

Role of sleep-disordered breathing in age-related macular degeneration

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To cite: Fang WY, Rama Raj P, Wu Z, *et al.* Role of sleep-disordered breathing in age-related macular degeneration. *BMJ Open Ophthalmology* 2023;**8**:e001203. doi:10.1136/bmjophth-2022-001203

Presented in part at The Association for Research in Vision and Ophthalmology Annual Meeting, 2021.

Received 7 November 2022
Accepted 26 April 2023



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ABSTRACT

Aims To examine the association between obstructive sleep apnoea (OSA) and age-related macular degeneration (AMD), and the subphenotype of AMD with reticular pseudodrusen (RPD).

Methods Case-control study with 351 participants (211 AMD and 140 controls) using the Epworth Sleepiness Scale (ESS) and the STOP-BANG Questionnaire (SBQ) validated sleep questionnaires. Participant risk of having moderate-to-severe OSA was determined using a binary risk scale based on the ESS and SBQ combined and an ordinal risk scale based on the SBQ. A prior diagnosis of OSA and whether receiving assisted breathing treatment was also ascertained. Retinal imaging allowed AMD and RPD determination.

Results Higher risk of moderate-to-severe OSA according to the binary and ordinal scales was not associated with the presence of AMD ($p \geq 0.519$) nor AMD with RPD ($p \geq 0.551$). Per point increase in ESS or SBQ questionnaire score was also not associated with AMD nor AMD with RPD ($p \geq 0.252$). However, being on assisted breathing treatment for diagnosed OSA was significantly associated with a higher likelihood of having AMD with RPD, but not all AMD, (OR 3.70; $p = 0.042$ and OR 2.70; $p = 0.149$, respectively), when compared with those without diagnosed OSA on treatment.

Conclusions Formally diagnosed OSA undergoing treatment, increased the likelihood of having AMD with RPD, but not overall AMD compared with those who were not undergoing treatment. Risk-based OSA questionnaires showed no difference in risk for all AMD or AMD with RPD. Future research, using formal sleep studies could further explore the potential role of nocturnal hypoxia in AMD.

INTRODUCTION

Age-related macular degeneration (AMD) is a complex genetic disease, affecting approximately 9% of people over 50 years of age and its prevalence is increasing, with an expected prevalence of 288 million worldwide by 2040.^{1,2} Apart from smoking cessation, dietary modifications, general lifestyle modification and nutritional supplementation, there has been limited progress in identifying additional modifiable risk factors that may prevent AMD or slow its progression to late vision threatening stages.³ Therefore, identifying new ways to reduce the incidence and

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The retina uses more oxygen at night, and diseases that cause nocturnal hypoxia, such as obstructive sleep apnoea, may contribute to the development of age-related macular degeneration (AMD).

WHAT THIS STUDY ADDS

⇒ This study uses two validated sleep questionnaires to assess the association between the risk of obstructive sleep apnoea and AMD. It also investigates this association in a subphenotype of AMD with reticular pseudodrusen.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Formal sleep studies are needed to further investigate the relationship between nocturnal hypoxia and AMD, and particularly its association with the reticular pseudodrusen subphenotype.

progression of AMD, through identifying modifiable risk factors, is urgently needed.

While advances have been made in determining underlying genetic associations with AMD and several mechanistic pathways, such as those involving oxidative stress, lipid biology, chronic inflammation and extracellular matrix homeostasis, the exact pathophysiology of AMD remains to be elucidated.⁴ Understanding the underlying pathological pathways is critical in advancing our ability to identify potentially modifiable risk factors that contribute to this disease. There is an increasing evidence to suggest that hypoxia may play a crucial role in the pathogenesis of AMD, with the retinal pigment epithelium (RPE) and photoreceptors being highly metabolically active and in high demand for oxygen and with the inner segments of the photoreceptors dominating retinal oxygen consumption.⁵ A lack of metabolic supply to the outer retina results in impaired health and function of the RPE and photoreceptors. There is evidence of oxidative stress and mitochondrial damage occurring in the RPE, which results in reduction of glucose supply to photoreceptors.^{6–8} Thus hypoxia-mediated

RPE and photoreceptor injury may play a crucial role in AMD development and progression.

