group. Evidence for significant differences of RNFL thickness between the two groups in superior quadrant and inferior quadrant was found in further analysis. However, that evidence was not found in nasal quadrant and temporal quadrant. In subgroup analysis based on AHI scores significant differences of RNFL thickness were only found in average between mild OSAHS and health control group, average and inferior quadrant between moderate OSAS and health control group and average, inferior, superior and nasal quadrant between severe OSAS patient and health control group. For temporal quadrant, no significant difference was found regardless of OSAS severity. According to the result of the above remind us OSAS can result in most quadrants of the RNFL thickness decreasing especially in severe OSAS.

In glaucoma, RNFL thickness decreases progressively. This thinning could appear earlier in glaucoma patients' eyes, which occurred before detectable changes in the visual field[7]. And the visual field may be seriously affected by cultural difference, cognitive difference, operation ability and response speed as we all known. If the decrease of RNFL can be reliably detected, the clinician may reduce the risk of developing glaucoma.

This Meta-analysis has several limitations that should be taken into account when its results are considered. First, the small number of studies included and the small sample of cases per trial give these analyses low power. Second, we could include only data from published articles, and it is possible that bias is introduced if studies with small or reverse effects exist but have not been published. Third, the species of devices of RNFL analyses and included racial didn't take into account in this research. Nevertheless, this Meta-analysis provides more powerful evidence than the individual reports alone, and we are unaware of any other similar Meta-analyses.

In conclusion, these findings suggest that peripapillary RNFL thickness might be used as a biomarker to early diagnosis and classification of OSAS patients. Of course, we had some shortcomings in this Meta-analysis such as did not analyze the type of OCT and did not considered racial difference. Thus, subsequent experiments are urgently required to confirm these findings and explanation why only temporal quadrant dose not reduce.

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**Conflicts of Interest: Wang JS,** None; **Xie HT,** None; **Jia Y,** None; **Zhang MC,** None.

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