Author/s:
Chaudhary, A;Abbott, CJ;Wu, Z;Fang, WY;Raj, PR;Naughton, M;Heriot, WJ;Guymer, RH

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Nocturnal hypoxia and age-related macular degeneration

Attiqa Chaudhary MBBS[1,2] | **Carla J. Abbott PhD**[1,2] | **Zhichao Wu PhD**[1,2] | **Wendy Y. Fang BMedSc(Hons), MD**[1,2,3] | **Palaniraj R. Raj MBBS, MMed(OphthSc)**[1,4] | **Matthew Naughton MBBS, MD**[5,6] | **Wilson J. Heriot MBBS**[1,2,7] | **Robyn H. Guymer MBBS, PhD**[1,2]

[1]Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, East Melbourne, Victoria, Australia

[2]Department of Surgery (Ophthalmology), The University of Melbourne, Parkville, Victoria, Australia

[3]Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Clayton, Victoria, Australia

[4]Discipline of Clinical Ophthalmology and Eye Health/Save Sight Institute, The University of Sydney, Sydney, New South Wales, Australia

[5]Department of Respiratory and Sleep Medicine, Alfred Hospital, Melbourne, Victoria, Australia

[6]Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, Victoria, Australia

[7]Retinology Institute, Glen Iris, Victoria, Australia

Correspondence
Robyn H. Guymer, Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, Level 7, 32 Gisborne Street, East Melbourne, VIC 3002, Australia.
Email: rh.guymer@unimelb.edu.au

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Abstract

Background: Nocturnal hypoxia is common, under-diagnosed and is found in the same demographic at risk of age-related macular degeneration (AMD). The objective of this study was to determine any association between nocturnal hypoxia and AMD, its severity, and the high-risk sub-phenotype of reticular pseudodrusen (RPD).

Methods: This cross-sectional study included participants aged ≥50 years with AMD, or normal controls, exclusive of those on treatment for obstructive sleep apnoea. All participants had at home, overnight (up to 3 nights) pulse oximetry recordings and multimodal imaging to classify AMD. Classification of Obstructive Sleep Apnea (OSA) was determined based on oxygen desaturation index [ODI] with mild having values of 5–15 and moderate-to-severe >15.

Results: A total of 225 participants were included with 76% having AMD, of which 42% had coexistent RPD. Of the AMD participants, 53% had early/intermediate AMD, 30% had geographic atrophy (GA) and 17% had neovascular AMD (nAMD). Overall, mild or moderate-to-severe OSAwas not associated with an increased odds of having AMD nor AMD with RPD ($p \geq 0.180$). However, moderate-to-severe OSA was associated with increased odds of having nAMD (odds ratio = 6.35; 95% confidence interval = 1.18 to 34.28; $p = 0.032$), but not early/intermediate AMD or GA, compared to controls ($p \geq 0.130$). Mild OSA was not associated with differences in odds of having AMD of any severity ($p \geq 0.277$).

Conclusions: There was an association between nocturnal hypoxia as measured by the ODI and nAMD. Hence, nocturnal hypoxia may be an underappreciated important modifiable risk factor for nAMD.

KEYWORDS

age-related macular degeneration, nocturnal hypoxia, oxygen desaturation index, pulse oximetry, sleep-disordered breathing

1 | INTRODUCTION

Age related macular degeneration (AMD) is a multifactorial disease, where the ageing retina is impacted by both genetic and environmental factors. The pathophysiology of AMD is not fully understood; however many pathways are implicated, including chronic inflammation, altered lipid metabolism, oxidative stress, impaired extracellular matrix maintenance and hypoxia.[1] Whilst there have been significant advances in understanding the genetic influences on AMD,[2] there have not been the same advances in the understanding of additional modifiable risk factors. To date, smoking, diet, systemic lipid levels and exercise have been reported as being contributory factors associated with AMD.[3] Identifying additional modifiable risk factors would add to current clinical risk mitigation strategies whilst we await targeted interventions, as well as increasing our understanding of AMD pathogenesis.

