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Association of sleep behaviour and pattern with the risk of glaucoma: a prospective cohort study in the UK Biobank

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ABSTRACT

Objectives Given the role of intraocular pressure in glaucoma, the patient's sleeping pattern might contribute to the development and progression of glaucoma. We performed a study to understand the association between sleep behaviours and glaucoma.

Design Our study was a prospective cohort study.

Setting This was a prospective cohort study in the UK Biobank. Self-reported data on five sleep behaviours were collected using a questionnaire at baseline. We identified four sleep patterns based on a cluster analysis of the sleep behaviours.

Participants In the UK Biobank, 409 053 participants were recruited between 2006 and 2010 and followed for a diagnosis of glaucoma. We identified glaucoma as any hospital admission with a diagnosis of glaucoma, based on UK Biobank inpatient hospital data. Individuals who withdrew from the UK Biobank, or were diagnosed with glaucoma before recruitment, or had self-reported surgery or laser treatment for glaucoma, or had no information on sleep behaviors were excluded.

Primary and secondary outcome measures We estimated hazard ratios (HRs) with 95% confidence intervals (CI) using Cox proportional hazards models to estimate the associations of different sleep behaviors, as well as identified sleep patterns, with the risk of glaucoma, adjusting for multiple confounders.

Results Compared with individuals who had a healthy sleep pattern, an excess risk of any glaucoma was observed among individuals with snoring and daytime sleepiness (HR 1.11, 95% CI 1.03 to 1.19) or insomnia and short/long sleep duration (HR 1.13, 95% CI 1.06 to 1.20), but not late chronotype sleep pattern (HR 0.98, 95% CI 0.93 to 1.03).

Conclusion Snoring, daytime sleepiness, insomnia, and short/long duration, individually or jointly, were all associated with the risk of glaucoma. These findings underscore the need for sleep intervention for individuals at high risk of glaucoma as well as potential ophthalmologic screening among individuals with chronic sleep problems for glaucoma prevention.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Based on the UK Biobank data, this is the first large prospective cohort study to comprehensively assess the association of sleep behaviours and patterns with glaucoma.
⇒ The application of cluster analyses (ie, multiple correspondence analysis (MCA) and a k-means clustering algorithm) enabled us to extract the most informative sleep patterns that inherently existed in the study population. Consequently, the exposed and reference groups in our analyses are realistic and mutually exclusive, leading to the most meaningful comparisons.
⇒ A wide range of important confounders were considered in the analyses since detailed information was available on sociodemographic factors, lifestyle, and somatic comorbidities.
⇒ The data were obtained from the UK Biobank but are not a representative sample of the entire UK population. The generalisation of our findings to the entire UK or other populations needs further assessment.

INTRODUCTION

Glaucoma is a leading cause of irreversible vision loss and currently affects more than 70 million people worldwide. It is estimated that glaucoma will affect 111.8 million people by 2040.[1] Glaucoma is characterised by progressive loss of retinal ganglion cells (RGC), especially intrinsically photosensitive retinal ganglion cells (ipRGC), and changes in neuro-retinal rim tissue in the optic nerve head and visual field constriction. The underlying mechanisms of glaucoma are still poorly understood and the factors contributing to its progression have not been fully characterised.[2] When left undetected and untreated, glaucoma can lead to blindness as the changes are irreversible. Therefore, glaucoma screening is pertinent to aid early detection. However, screening the general population may not be cost-effective. Instead, identifying high-risk groups to guide screening efforts for early detection may be an effective solution.

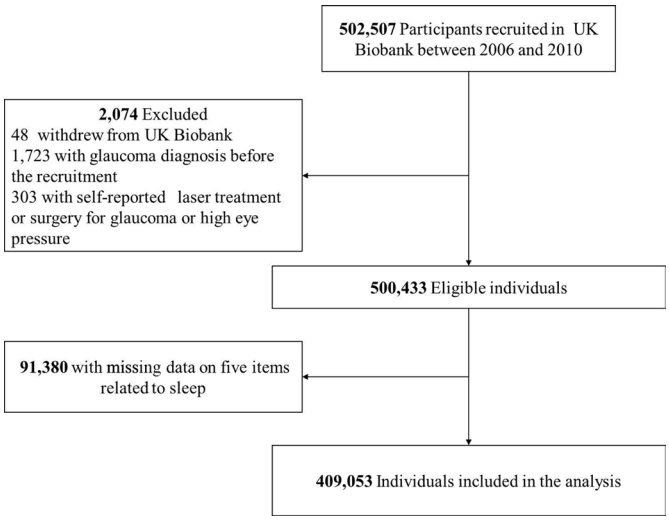

Figure 1 Flow chart of the study.