The choroid is the main source of oxygen and nutrient supply to the outer retina, with computational modelling of oxygen distribution in the outer retina suggesting that reduction in oxygen diffusion and transport from the choroid to the outer retina, due to the presence of drusen, could potentially link hypoxia to AMD progression.⁸ Even under normal conditions, oxygen tension in the outer retina, particularly at the photoreceptor inner segments, is reduced to a very low level in darkness, due to retinal oxygen consumption being highest in darkness. The retina requires 50% more oxygen in the dark than in the light, due in large part to the need to maintain the dark current.^{9–11} Thus, any additional factors that alter this tenuous metabolic supply and oxygen delivery to the outer retina, will likely increase hypoxia in the outer retina, creating an environment that predisposes to AMD and its progression.

A common group of disorders that cause nocturnal hypoxia are known as sleep-disordered breathing (SDB),^{12–13} and includes several disorders, the most common being obstructive sleep apnoea (OSA).^{14–15} Like AMD, the prevalence of SDB increases with age, with 24% of people over 65 thought to experience some degree of SDB.¹⁶ In SDB, repetitive episodes of upper airway collapse cause apnoeas and hypopneas during sleep, thereby resulting in a prolonged state of recurring nocturnal hypoxia. OSA has been associated with several ophthalmic conditions, such as glaucoma, diabetic retinopathy, nonarteritic anterior ischaemic optic neuropathy, retinal vein occlusion, central serous chorioretinopathy and floppy eye lid syndrome.^{17–21}

There is no established consensus regarding the association between AMD and SDB, with only a small number of studies having explored this relationship. In a study of 5604 participants, Nau reported that those with sleep disorders were more than twice as likely to have AMD.²² In this study, the definition of sleep disorder encompassed a myriad of different conditions such as OSA, insomnia and snoring, some of which are not considered SDB and do not cause nocturnal hypoxia. In a prospective cohort study of more than 500 000 participants, Han *et al* found that people with OSA were significantly more likely to develop AMD compared with controls (HR=1.39, $p<0.001$).²³ A record linkage study of approximately 45 000 individuals also observed that the risk of having a subsequent hospital record of AMD was higher for those with a hospital record of OSA than those that did not (rate ratio 1.44; 95% CI 1.32 to 1.57).²⁴ A cross-sectional study also reported an increased prevalence of OSA across all AMD subtypes in comparison to estimated population norms (11–28% vs 3–7%). However, this study did not investigate the association using a model that adjusted for relevant confounders.²⁵ Several studies have investigated an association between OSA and response to treatment with anti-VEGF therapy for neovascular AMD citing a poorer treatment response in those with OSA.^{26–27}

Typically, studies investigating SDB use questionnaires to assess the risk of SDB. Two commonly used, validated, questionnaires are the Epworth Sleepiness Scale (ESS) and the STOP-Bang questionnaire (SBQ) which provide risk assessment for having SDB.^{28–29} Individuals in a high-risk category would usually be referred onto formal sleep studies with in-laboratory polysomnography to confirm the presence of nocturnal hypoxia.

The purpose of this study is to further investigate the association between the risk of moderate-to-severe OSA and AMD using validated questionnaires in a carefully phenotyped cohort. The role of nocturnal hypoxia in the AMD phenotype with reticular pseudodrusen (RPD) is also of particular interest given their association with poor rod function, where rod photoreceptors are dependent on the highly metabolically demanding nocturnal recycling of outer segments and visual pigment regeneration. Several studies have also reported increase in choriocapillaris flow deficits in those with RPD which could potentially compound any other cause of low oxygen to the outer retina.^{30–31} This could be further compromised by low retinal oxygen levels.^{32–33} If OSA-mediated nocturnal hypoxia is associated with a higher risk of AMD, a viable treatment option presents itself through devices delivering continuous positive airway pressure (CPAP) such as is used routinely to treat OSA.