There is a renewed interest in exploring the potential role of outer retinal hypoxia in AMD. Recently OCT-A studies have reported flow deficits and decreased choriocapillaris thickness in AMD compared to an age-matched normal population, suggesting links with outer retinal hypoxia.[4,5] The outer retina requires the highest oxygen supply per unit volume of any tissue of the body.[6] The oxygen demand increases at night in order to maintain the high energy consuming processes such as the dark current when photoreceptors are continuously depolarized and generating neurotransmitters. Hence, any factor that could potentially reduce this critical supply of oxygen overnight could put retinal health at risk.[7,8]

Nocturnal hypoxia occurs in a group of disorders known as sleep disordered breathing (SDB).[9] Obstructive sleep apnea (OSA) is the most common form of SDB, where prevalence increases with age.[9] Global prevalence of OSA is estimated to be around 1 billion people, with most being undiagnosed.[10,11] It is characterised by recurrent episodes of complete cessation of breathing (apnea) or partial cessation of breathing (hypopnea)[12] leading to chronic hypoxia, increased sympathetic activity, autonomic system dysregulation, increased arousals and sleep fragmentation.[9] Age, obesity, and male gender are considered major risk factors associated with OSA, which is associated with poor quality of life, impaired cognitive function, poor cardiovascular health and depression.[13–15]

Several studies have explored the association of OSA with various ocular conditions, with a few investigating the association of OSA with AMD.[16,17] A record linkage study by Kennan et al, found a positive association between AMD and OSA, where most cases in this study had nAMD.[18] Han et al, investigated the relationship between OSA and incident cases of AMD using the data from the UK biobank and Canadian Longitudinal Study on Aging, where AMD and OSA were identified through patient records or self-reported data, and also found an increased risk for AMD in OSA.[19] We recently conducted a case control study to investigate these associations, using sleep questionnaires, where we found that being on assisted breathing treatment for diagnosed OSA was significantly associated with a higher likelihood of having AMD with the RPD phenotype.[20] This finding is particularly interesting given RPD are associated with poor rod photoreceptor function,[21] where rods are dependent on the nocturnal recycling of vitamin A derivatives for outer segment renewal.[21,22]

Sleep questionnaires are useful screening tools but are subjective in nature, have significant limitations and variability.[23] We therefore wished to further explore the relationship between OSA and AMD using more objective methods. Polysomnography, (a laboratory based sleep study) is the gold standard, objective, diagnostic tool to diagnose OSA, but has limited availability, is expensive and time consuming and therefore is not feasible for large-scale screening. However, pulse oximetry, which measures oxyhemoglobin levels, is objective, portable, low cost and has been validated as a screening tool for OSA.[24] Previous studies have used pulse oximetry in at risk paediatric and adult populations to identify moderate to high risk OSA.[25,26] When measuring intermittent hypoxia, the apnea–hypopnea index (AHI) is often used in the polysomnography setting and is defined as the number of apneas and hypopneas per hour of sleep. However AHI has several limitations and controversies still exist as to relevant definitions.[27–29] The oxygen desaturation index (ODI) is a count of the number of times per hour that oxygen desaturates by a certain percentage (such as 4%) and has been validated as an alternative measure and is considered to have high reproducibility and to be more relevant in a clinical setting compared to AHI.[29]

In this study we used in-the-home, overnight pulse oximetry, as an objective measurement of nocturnal hypoxia, to investigate the association between nocturnal hypoxia, as measured by ODI, and AMD. We assessed if there was an association with AMD, AMD severity and the high-risk AMD sub-phenotype with coexistent RPD.

2 | METHODS

This study was a prospective, observational case control study approved by the Royal Victorian Eye and Ear Hospital Human Research Ethics Committee (#20-1459H) and was conducted in accordance with the tenets of the

Declaration of Helsinki. Written informed consent was obtained from all participants prior to data collection.