Elevated intraocular pressure (IOP) is a major risk factor for glaucoma[3] while reduction of IOP is the only proven treatment for glaucoma.[4] The fact that peak IOP occurs during the nocturnal period due to the head and body position during sleep[5] while the increase in IOP might be as large as 4 mmHg among patients with glaucoma after changing from a sitting to a supine position[6] suggests that sleeping pattern might contribute to the development and progression of glaucoma. Indeed, the National Health and Nutrition Examination Survey (NHANES) has demonstrated that the prevalence of glaucoma was lowest among individuals who slept for 7 hours per night and highest among individuals who slept for ≤3 hours or ≥10 hours per night.[7] A cross-sectional study of 9410 Koreans showed the prevalence of glaucoma was highest among individuals who slept for <5 hours or ≥9 hours per night.[8] On the other hand, glaucoma might also influence sleep and patients with glaucoma, especially patients with progressed glaucoma, have been reported to have altered sleep quality, such as excessive daytime sleepiness, a low sleep latency score, snoring, and insomnia.[5 9–13] Several studies have also shown high prevalence of sleep disorders among patients with glaucoma,[14 15] with obstructive sleep apnea (OSA) being the most often reported sleep disorder. Whether patients with glaucoma have higher than expected prevalence of sleep disorders is as yet inconclusicontroversial. For instance, some studies have shown a higher prevalence of OSA among patients with glaucoma than the general population,[16] whereas other studies have failed to do so.[17 18]

The aim of the present study was therefore to evaluate the risk of glaucoma among individuals with different sleep behaviours (ie, sleep duration, chronotype, insomnia symptoms, subjective daytime sleepiness, and snoring) based on data from the UK Biobank. Furthermore, we aimed to study different types of glaucoma as well as major sleep patterns identified based on individual sleep behaviours.

METHODS

Study population

The UK Biobank is a community-based cohort study which recruited over 500 000 participants aged 40–69 years across England, Scotland, and Wales during 2006–2010. Baseline information on sociodemographic, lifestyle, and health-related factors was collected using questionnaires at recruitment. Health-related outcomes were obtained with participants' consent by periodical linkage with health and medical records in the UK (eg, inpatient hospital data and death registers).

In the present study, we conducted a cohort study including 502 507 participants of the UK Biobank. We excluded individuals who withdrew from the UK Biobank (n=48), were diagnosed with glaucoma before recruitment (n=1723), had self-reported surgery or laser treatment for glaucoma or high eye pressure (n=303), or had no information on sleep behaviours (n=91 380), leaving 409 053 participants in the final analysis (figure 1). All study participants were followed from the date of recruitment until a first diagnosis of glaucoma, death, emigration, or the end of follow-up (31 March 2021), whichever occurred first.

Assessment of sleep behaviours and the identification of sleep patterns

Information on five sleep behaviours (ie, sleep duration, chronotype, insomnia symptoms, subjective daytime sleepiness, and snoring)[19] was collected at baseline through a touchscreen questionnaire. In the analyses, we categorised the sleep duration by sleep hours per day, as normal (≥7 to <9 h/day) or short or long (<7 h/day or≥9 h/day). Early chronotype was considered if the answer 'definitely a morning person' or 'more a morning than evening person' was chosen, while the others indicated late chronotype. The severity of insomnia symptoms (eg, have trouble falling asleep at night or wake up in the middle of the night) was classified as never/sometimes (ie, never/rarely or sometimes) or usually, whereas subjective daytime sleepiness was categorised as never/rarely, sometimes, or frequent (ie, often, or all of the time). Snoring was labelled as yes or no, according to the original variable from the questionnaire. Details about the original questions and variables used in the analyses are available in online supplemental table 1.