MATERIALS AND METHODS

Participants

Participants with AMD were recruited from existing natural history studies at the Centre for Eye Research Australia and from ophthalmology practices. AMD participants were required to be 50 years or older and have at least intermediate AMD according to the Beckman classification.³⁴ Control participants were recruited from among staff, friends and unrelated family members of the AMD participants or from clinics and were required to have no evidence of drusen $>63\mu\text{m}$ on optical coherence tomography (OCT) imaging (see below). Participants were excluded if they had a prior diagnosis of an ophthalmic condition that has previously been associated with nocturnal hypoxia such as glaucoma, diabetic retinopathy, retinal vein occlusion or central serous chorioretinopathy. Participants with other retinal conditions, as well as participants with systemic conditions or medications that could affect the appearance of the retina, were also excluded. Any conditions requiring daytime oxygen therapy such as chronic obstructive pulmonary disease or congestive heart failure were also excluded. Demographic and participant risk data including age, sex and smoking status were recorded.

SDB risk assessment

All participants completed the ESS and the SBQ to obtain a risk assessment for SDB.^{28–29} The ESS is a questionnaire involving eight questions that allows participants to subjectively assess their sleepiness in eight different situations. The SBQ is a questionnaire with eight questions

assessing factors contributing to an increased risk of OSA. Participants were surveyed face-to-face, or via phone interviews, or completed the questionnaire at home and returned via mail. During the questionnaire, participants were also asked if they already had a diagnosis on OSA and whether they were currently receiving treatment at night through using an assisted breathing device.

Imaging and image grading

All participants had spectral domain OCT (SD-OCT) scans performed using the Spectralis HRA+OCT (Heidelberg Engineering; Heidelberg, Germany) and in some control participants the Cirrus HD-OCT (Carl Zeiss Meditec; Dublin, California, USA), was used instead. Participants with AMD underwent additional multimodal retinal imaging to allow AMD staging using the Beckman classification and RPD status to be graded, including: near infrared reflectance, fundus autofluorescence (Spectralis HRA+OCT, Heidelberg Engineering, Heidelberg, Germany), and colour fundus photography (CFP) (Canon, CR6-45NM Canon; Saitama, Japan or TRC-50DX Topcon; Tokyo, Japan). For SD-OCT volume scans on the Spectralis HRA+OCT, 49 horizontal B-scans within the central 20°×20° of retina were obtained in high-resolution mode, while volume scans on the Cirrus HD-OCT 5000 were acquired with a protocol capturing 128B-scans. Foveal centred 45° field CFPs were also taken. RPD presence was defined as having five or more subretinal deposits of RPD, on SD-OCT, in more than one B-scan and presence confirmed with at least one en face imaging modality, in at least one eye.^{27 33} RPD could be questionably present or absent if they did not satisfy the criteria for definitely present. Retinal imaging was obtained within 6 months of conducting the sleep questionnaires. AMD and RPD status were determined by at least one experienced grader and validated by a senior retinal specialist (RHG) for AMD stage and RPD status. Any disagreement on grading was then reviewed by the two graders and disease status, mutually agreed.

Statistical analysis

This pilot study uses two questionnaires, the ESS and SBQ to investigate the association between AMD and risk of moderate-to-severe OSA. Analysis was performed with two different risk scales: a binary scale based on the ESS and SBQ results combined, and an ordinal risk scale based on the SBQ results only. The binary risk scale used was based on an Australian validation study that determined the sensitivity and specificity of combining the ESS and SBQ.³⁵ Using this data, participants at high risk of moderate-to-severe OSA was defined as having an ESS score ≥8 and SBQ score ≥2, or ESS score <8 and SBQ score ≥5.³⁵ The ordinal risk scale classified participants' results into low, moderate and high risk of moderate-to-severe OSA, using only a validated SBQ scoring algorithm.^{36 37} The binary risk scale has an estimated

specificity of 90% while the ordinal risk scale has an estimated sensitivity of 90%.^{35 38}

Binary logistic regression analyses were performed to assess the association between AMD and risk of moderate-to-severe OSA. Logistic regression analyses were also used to assess the association between AMD with a RPD phenotype and the risk of moderate-to-severe OSA. All logistic regression models adjusted for key confounders of AMD (age, gender and smoking). All analyses were performed in Stata/SE V.17.0 (StataCorp).