2.1 | Participants

Participants were recruited from natural history studies at the Centre for Eye Research Australia. All participants were aged 50 years or older. AMD was defined by the presence of at least medium (≥63 μm) drusen in at least one eye as seen on colour fundus photography (Beckman classification).[30] Participants in the control group had no apparent ageing changes (no drusen) or normal ageing changes (small drusen <63 μm). All controls were also required to have no RPD on multimodal imaging (MMI). Participants were excluded if they had any pre-existing ophthalmic condition associated with OSA (i.e., glaucoma, retinal vein occlusion, diabetic retinopathy, or floppy eye lid syndrome) or any retinal condition that mimics AMD. Participants with a prior diagnosis of OSA and who were also currently on any treatment for the condition, such as continuous positive airway pressure (CPAP) were also excluded, as treatment would confound the overnight pulse oximeter recordings.

2.2 | Medical and demographic history

A comprehensive medical and demographic history including body mass index (BMI) and sleep questionnaires to assess risk of OSA (STOP Bang Questionnaire and Epworth Sleepiness Scale), (results not presented here) was obtained.

2.3 | Imaging and grading

All participants had their pupils dilated prior to multi modal imaging (MMI) which included spectral domain optical coherence tomography volume scans of the central 20° × 20° region (SD-OCT; Spectralis, Heidelberg Engineering, and Cirrus HD-OCT 5000, Zeiss), near infrared reflectance (NIR; Spectralis, Heidelberg Engineering), fundus autofluorescence (FAF; Spectralis, Heidelberg Engineering) and foveal-centred colour fundus photography (CFP; Canon, Japan or Topcon, Japan).

All imaging modalities were used to assess the AMD status and severity, or no disease status, which was classified according to the Beckman classification. Early AMD was defined as at least one eye with medium sized drusen (≥63 to <125 μm), but without pigmentary abnormalities. Intermediate AMD was defined as having at least one eye with large drusen >125 μm, or with pigmentary abnormalities associated with at least medium drusen. Late stage AMD was defined as at least one eye with lesions associated with exudative neovascular AMD (nAMD) and/or geographic atrophy (GA).[30] RPD presence was defined on MMI as five or more definite RPD on SD-OCT in more than one B-scan and confirmation on at least one *en face* imaging modality (CFP, NIR or FAF).[31]

2.4 | Pulse oximetry

Each participant was given a wrist pulse oximeter (Model 3150; Nonin Medical, Plymouth, Minnesota, USA) to wear for 7 h overnight for three consecutive nights, to obtain nocturnal measurements of oxygen saturation in the blood (SpO_2). Multiple nights were collected as it is known that variability increases with abnormal values.[32] Participants were instructed to wear the oximeter when they went to bed and remove it in the morning when they woke up, with data collected from 11 pm to 6 am. They were to wear the oximeter on the same finger each night and to remove any nail colour to avoid interference with the light sensor. A phone call was made after the first night of recording to discuss any issues. SpO_2 data was extracted using nVision software (Version 6.5.1.2, Nonin Medical Inc. Minneapolis, MN USA).

Oximetry data was included in the analysis if there was high-quality continuous recording of ≥4 h over at least two nights. Recording artefacts were removed, including the first 30 min when the participants were unlikely to be asleep. Whilst several parameters can be derived from oximetry, we analysed the oxygen desaturation index (ODI), defined as the number of desaturation events (based on a >4% drop in SpO_2 from baseline) per hour.[33,34] ODI has been shown to correlate with the apnea and hypopnea index (AHI), the gold standard diagnostic parameter of polysomnography.[33] The cyclical drop in SpO_2 from baseline is calculated by ODI automatically from the waveform of SpO_2 versus time.[34]

For the analysis of the associations with the ODI (described further below), all eligible readings from each participant across the three nights were included. The mean ODI values from the all nights of recordings – used to define the severity of OSAwas thus categorised as follows: normal (<5 episodes of >4% drop in SpO_2 from baseline per hour), mild,[5–15] moderate,[16–30] or severe (>30 episodes) nocturnal hypoxia.[27]

2.5 | Statistical analysis

The associations between the ODI measure with age, sex, smoking history, and BMI were examined using linear

mixed models, to account for the correlations between multiple recordings from each participant. The odds of having AMD or the RPD sub-phenotype (compared to their absence) in this cohort based on having mild or moderate-to-severe OSA (based on ODI values 5–15 and >15 respectively), as well as potential confounders such as age, sex, smoking history, and BMI, was evaluated using multivariable binary logistic regression analyses. The odds of having AMD of different severity (early or intermediate, late atrophic AMD, or late nAMD) compared to not having AMD was evaluated using multivariable multinomial logistic regression analysis using the same independent variables above. Smoking was categorised as ever smoked (past and current), compared to never smoked (due to very few current smokers). All statistical analyses were performed using Stata (Stata Corp LLC, College Station, TX, USA).

