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Associations between obstructive sleep apnoea, primary open angle glaucoma and age-related macular degeneration: record linkage study

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ABSTRACT

Background Primary open angle glaucoma (POAG) is thought to be associated with obstructive sleep apnoea (OSA) but previous studies are conflicting and have methodological limitations. This potential relationship has implications for investigation and treatment strategies, and may provide insights into disease pathogenesis. The relationship between OSA and age-related macular degeneration (AMD) is unknown.

Methods A sleep apnoea cohort of 67 786 people was constructed from linked English hospital episode statistics (1999–2011). We compared this cohort with a reference cohort (2 684 131 people) for rates of subsequent POAG and AMD. A POAG cohort (comprising 87 435 people) and an AMD cohort (248 408 people) were also constructed and compared with the reference cohort for rates of subsequent sleep apnoea. All analyses were restricted to people aged 55 and over and, within this age range, were age standardised using 5-year age groups.

Results Risk of POAG following sleep apnoea was not elevated: the rate ratio for POAG was 1.01 (95% CI 0.85 to 1.19). Similarly, the risk of sleep apnoea following POAG was not elevated: the rate ratio was 1.00 (0.86 to 1.17). These findings held true across subgroup analysis according to sex and age group. By contrast, the risk of AMD following sleep apnoea was significantly elevated, with rate ratio 1.44 (1.32 to 1.57).

Conclusions Although plausible mechanisms exist to consider a link between OSA and POAG, the two conditions are not positively associated. This holds true in either temporal direction. By contrast, OSA is positively associated with AMD. While potential confounding factors may contribute, obesity does not appear sufficient to explain this association.

INTRODUCTION

Obstructive sleep apnoea (OSA) is a common disorder of the adult population that is characterised by repetitive episodes of upper airway collapse during sleep.[1] Over time, recurrent episodes of hypoxia have sequelae including increased risk of cardiovascular disease, metabolic impairment and stroke.[2] In recent years, considerable interest has grown in the potential association between OSA and primary open angle glaucoma (POAG),[3 4] such that this topic receives its own chapter in contemporary glaucoma textbooks.[5] The rationale is that recurrent episodes of hypoxia are associated with reduced optic nerve head perfusion, leading to increased risk or progression in glaucomatous optic neuropathy, while mechanical factors affecting intraocular pressure (IOP) may be involved.[3 4]

This potential association is important as it may provide insights into POAG pathophysiology, including the contributions of vascular dysfunction, particularly in normal tension glaucoma (NTG). Also, a definite association might suggest that individuals with one condition should be screened for the other.[3 6] For example, patients with primary open angle glaucoma with undiagnosed OSA might potentially require OSA treatment as well as conventional IOP reduction for optimal glaucoma therapy. However, previous studies have reported conflicting results, with some finding a positive association[7 8] and others observing none.[9 10] The majority of these studies have significant methodological limitations in terms of size (hence statistical power) and design.

We have recently used record linkage in the English population to analyse the relationships between various ocular and systemic conditions, including POAG, age-related macular degeneration (AMD), dementia and arthritis.[11–13] Using similar methods, the aim of this study was to examine the potential association between OSA and POAG. We used record linkage to determine whether individuals admitted to hospital with sleep apnoea were significantly more or less likely than others to develop POAG in subsequent years, and vice versa. We also analysed the potential association between sleep apnoea and AMD, as one recent report has suggested that patients with neovascular AMD who respond poorly to anti-vascular endothelial growth factor (anti-VEGF) therapy may have increased risk of OSA.[14]

METHODS

The methodology used was similar to that described in previous studies.[11–13] In short, we used a data set of linked English national hospital episode statistics (HES), from 1 January 1999 to 31 December 2011, to build several cohorts of patients based upon their hospital records. HES comprise demographic and medical data recorded for all patients undergoing admission to English National Health Service (NHS) hospitals and treatment centres on behalf of the NHS. This includes both day case admissions and inpatient care. The records are linked so that individuals can be traced through multiple hospital episodes over time. To censor for death, we linked the HES records to mortality records obtained from the Office for National Statistics.