We applied a two-step method to identify sleep patterns.[20 21] First, we used the multiple correspondence analysis (MCA) – a principal component method – to summarise and visualise a data matrix containing a set of categorical dependent variables.[22] Specifically, categorical variables were recoded as dummy variables (ie, 0 or 1). The MCA then converted all dummy variables into multi-dimensional Euclidean coordinates and generated numbers of components. We retained the first four components with the highest eigenvalues, which cumulatively explained over 75% of the variance (online supplemental table 2). Second, we used the k-means clustering algorithm to these components to identify

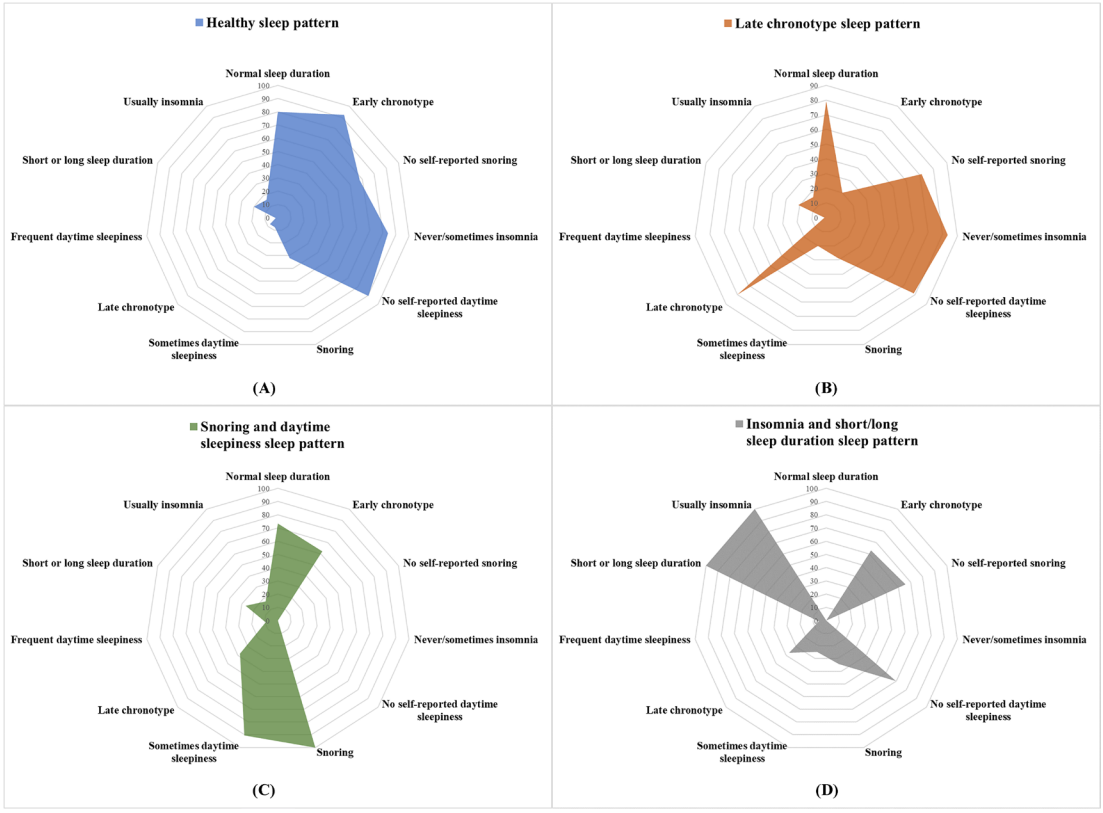

Figure 2 The characteristics of identified sleep patterns. (A-D) The radar of loading values of five sleep behaviours (ie, sleep duration, chronotype, insomnia symptoms, subjective daytime sleepiness, and snoring) for the identified four sleep patterns, identified by the multiple correspondence analysis and the k-means clustering algorithm.

groups of partcipants with distinct sleep patterns.[21] In total we identified four sleep patterns and labelled each according to its contributing variables with top loading values (figure 2). In order of impairment degree (from low to high), these were named as healthy sleep pattern, late chronotype sleep pattern, snoring and daytime sleepiness sleep pattern, and insomnia and short/long sleep duration sleep pattern, respectively.

Identifying glaucoma

We identified glaucoma as any hospital admission with a diagnosis of glaucoma, using International Classification of Diseases (ICD) 10th Revision codes (online supplemental table 3), based on UK Biobank inpatient hospital data available for all participants since 1998. In subanalyses, we considered two common subtypes of glaucoma (ie, primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG)).

Covariates

We retrieved information on sociodemographic (ie, birth year, sex, race/ethnicity, and educational attainment) and lifestyle (ie, smoking, alcohol use, and physical activity) factors through questionnaire data collected at recruitment. Body mass index (BMI) was calculated using kilograms divided by the square of height in metres, using anthropometry measured in the assessment centre at the patient's baseline visit. IOPs for both eyes were measured in the assessment centre at baseline. The Townsend deprivation index (TDI), a proxy of area-level socioeconomic deprivation,[23] was assigned to each participant according to the postcode of their address. Physical activity was measured using total metabolic equivalent of task (MET) minutes per week calculated based on self-reported physical activities. History of hypertension and diabetes (online supplemental table 3) were defined as any hospital admission with a diagnosis of these diseases from the UK Biobank inpatient hospital data, before recruitment. Finally, to understand the role of clinically diagnosed sleep disorders in the studied associations, we also identified diagnoses of sleep disorders during the follow-up, using the inpatient hospital data (online supplemental table 3).