3 | RESULTS

From a total of 269 participants consenting to the study, 225 were included in the final analysis, with 44 participants excluded. Of the exclusions, six participants did not meet the inclusion criteria; (three had a retinal disease, one had glaucoma and two already had a diagnosis of OSA on CPAP therapy). An additional 34 participants were excluded for not having returned any data available (faulty batteries or faulty technique), another three for not having at least 4 h of artefact-free recordings on two nights, and one for not having at least two nights of recordings as shown in Figure 1. The main demographic characteristics and retinal disease status of those excluded did not differ from those whose data was included in the final analysis.

The final cohort consisted of 171 (76%) participants with AMD and 54 (24%) control participants, with 72 (42%) of the AMD participants having coexistent RPD. Amongst those with AMD, 90 (53%) participants had early or intermediate AMD, and 51 (30%) and 30 (17%) participants had late atrophic GA and exudative nAMD respectively. A total of 184 (82%) and 41 (18%) participants had high-quality continuous recordings of ≥4 h over three and two nights respectively. Hours of useable recordings ranged from 7 h over 2 nights as a minimum to 19.5 h as a maximum number of hours analysed, given the first 30 min were always excluded assuming the participant was not yet asleep. Approximately half the entire cohort had a normal ODI (43% in control participants and 42% in those with AMD). Mild ODI severity was in 54% and 50% of the controls and AMD cases respectively, with 7% and 12% with moderate or severe ODI levels in controls and cases respectively. The AMD sub-phenotype with RPD had the same proportion with moderate or severe risk of OSA (13%) as those with AMD without RPD (11%). The characteristics of the final cohort are summarised in Table 1. Note that higher ODI values were significantly associated with increasing age ($p = 0.014$) and increasing BMI ($p < 0.001$), but not smoking history ($p = 0.060$) nor sex ($p = 0.991$).

3.1 | Associations with AMD and RPD

Overall, there was a significantly higher odds of having AMD (compared to not having AMD) in this cohort based on a history of smoking (past or current, compared to never; $p = 0.004$), but no significant difference based on age, sex, BMI and having mild or moderate-to-severe SDB ($p \geq 0.180$). There was also a significantly higher odds of having RPD in this cohort based on older age and female sex ($p \leq 0.009$), but no significant differences based on BMI, smoking history, and having moderate-to-severe SDB ($p \geq 0.101$). These findings are summarised in Table 2.

When evaluating the outcome of having different AMD severities, there was a significantly higher odds of having either late atrophic AMD or nAMD based on older age ($p \leq 0.012$) and having any severity of AMD based on a history of smoking ($p \leq 0.037$). There were also significantly higher odds of having nAMD based on having moderate-to-severe SDB ($p = 0.032$). All other factors were otherwise not statistically significant ($p \geq 0.130$), and these findings are summarised in Table 3.

4 | DISCUSSION

Identifying new modifiable risk factors associated with AMD could provide potential new intervention strategies and offer new insights into disease mechanisms. Several studies, including our own sleep questionnaire study, have suggested that OSA may be a potential risk factor associated with AMD.[18,20,35,36] The current study investigated the association between nocturnal hypoxia and AMD, its severity and an AMD sub-phenotype with RPD, by objectively measuring the nocturnal SpO_2 levels with a home based pulse oximeter. The ODI was specifically used for analyses as it is considered a robust indication of overnight hypoxia.[27] A strength of the study was that all participants underwent recordings over two to three nights, rather than just a single night. This allowed us to use all recordings as observations within the linear mixed model to increase the study power, whilst accounting for multiple recordings from each participant. We were also