A sleep apnoea cohort was constructed by identifying all people in the linked HES data set aged

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55 years or more who had a record of an admission or day case care where sleep apnoea was recorded (International Classification of Diseases Revision 10 (ICD10) code G47.3), either as primary diagnosis or elsewhere on the hospital record (ie, as comorbidity during an admission for another medical or surgical condition). For each person, the earliest known record of sleep apnoea was the record used in the analysis. A reference cohort was constructed by identifying people aged 55 years or more without sleep apnoea who were admitted to hospital for various other conditions (see table footnotes).

We then analysed the cohorts for subsequent hospital episodes with POAG (ICD10 code H40.1) or AMD (ICD10 code H35.3), again including diagnoses anywhere on the hospital record. The assumption was that rates of hospital episodes for POAG and AMD in the reference cohort would be similar to those in the local general population. Further analysis was performed using the same methodology and the same reference cohort, but considering the diseases in reverse, that is, sleep apnoea in people with POAG or AMD.

It was considered that obesity might confound any association found between sleep apnoea and the ocular conditions. A cohort of individuals with hospital records of obesity (ICD10 E66; body mass index ≥30; diagnosis anywhere on the hospital record) was therefore constructed and analysed in the same way as the sleep apnoea cohort for comparison.

The statistical methods are described in more detail elsewhere in a study of a different topic using the same record linkage design.[11] In brief, rates of people with, for example, POAG in the sleep apnoea cohort and the reference cohort were calculated based on person-days 'at risk' (ie, from first recorded sleep apnoea/reference admission to first recorded POAG admission, death or end of study period, whichever occurred first). We compared the rate of POAG in the sleep apnoea cohort with that in the reference cohort to generate rate ratios. Adjustments were made by stratifying the analyses for age (in 5-year bands), sex, year of admission, region of residence, and Index of Multiple Deprivation score, using the indirect method of standardisation.

RESULTS

The sleep apnoea cohort contained 67 786 people (27% female), the POAG cohort 87 435 people (54% female), the AMD cohort 248 408 people (65% female) and the reference cohort 2 684 131 people. Age and sex distributions are shown in table 1.

Table 2 shows the observed and expected numbers in the sleep apnoea cohort and the reference cohort that had subsequent hospital episodes with POAG. For people with sleep apnoea, there was no significant increase in the risk of POAG: the rate ratio was 1.01 (95% CI 0.85 to 1.19), with 143 expected and 145 observed cases of POAG. The table also shows the reverse situation, that is, the risk of sleep apnoea following POAG. Again, there was no significant increase in the risk of sleep apnoea: the rate ratio was 1.00 (0.86 to 1.17), with 168 expected and 169 observed cases.

Table 3 shows similar data for AMD. For people with sleep apnoea, there was a significant increase in the risk of subsequent AMD episodes: the rate ratio was 1.44 (1.32 to 1.57), with 375 expected and 539 observed cases of AMD.

Results were further analysed by sex, age group and time interval between diagnoses. For the relationship between sleep apnoea and POAG, results were generally similar in men and women, that is, no significant increase in risk was observed in either temporal direction for either men or women. For example, the rate ratio of POAG followed by sleep apnoea was 1.04 (0.87 to 1.23) for men and 0.99 (0.75 to 1.29) for women. For age group, again, no significant increase in risk was observed in either temporal direction for any age group (55–64, 65–74, 75–84 and 85+ years). However, interesting results were observed for analysis according to time interval between the two conditions. Despite overall rate ratios being extremely close to 1, the rate ratio for sleep apnoea within 1 year of first POAG episode was significantly raised (1.50, 1.12 to 1.97). However, this short-term effect was balanced by the rate ratio in subsequent years falling to <1 (0.92, 0.78 to 1.08).

For the relationship between sleep apnoea and AMD, results were also generally similar in men and women. For example, the rate ratio for sleep apnoea followed by AMD was 1.5 (1.36 to 1.65) for men and 1.39 (1.20 to 1.61) for women. Results were also relatively consistent across age groups and time intervals between diagnoses, that is, significantly increased risk was observed in both temporal directions for nearly all age groups and in all time interval categories (<1, 1–4 and 5+ years).