Statistical analysis

We assessed the associations between individual sleep behaviours, as well as the identified sleep patterns, and glaucoma, using hazard ratios (HRs) with 95% confidence intervals (CI) derived from a Cox proportional hazards model. The models were adjusted for birth year (as a continuous variable), race/ethnicity (white or others), TDI (as a continuous variable), college/university degree (yes, no, or unknown), BMI (<18.5, 18.5–24.9, 25.0–29.9, ≥30.0 kg/m^2, or unknown), alcohol use (never, ever, or unknown), smoking status (never, ever, or unknown), level of physical activity (low, moderate, high, or unknown), history of hypertension (yes or no) and

Table 1 Characteristics of the study cohort

	No glaucoma (N=400 363)	Glaucoma (N=8690)	All (N=409 053)
Follow-up time, mean (SD), y	10.7 (1.50)	7.31 (3.14)	10.7 (1.63)
Age at recruitment, mean (SD), y	56.9 (8.10)	62.2 (6.14)	57.0 (8.09)
Age at recruitment, No. (%), y			
<53	135 449 (33.83%)	870 (10.01%)	136 319 (33.33%)
54–61	133 817 (33.42%)	2545 (29.29%)	136 362 (33.34%)
>62	131 097 (32.74%)	5275 (60.70%)	136 372 (33.34%)
Sex, No. (%)			
Female	220 599 (55.10%)	4571 (52.60%)	225 170 (55.05%)
Male	179 764 (44.90%)	4119 (47.40%)	183 883 (44.95%)
Race/ethnicity, No. (%)			
White	379 531 (94.80%)	8125 (93.50%)	387 656 (94.77%)
Others	20 832 (5.20%)	565 (6.50%)	21 397 (5.23%)
Townsend deprivation index, mean (SD)	−1.41 (3.03)	−1.35 (3.11)	−1.41 (3.03)
College or university degree, No. (%)			
Yes	131 475 (32.84%)	2455 (28.25%)	133 930 (32.74%)
No	199 612 (49.86%)	4139 (47.63%)	203 751 (49.81%)
Unknown	69 276 (17.30%)	2096 (24.12%)	71 372 (17.45%)
Body mass index, No. (%), kg/m^2			
<18.5	2046 (0.51%)	42 (0.48%)	2088 (0.51%)
[18.5, 25)	130 465 (32.59%)	2666 (30.68%)	133 131 (32.55%)
[25, 30)	169 609 (42.36%)	3716 (42.76%)	173 325 (42.37%)
≥30	96 304 (24.05%)	2224 (25.59%)	98 528 (24.09%)
Unknown	1939 (0.48%)	42 (0.48%)	1981 (0.48%)
Smoking status, No. (%)			
Never	217 966 (54.44%)	4439 (51.08%)	222 405 (54.37%)
Ever	181 221 (45.26%)	4222 (48.58%)	185 443 (45.33%)
Unknown	1176 (0.29%)	29 (0.33%)	1205 (0.29%)
Alcohol status, No. (%)			
Never	16 684 (4.17%)	437 (5.03%)	17 121 (4.19%)
Ever	383 398 (95.76%)	8250 (94.94%)	391 648 (95.75%)
Unknown	281 (0.07%)	3 (0.03%)	284 (0.07%)
Physical activity, No. (%)			
Low	61 844 (15.45%)	1318 (15.17%)	63 162 (15.44%)
Moderate	135 284 (33.79%)	2953 (33.98%)	138 237 (33.79%)
High	134 663 (33.64%)	2775 (31.93%)	137 438 (33.60%)
Unknown	68 572 (17.13%)	1644 (18.92%)	70 216 (17.17%)
History of hypertension, No. (%)			
Yes	30 283 (7.56%)	1119 (12.88%)	31 402 (7.68%)
No	370 080 (92.44%)	7571 (87.12%)	377 651 (92.32%)
History of diabetes, No. (%)			
Yes	8116 (2.03%)	379 (4.36%)	8495 (2.08%)
No	392 247 (97.97%)	8311 (95.64%)	400 558 (97.92%)
History of psychiatric disorders, No. (%)			
Yes	8586 (2.14%)	215 (2.47%)	8801 (2.15%)
No	391 777 (97.86%)	8475 (97.53%)	400 252 (97.85%)
Psychiatric disorders during follow-up, No. (%)			