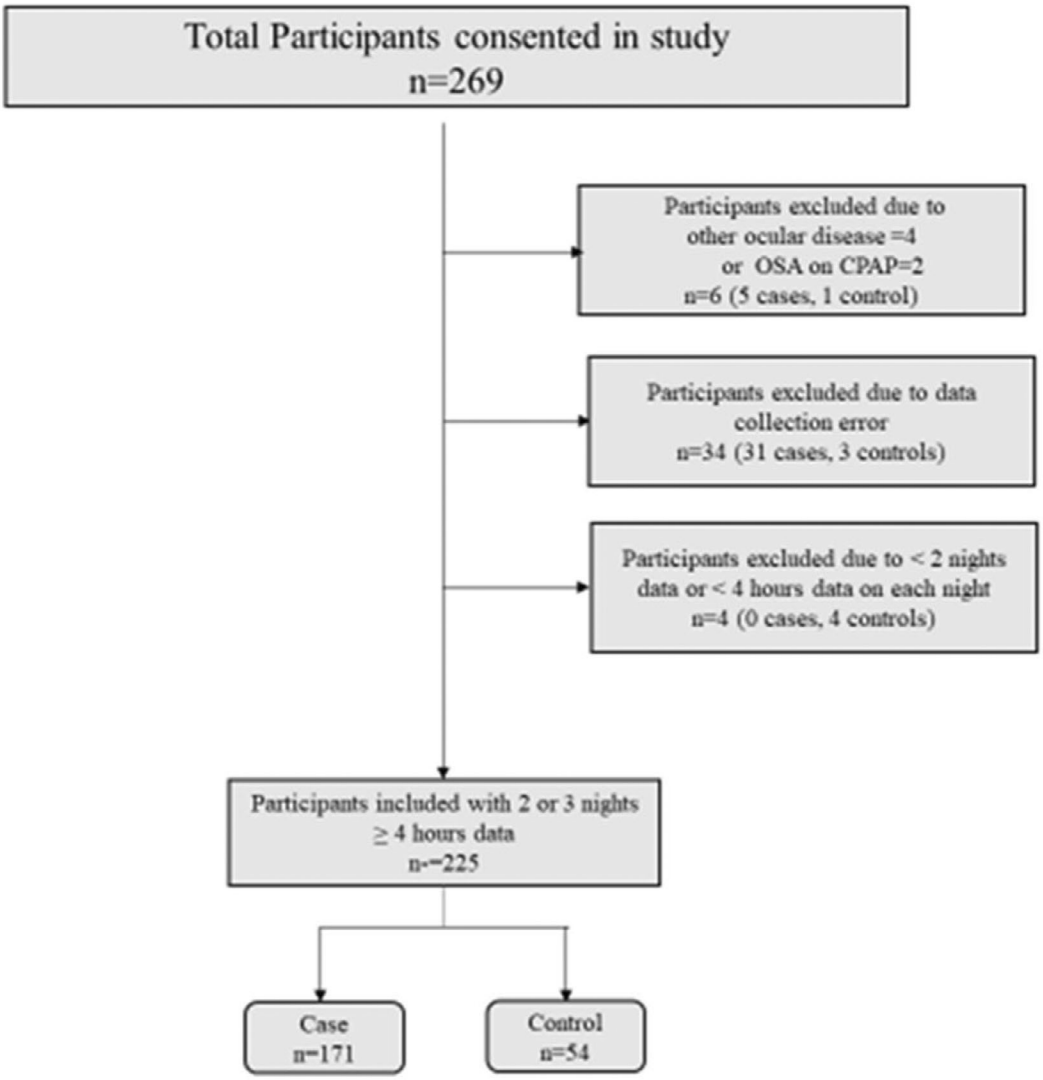

FIGURE 1 Flow diagram of participant recruitment.

able to find the known associations of higher ODI measurements with age and BMI giving confidence of the validity of the overnight oximeter recordings.