RESULTS

A total of 351 participants were included in the study; where 211 (60.1%) had AMD and 140 (39.9%) were control participants with normal maculae. The mean age of the AMD group (75.6±8.1 years) was significantly older than that of the control group (71.3±7.9 years, $p<0.001$). Compared with the control group, the AMD group had a higher proportion of females (69.7% vs 54.3%, $p=0.003$), but there was no significant difference in the proportion of individuals who had a history of past or current smoking between the two groups ($p=0.185$). Within the AMD group, there were 102 participants (48.3%) with intermediate AMD (bilateral large drusen) and 109 participants (51.7%) with late AMD. Within this group of 211 AMD participants, 107 (50.7%) had coexisting RPD.

Associations based on sleep apnoea diagnosis and use of assisted breathing device

Based on the evaluation of all 351 participants, a prior formal diagnosis of OSA was noted in 22 (6.3%) participants, 15 (68%) had AMD and 7 (32%) were controls. A formal diagnosis of OSA was not associated with a significantly higher likelihood of having AMD present (OR (OR), 1.63; $p=0.319$, table 1), nor with a higher likelihood of having RPD coexistent with AMD (OR, 1.97; $p=0.187$, table 1) compared with those without a formal diagnosis of OSA. Among individuals who had a formal diagnosis of OSA, and treatment using an assisted breathing device (14 (4.0%) participants in this cohort), there was no association with AMD (OR 2.70; $p=0.149$, table 1). However, having a formal OSA diagnosis and having treatment with an assisted breathing device was significantly associated with an increased likelihood of RPD coexistent with AMD (OR 3.70; $p=0.042$, table 1).

Associations based on sleep questionnaire results

In a subset of 337 participants (those who were not under treatment for OSA using an assisted breathing device) with complete data on the SBQ and ESS, logistic regression analysis for the assessment of OSA risk using the binary scale showed no association of high-risk of moderate-to-severe OSA with AMD presence (OR, 1.13; $p=0.698$, table 2), or with RPD coexistent with AMD (OR, 1.05; $p=0.885$, table 2). Based on the assessment of OSA risk using the ordinal scale, having an intermediate or high risk of having moderate-to-severe OSA was also not



Table 1 Association between a formal diagnosis of obstructive sleep apnoea and use of an assisted breathing device with the likelihood of having age-related macular degeneration (AMD) or reticular pseudodrusen (RPD) coexistent with AMD (n=351)

| Parameter | AMD | | RPD coexistent with AMD | |
|---|----------------------|---------|-------------------------|---------|
| | OR (95% CI) | P Value | OR (95% CI) | P Value |
| Formal obstructive sleep apnoea diagnosis | | | | |
| No (n=329) | Ref | 0.319 | Ref | 0.187 |
| Yes (n=22) | 1.63 (0.62 to 4.33) | | 1.97 (0.72 to 5.41) | |
| Formal obstructive sleep apnoea diagnosis and assisted breathing device use | | | | |
| No (n=337) | Ref | 0.149 | Ref | 0.042 |
| Yes (n=14) | 2.70 (0.70 to 10.44) | | 3.70 (1.05 to 13.00) | |

Evaluation of each parameter was performed adjusting for age, gender and smoking history.

associated with AMD presence ($p=0.519$, table 2), nor with RPD coexistent with AMD ($p=0.551$, table 2).