The relationship between obesity and AMD was significantly less strong than the relationship between sleep apnoea and AMD. Comparing the obesity cohort (469 823 people) with the reference cohort, the rate ratio for AMD was 1.24 (1.19 to 1.29). The rate ratio for obesity in the AMD cohort was 1.05 (1.01 to 1.09).

DISCUSSION

These data support the hypothesis that OSA is not positively associated with POAG. In our study, this finding held true for the two conditions considered in either temporal direction. Indeed, rate ratios were strikingly close to one in both directions. The result also held true throughout subgroup analysis according to sex and age group.

This consistent finding occurred despite great interest in recent years over the likely association between the conditions. For example, some authors have argued that 'ophthalmic evaluation should be recommended in patients with severe OSA/hypopnea syndrome, and the presence of sleep disorders should be investigated in patients with glaucoma',[3] while others have said that 'it may be prudent to administer an OSA questionnaire to patients with progressive glaucomatous optic neuropathy despite apparently good IOP control'.[6] Because of this publicity, one might have expected some evidence of increased rate ratios, even in the absence of a genuine association.

However, analysis according to time interval provided interesting insights on this issue. Despite overall rate ratios being extremely close to 1, the rate ratio for sleep apnoea within 1 year of POAG admission was significantly >1, but this was balanced by the rate ratio falling to <1 in subsequent years. This suggests that POAG diagnoses may have led to some additional sleep apnoea diagnoses in the short term, presumably through referral by ophthalmologists, but that these diagnoses were merely brought forward in time rather than representing a genuinely positive association.

Previous studies have reported conflicting results for an association between OSA and POAG. However, two meta-analyses have been published in recent years.[15 16] Shi *et al*[15] conducted a meta-analysis of 16 studies. Only one cohort study met the inclusion criteria; it reported that OSA carried a risk ratio for OAG of 1.67 (1.30 to 2.17), after adjustment for factors including diabetes mellitus and cardiovascular disease.[17] However, the study was carried out in Taiwan so the results may not be fully applicable to Caucasian populations. Six case–control studies met the inclusion criteria; four found no association while two

Table 1 The number (N) and age–sex distribution of the people who entered the sleep apnoea* cohort, the primary open angle glaucoma (POAG)† cohort, the age-related macular degeneration (AMD)‡ cohort and the reference cohort§

		Sleep apnoea cohort		POAG cohort			AMD cohort			Reference cohort		
Age	N	(% of total)	Female, %	N	(% of total)	Female, %	N	(% of total)	Female, %	N	(% of total)	Female, %
55–59	20 739	(30.6)	26.5	3082	(3.5)	43.9	5222	(2.1)	55.1	458 833	(17.1)	47.6
60–64	18 557	(27.4)	24.8	5100	(5.8)	46.5	10 076	(4.1)	60.5	465 934	(17.4)	47.3
65–69	12 595	(18.6)	25.9	8227	(9.4)	48.3	17 031	(6.9)	61.4	438 573	(16.3)	49.0
70–74	8358	(12.3)	27.4	13 005	(14.9)	50.1	27 660	(11.1)	60.8	419 917	(15.6)	51.6
75–79	4872	(7.2)	30.7	19 137	(21.9)	52.3	45 277	(18.2)	61.7	380 142	(14.2)	55.4
80–84	1951	(2.9)	35.4	20 077	(23.0)	56.1	59 764	(24.1)	64.5	273 920	(10.2)	60.9
85+	714	(1.1)	42.3	18 807	(21.5)	62.3	83 378	(33.6)	70.1	246 812	(9.2)	71.2
Total	67 786	(100)	26.8	87 435	(100)	54.0	248 408	(100)	64.9	2 684 131	(100)	53.0