The multivariable analysis, adjusting for confounders of age, sex, smoking status, and BMI, found a significant difference in the association of ODI with AMD severity, with individuals with moderate to severe SDB having a greater risk of exudative nAMD. We did not find any association of moderate to severe SDB with the GA form of late AMD and no association with AMD with RPD. The finding of an association with nAMD is in line with previous studies investigating OSA and AMD.[18,36] These very large cohorts relied on non-objective questionnaires to gauge OSA risk and often relied on self-report diagnosis of AMD or hospital records that may have under-reported earlier stages of AMD. The advantage of our study was the use of an objective measure of nocturnal hypoxia, and the manual grading of retinal images instead of relying on self-report or records for the diagnosis of AMD.

In our cohort, we excluded people already on treatment for diagnosed OSA, as the ongoing treatment made it not possible to interpret their overnight oxygen levels. However, this exclusion meant that there was a possibility of people with both AMD and OSA being underrepresented in the cohort. The importance of this is shown in our previous sleep questionnaire data, where the only significant result was in those already on treatment for OSA.[20] There was also a high internight variability in the ODI results when the results were abnormal.[32] suggesting that even collecting 2 to 3 nights of recording may not be enough to gain an accurate picture of a participant's true nocturnal hypoxic episodes. Together this suggests, our findings may be more significant if those with diagnosed SDB requiring treatment could be included and in a

TABLE 1 Characteristics of the participants included in this study.

	Age-related macular degeneration (AMD)			
	Control	All AMD	AMD − RPD	AMD + RPD
Parameter	***n* = 54**	***n* = 171**	***n* = 99**	***n* = 72**
Age (years)	72 ± 9	74 ± 8	72 ± 8	77 ± 6
Sex				
Female	32 (59%)	115 (67)	61 (62%)	54 (75%)
Male	22 (41%)	56 (33)	38 (38%)	18 (25%)
Smoking history				
Never	37 (69%)	84 (49%)	47 (47%)	37 (51%)
Present or former[a]	17 (31%)	87 (51%)	52 (53%)	35 (49%)
Body mass index (kg/m^2)	27 ± 4	27 ± 5	27 ± 5	26 ± 5
ODI Severity[b]				
Normal (<5)	29 (54%)	86 (50%)	49 (49%)	37 (51%)
Mild (5–15)	21 (39%)	65 (38%)	39 (39%)	26 (36%)
Moderate (16–30)	4 (7%)	16 (9%)	9 (9%)	7 (10%)
Severe (>30)	0 (0%)	4 (2%)	2 (2%)	2 (3%)

Note: All data is presented either as the mean ± standard deviation, or *n* (%).
Abbreviations: AMD, Age related macular degeneration; ODI, oxygen desaturation index; RPD, reticular pseudodrusen.
[a]These two categories were combined as only five participants with AMD and one control participants were current smokers.
[b]Based on the mean value across all available nights of recordings.

TABLE 2 Multivariable binary logistic regression analysis of having age-related macular degeneration (AMD) or reticular pseudodrusen (RPD).

	AMD versus Control		AMD + RPD versus No RPD	
	Odds ratio	*p*	Odds ratio	*p*
Age (per decade)	1.28 (0.86 to 1.91)	0.228	2.76 (1.76 to 4.32)	<0.001
Sex (female vs. male)	1.75 (0.90 to 3.42)	0.101	2.50 (1.25 to 4.98)	0.009
Smoking history (present or former[a] vs. never)	2.71 (1.38 to 5.35)	0.004	1.54 (0.82 to 2.87)	0.179
Body mass index (per kg/m^2)	0.97 (0.90 to 1.05)	0.414	0.99 (0.92 to 1.06)	0.694
Obstructive sleep apnea[b] (vs. absent)				
Mild	1.35 (0.68 to 2.71)	0.392	1.00 (0.51 to 1.95)	0.992
Moderate-to-Severe	2.56 (0.65 to 10.11)	0.180	0.87 (0.29 to 2.68)	0.813

Note: Values in parentheses represent the 95% confidence interval.
[a]These two categories were combined as only five participants with AMD and one control participants were current smokers.
[b]Mild and moderate-to-severe Obstructive Sleep Apnea defined by a value of 5–15 and >15 respectively for the oxygen desaturation index (ODI; or the number of desaturation events – based on a >4% drop in SpO_2 from baseline – per hour, averaged over all the recordings available).