Per point increase in SBQ score alone was also not associated with presence of AMD (OR 1.09; $p=0.441$, table 2) nor RPD coexistent with AMD (OR 1.16; $p=0.252$, table 2). Per point increase in the ESS score also lacked association with AMD (OR 1.04; $p=0.353$, table 2) and RPD coexistent with AMD (OR 1.02; $p=0.679$, table 2).

In an exploratory analysis where all individuals with a formal diagnosis of OSA and also on treatment with assisted breathing (n=14) were arbitrarily assigned the maximum possible score for the SBQ and ESS, then the per point increase in the SBQ score was associated with the presence of the RPD subphenotype of AMD (OR=1.24; $p=0.014$); all other analyses as performed in table 2 were otherwise not significant ($p\geq 0.052$).

DISCUSSION

This study investigated the possible association between clinically diagnosed OSA, treated OSA and OSA risk with

the likelihood of having AMD, or the AMD subphenotype with RPD. We used two different risk scales based on validated sleep questionnaires (ESS and SBQ) to determine the risk of having moderate-to-severe OSA. After adjusting for age, gender and smoking history, a clinical diagnosis of OSA or being at higher risk of moderate-to-severe OSA, based on the validated questionnaires, was not associated with a higher likelihood of having AMD, nor with the presence of RPD coexistent with AMD. However, when considering individuals with a formal diagnosis of OSA, who were also receiving treatment using an assisted breathing device, while they were not more likely to have AMD, they were 3.7 times more likely to have RPD coexistent with AMD compared with those who were not receiving treatment for OSA.

The lack of association could be due to the fact that the sleep questionnaires are only screening tools for the diagnosis of OSA, since being at high risk of OSA does not necessarily mean that one has OSA or experiences hypoxic episodes at night and similarly not showing

Table 2 Association between obstructive sleep apnoea (OSA) risk determined by the STOP-BANG questionnaire (SBQ) and Epworth Sleepiness Scale (ESS) with the likelihood of having age-related macular degeneration (AMD) or reticular pseudodrusen (RPD) coexistent with AMD (n=337)

| Parameters | AMD | | RPD coexistent with AMD | |
|----------------------------|---------------------|---------|-------------------------|---------|
| | OR (95% CI) | P Value | OR (95% CI) | P Value |
| OSA risk (SBQ+ESS; binary) | | | | |
| Non-high risk (n=274) | Ref | 0.698 | Ref | 0.885 |
| High risk (n=63) | 1.13 (0.61 to 2.07) | | 1.05 (0.53 to 2.11) | |
| OSA risk (SBQ; ordinal) | | | | |
| Low risk (n=169) | Ref | 0.519 | Ref | 0.551 |
| Intermediate risk (n=142) | 1.35 (0.79 to 2.31) | | 1.36 (0.75 to 2.46) | |
| High risk (n=26) | 1.39 (0.53 to 3.65) | | 1.55 (0.49 to 4.93) | |
| SBQ score (continuous) | | | | |
| Per point increase | 1.09 (0.88 to 1.36) | 0.441 | 1.16 (0.90 to 1.51) | 0.252 |
| ESS score (continuous) | | | | |
| Per point increase | 1.04 (0.96 to 1.12) | 0.353 | 1.02 (0.94 to 1.11) | 0.679 |

Evaluation of each parameter was performed adjusting for age, gender and smoking history.
ESS, Epworth Sleepiness Scale.

increased risk on the sleep questionnaire does not mean that they do not have OSA. Hence, the potential mismatch between those identified as being at high risk and those who actually experience hypoxia at night may have contributed to the lack of association.