All analyses were done within age–sex–year–region–index of multiple deprivation (IMD) strata. For example, in the analysis of sleep apnoea as an 'exposure' and POAG as an 'outcome', the 20 739 people in the sleep apnoea cohort aged 55–59 (stratified further by sex, year of admission, region and IMD quintile) were compared with the 458 833 people in the reference cohort aged 55–59. From this was calculated an 'expected' number of people with POAG in each stratum of each cohort. The stratum-specific numbers were then summed for each cohort to give a total number expected, which was compared with the total number observed.
*ICD10 code G47.3.
†ICD10 code H40.1.
‡ICD10 code H35.3.
§The reference cohort comprised people admitted with inguinal hernia, selected limb fractures, superficial injury and contusion, dislocations sprains and strains, haemorrhoids, varicose veins, internal derangement of knee, impacted tooth and other disorders of teeth, in-grown toenail and other diseases of nail, sebaceous cyst, otitis externa and otitis media, bunion, appendectomy, dilation and curettage, hip replacement and knee replacement.

reported positive associations. The pooled OR was 1.96 (1.37 to 2.80), but the authors conceded that interpretation was limited as most studies did not adjust for potential confounding variables. Similarly, nine cross-sectional studies met the inclusion criteria, with a pooled OR of 1.41 (1.11 to 1.79). However, again, most of the studies did not adjust for potential confounders. Indeed, the only two studies that did adjust for confounding[18 19] found no significant association, with ORs of 1.01 (0.98 to 1.05) and 1.13 (0.87 to 1.47), that is, consistent with our results.

Another meta-analysis of 12 case–control and cohort studies[16] included nine of the same studies as the previous meta-analysis. Unsurprisingly, this meta-analysis also reported an overall OR of 1.65 (1.44 to 1.88), though the same limitations apply.

The reports described above highlight some of the difficulties in combining results to address this question. In particular, these studies were generally of small size, had methodological limitations, were conducted in different countries (both Caucasian and Asian) where OAG may differ in pathophysiology, were diverse in terms of including only NTG or all POAG and differed substantially in methods of specifying OSA (eg, by questionnaire alone or requiring polysomnography).

The study presented here has important advantages. It is one of the largest and longest studies examining this question; it involves analysis of sleep apnoea and POAG in both temporal directions and includes subgroup analysis according to sex, age group and time interval. We have used a similar record linkage methodology in previous studies of ocular conditions, including both AMD and POAG.[11–13] Potential limitations to the methodology have been described in these reports. These include the fact that the data are based on day case care and hospital admissions; as such, our cohorts do not necessarily contain all patients in the general population with the relevant condition and are likely to represent the more severe end of the disease spectrum. However, we sought to maximise the size of our cohorts (hence analysis power) and the sensitivity of case detection by capturing diagnoses with the relevant condition anywhere on the hospital record (rather than just those with the relevant condition as primary diagnosis). For example, for POAG, patients are captured when they undergo laser trabeculoplasty, glaucoma surgery, day phasing, other ophthalmic procedures such as cataract surgery (where POAG is listed as an additional diagnosis) or admission for an unrelated medical/surgical condition (where POAG is listed as a comorbidity). Given that our POAG cohort is likely to represent the more severe end

Table 2 Observed (O) and expected (E) numbers of people in the sleep apnoea cohort who received a subsequent hospital record of primary open angle glaucoma (POAG), and of people in the POAG cohort who received a subsequent hospital record of sleep apnoea; observed (O^{ref}) and expected (E^{ref}) numbers of people in the reference cohort who received a subsequent hospital record of POAG or sleep apnoea; standardised rate ratios (RR) and 95% CIs

Exposure	Outcome	O	E	O^{ref}	E^{ref}	RR (95% CI)
Sleep apnoea	POAG	145	143.2	12 533	12 534.8	1.01 (0.85 to 1.19)
POAG	Sleep apnoea	169	168.4	10 052	10 052.6	1.00 (0.86 to1.17)

Table 3 Observed (O) and expected (E) numbers of people in the sleep apnoea cohort who received a subsequent hospital record of AMD, and of people in the AMD cohort who received a subsequent hospital record of sleep apnoea; observed (O^{ref}) and expected (E^{ref}) numbers of people in the reference cohort who received a subsequent hospital record of AMD or sleep apnoea; standardised rate ratios (RR) and 95% CIs

Exposure	Outcome	O	E	O^{ref}	E^{ref}	RR (95% CI)
Sleep apnoea	AMD	539	375	44 852	45 016.0	1.44 (1.32 to 1.57)
AMD	Sleep apnoea	405	329.2	9982	10 057.8	1.24 (1.12 to 1.37)