larger cohort, given that abnormal ODI results often have high variability.[32]

This study reiterates that smoking remains a significant modifiable risk factor for AMD, also recognised as a risk factor for SDB (although didn't reach significance in this study). Both OSA and smoking cause oxidative stress, inflammatory response and endothelial dysfunction which are considered as culminating factors leading to pathophysiological changes leading to AMD. Our previous study, using sleep questionnaires, found an association between a cohort diagnosed with a high risk of OSA with the sub-phenotype of AMD with coexistent RPD. Given that RPD are associated with poor rod photoreceptor function,[21] and rods are the photoreceptor most dependent on the nocturnal recycling of vitamin A derivatives for outer segments,[21,22] we had hypothesised there

TABLE 3 Multivariable multinomial logistic regression analysis of having different severities of age-related macular degeneration (AMD) compared to the control group.

	Early or Intermediate AMD		Late AMD – Geographic atrophy		Late AMD – Neovascular AMD	
	Odds ratio	***p***	**Odds ratio**	***p***	**Odds ratio**	***p***
Age (per decade)	0.79 (0.50 to 1.25)	0.309	2.59 (1.45 to 4.62)	0.001	2.43 (1.21 to 4.87)	0.012
Sex (female vs. male)	1.76 (0.84 to 3.68)	0.135	1.53 (0.66 to 3.58)	0.324	2.22 (0.78 to 6.27)	0.134
Smoking history (present or former[a] vs. never)	2.66 (1.27 to 5.56)	0.009	2.47 (1.06 to 5.78)	0.037	3.49 (1.29 to 9.49)	0.014
Body mass index (per kg/m^2)	0.95 (0.87 to 1.03)	0.188	1.02 (0.92 to 1.12)	0.761	0.96 (0.86 to 1.07)	0.491
Obstructive sleep apnea[b] (vs. absent)						
Mild	1.53 (0.71 to 3.29)	0.277	1.03 (0.43 to 2.47)	0.946	1.41 (0.48 to 4.12)	0.530
Moderate-to-Severe	3.14 (0.71 to 13.8)	0.130	0.59 (0.08 to 4.3)	0.600	6.35 (1.18 to 34.28)	0.032

Note: Values in parentheses represent the 95% confidence interval.

[a]These two categories were combined as only five participants with AMD and one control participants were current smokers.

[b]Mild and moderate-to-severe obstructive sleep apnea defined by a value of 5–15 and >15 respectively for the oxygen desaturation index (ODI; or the number of desaturation events – based on a >4% drop in SpO_2 from baseline – per hour, averaged over all the recordings available).

would be a greater association with AMD with RPD. However, we did not find this in our cohort, which may be due to the small sample size, or related to the fact that in late-stage AMD, the RPD are often no longer visible, even though they had been present earlier in the disease, leading to their under-detection.

Given the biological rationale for hypothesising a potential relationship between nocturnal hypoxia and AMD, prior positive associations in the literature, the variability of ODI readings and the large number of the elderly population with undiagnosed nocturnal hypoxia, larger studies, with formalised polysomnography would be beneficial to try to confirm or refute our findings.

4.1 | Conclusion

We found an association between moderate to severe OSA with nAMD using oxygen saturation measurements obtained with objective, overnight pulse oximetry. This indicates that nocturnal hypoxia is potentially a new additional modifiable risk factor potentially for all AMD, but in particular, in this study for nAMD. These findings may assist in providing much needed additional strategies to mitigate the risk of developing the severe vision threatening late form of nAMD. Larger studies, including longitudinal studies, as well as studies with formal polysomnography, would further explore this association of nocturnal hypoxia with AMD.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ORCID

Attiqa Chaudhary https://orcid.org/0000-0003-2446-7791
Carla J. Abbott https://orcid.org/0000-0002-1432-8977
Zhichao Wu https://orcid.org/0000-0002-8623-6684
Robyn H. Guymer https://orcid.org/0000-0002-9441-4356

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