Interestingly, participants with a formal diagnosis of OSA who were receiving treatment with an assisted breathing device, which we considered indicated a higher degree of nocturnal hypoxia, were more likely to have RPD coexistent with AMD, compared with those not undergoing this treatment for OSA. In the current analysis, those participants with a formal diagnosis of OSA and who were using an assisted breathing device were not included in the questionnaire analysis, as we felt the treatment would alter the responses. This, therefore, biases the questionnaire cohort towards those without OSA. When those with a formal diagnosis of OSA on treatment were arbitrarily assigned a maximum score, there was a significant association between the SBQ score and AMD with coexistent RPD. This adds weight to the possible association between OSA and the subphenotype of AMD with RPD. The AMD sub phenotype with RPD was hypothesised to be potentially more likely associated with OSA due to the possibility that rod dysfunction, known to be a hallmark of RPD, could result from the inability to meet the nocturnal metabolic demands required for rod photoreceptor recycling. If, in addition, there are deficits in choriocapillary flow in those with RPD, the hypoxic environment would be further aggravated.³⁰

The gold standard for the diagnosis of OSA is in-laboratory polysomnography testing with a sleep specialist to interpret the recordings together with clinical and medical history.^{39 40} Indeed, several of the participants in this study who were assessed as being at high risk of OSA went on to have formal polysomnography testing and were diagnosed with OSA. However, home-based pulse oximetry can be used to monitor oxygen levels at night and could serve as a more accurate screening test than questionnaires for OSA. Home-based nocturnal oximetry may be a practical approach for further studies to directly measure oxygen levels at night to further address this important potential association. If nocturnal hypoxia could be validated as a risk factor for AMD, or only AMD cases with RPD, it raises the possibility of using an already available treatment such as CPAP therapy, to either reduce AMD incidence or its progression.

The strengths of our study were the extensive questionnaire-based risk assessment of OSA in individuals who also had extensive retinal imaging to assess AMD and RPD. The size of the cohort allowed us to consider the association of OSA with all AMD as well as AMD with and without the RPD phenotype. In addition, adjusting for confounders such as age, which have been strongly associated with AMD and OSA increased the validity of our results. The combined use of two validated sleep questionnaires and two different validated risk scoring algorithms provided complementary approaches for assessing

the risk of OSA with different levels of sensitivities and specificities. However, the study may have been underpowered to find significant results as the trend in the results was consistent in showing an association and other studies with larger sample sizes were able to find a significant association.^{22 23} The finding of an increased likelihood of having the AMD subphenotype with RPD in those being treated for a formal diagnosis of OSA, when compared with those who were not receiving treatment for OSA, is limited by the small number of participants on treatment for OSA, which resulted in wide CIs for the estimates, but these findings were nonetheless statistically significant.

In summary, our study found that participants who are on treatment for previously diagnosed OSA, a type of SDB that is highly prevalent in our older community and a major cause of nocturnal hypoxia, have significantly higher risk of having RPD coexistent with AMD. However, having a higher risk of moderate-to-severe OSA based on sleep questionnaires was not associated with a significantly increased likelihood of AMD presence, nor with the presence of the RPD subphenotype coexistent with AMD. The preliminary findings confirm the need for further research exploring the role of nocturnal hypoxia as a risk factor in the development of AMD and its progression to late-stage disease, especially the links to AMD with RPD. Studies involving nocturnal pulse oximetry or formal polysomnography with appropriately experienced clinicians to interpret the results would be an ideal study design to further investigate a possible relationship between AMD and nocturnal hypoxia.

Contributors WYF contributed to data collection, data analysis and manuscript preparation. PRR contributed to data collection. ZW contributed to data analysis and manuscript review. CA contributed to manuscript review and oversight of research project. CDL contributed to manuscript review and oversight of research project. MN contributed to manuscript review. RHG contributed to manuscript review, oversight of research project, and is responsible for the overall content as guarantor.

Funding This work was supported by National Health and Medical Research Council of Australia grants GNT1181010 (RHJ) and fellowship GNT1103013 (RHG) and the Macular Disease Foundation Australia grant (CL). The Centre for Eye Research Australia (CERA) receives operational infrastructure support from the Victorian Government.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Royal Victorian Eye and Ear Hospital Human Research Ethics Committee. Reference number: HREC 20/1459H. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement Data are available on reasonable request. Data are available on reasonable request. Data are deidentified participant data and are available from RHG (rh.guymer@unimelb.edu.au). Data reuse is only permitted with permission from RHG.

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