AMD, age-related macular degeneration.

of the spectrum (eg, high representation of patients requiring laser or surgery), this should actually have brought out more clearly any potential association with OSA, given that OAG associated with OSA might be less amenable to topical therapy alone. Similarly, for AMD, patients are captured when they undergo treatment for AMD itself, for another ophthalmic condition requiring surgery or laser, or admission for an unrelated condition (where AMD is listed as a comorbidity). In fact, the large majority of cases captured comprise patients undergoing intravitreal anti-VEGF therapy.[20] This is because, as described previously,[11] patients treated in the English NHS receive anti-VEGF therapy in a 'day case' setting, such that these admissions are captured by English national HES. This has the important implication that we have essentially analysed the association between sleep apnoea and neovascular AMD. Similarly, for sleep apnoea, patients are captured when they undergo admission for diagnosis/treatment of sleep apnoea (especially overnight admission for polysomnography) or admission for another medical/surgical condition (where sleep apnoea is listed as a comorbidity). Again, the need for hospital admission may be an advantage, meaning that individuals included in our study are more likely to have had formal diagnosis by polysomnography.

The power of the analyses is limited to a degree by differences in the age distributions of the conditions studied (see table 1), as these differences decrease the potential number of individuals likely to develop one condition followed by another (especially in the order AMD or POAG followed by sleep apnoea). Despite this, because of the very large size of the cohorts and the long duration of follow-up, these analyses remain the most highly powered of individual analyses conducted in this area. In the case of our sleep apnoea/POAG analysis, CIs were relatively narrow and centred on 1.0, but we are unable to rule out the possibility of type 2 error (a false-negative result). However, even in this event, the CIs suggest that any true association is unlikely to be strong. It is also worth emphasising that the methodology does not rely on matching the age distributions between the cohorts, as comparisons are made between individual age–sex–year–region–index of multiple deprivation (IMD) strata.

The second main finding in this study was a significant positive association between OSA and neovascular AMD. To our knowledge, this is the first report of this association, though one small study has recently reported a related finding: that patients with neovascular AMD responding poorly to intravitreal bevacizumab were more likely to have OSA.[14] It is possible that one or more confounding variables may be partly responsible for this association. For example, obesity is a known risk factor for OSA,[1] and a weak risk factor for AMD.[21] However, our results have shown that the relationship between obesity and AMD is significantly weaker than that between OSA and AMD, indicating a significant independent effect of OSA. Potential mechanisms to explain the association may include the fact that recurrent hypoxia in OSA is known to result in increased oxidative stress and inflammation,[22 23] which are strongly implicated in AMD pathogenesis.[24 25] Recurrent hypoxia might also alter the balance of angiogenic factors, helping drive choroidal neovascularisation.

The association between OSA and neovascular AMD, if confirmed as causal, has important implications. If untreated OSA were to increase the risk of progression from early AMD to neovascular disease, then patients with early AMD would benefit from direct questioning on sleep symptoms, leading in some individuals to referral for polysomnography. In addition, patients with incipient neovascular AMD might benefit from early identification of coexisting OSA. As suggested by one previous study,[14] this subset of patients might require prompt OSA treatment in order to achieve optimum visual outcomes from anti-VEGF therapy.

In conclusion, we provide strong evidence that there is no positive association between hospitalised OSA and POAG in a predominantly Caucasian population. This was true of the two conditions considered in either temporal direction and also held true throughout subgroup analysis by sex and age group. One implication might be that ophthalmologists need not look for OSA symptoms and/or refer for sleep studies in patients diagnosed with POAG. However, even in the absence of a positive association, it might still be relevant to identify those patients with genuine co-existence of OSA and POAG, particularly if evidence were to emerge in the future that OSA treatment could reduce glaucomatous progression. In addition, we have made the novel finding of a positive association between OSA and AMD. This relationship has important implications for understanding the pathophysiology of, and risk factors for, both conditions and warrants further research. In particular, patients with AMD might require questioning on sleep symptoms and identification of coexisting OSA to reduce the risk of neovascular disease and to achieve optimum visual outcomes from anti-VEGF therapy.

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