Continued

Table 1 Continued

	No glaucoma (N=400 363)	Glaucoma (N=8690)	All (N=409 053)
Yes	48 599 (12.14%)	1929 (22.20%)	50 528 (12.35%)
No	351 764 (87.86%)	6761 (77.80%)	358 525 (87.65%)
History of sleep disorder, No. (%)			
Yes	2365 (0.59%)	93 (1.07%)	2458 (0.60%)
No	397 998 (99.41%)	8597 (98.93%)	406 595 (99.40%)
Sleep disorder during follow-up, No. (%)			
Yes	6452 (1.61%)	242 (2.78%)	6694 (1.64%)
No	393 911 (98.39%)	8448 (97.22%)	402 359 (98.36%)

SD, standard deviation.

diabetes (yes or no). In addition to studying the identified sleep patterns individually, we also tested the potential dose-response relationship by using sleep pattern as an ordinal variable to reflect the degree of sleep impairment. Further, besides considering all glaucoma as one group (any glaucoma), we also studied POAG, PACG, and glaucoma excluding PACG, separately.

In addition, we conducted subgroup analyses by age at recruitment (by tertile distribution: ≤53, 54–61, or ≥62 years), sex, race/ethnicity, BMI, smoking status, physical activity, IOP measured at baseline (<21 mmHg for both eyes or ≥21 mmHg for either eye), and history of hypertension or diabetes. Also, the role of sleep and psychiatric disorders on the studied associations was detected by either additionally adjusting for the presence of such a diagnosis (yes or no) during follow-up in the models or restricting the analysis to individuals without this condition at baseline (n=397 993). Finally, to test the robustness of our findings, in a sensitivity analysis, we repeated the main analysis among individuals without night shift work. All the analyses were done with R software (version 4.0). A two-sided p<0.05 was considered statistically significant.

Patient and public involvement

No patients were engaged in setting the research question or the outcome measures, nor were any patients involved in the study's design or implementation. There are no plans to disseminate the results of the research directly to study participants or the relevant patient community. However, study results are routinely disseminated to UK Biobank participants via the study website and social media outlets.

RESULTS

The mean age at recruitment was 57.0 years (standard deviation (SD) 8.09) for the participants of the final analysis which was 44.95% male. During a mean follow-up of 10.7 years, 8690 cases of glaucoma were identified. Table 1 shows the characteristics of study participants by occurrence of glaucoma during follow-up. Compared with glaucoma-free individuals, those with a glaucoma diagnosis during follow-up were more likely to be older (62.2 vs 56.9 years), male (47.4% vs 44.9%), an ever time smoker (48.6% vs 45.3%), and those with a history of hypertension (12.9% vs 7.6%) or diabetes (4.4% vs 2.0%) at recruitment.

According to the fully adjusted Cox proportional hazards models, except for chronotype, the other four sleep behaviours were all associated with an excess risk of glaucoma, including short or long sleep duration (HR=1.08, 95% CI 1.03 to 1.13), usually insomnia (HR=1.12, 95% CI 1.07 to 1.17), snoring (HR=1.04, 95% CI 1.00 to 1.109), and frequent daytime sleepiness (HR=1.20, 95% CI 1.07 to 1.34) (table 2). In the analyses of glaucoma types, subjective daytime sleepiness was associated with the risk of POAG but not PACG, whereas other sleep behaviours had similar associations with different types of glaucoma.

In the analyses of sleep pattern, we found that compared with individuals with a healthy sleep pattern, a risk elevation of glaucoma was observed among individuals with snoring and daytime sleepiness (HR 1.10, 95% CI 1.02 to 1.18) or insomnia and short/long sleep duration sleep pattern (HR 1.13, 95% CI 1.06 to 1.20), but not among individuals with a late chronotype sleep pattern (table 3). The results for different types of glaucoma were largely similar.

Subgroup analyses indicated that the associations of sleep patterns with glaucoma did not differ by age at recruitment, sex, race/ethnicity, BMI, lifestyle factors (ie, smoking status and physical activity), and history of hypertension (online supplemental table 4). Neither additional adjustment for the diagnosis of sleep or psychiatric disorders during follow-up nor restricting the analysis to participants without these conditions substantially modified the estimates (online supplemental table 5). However, the association of snoring and daytime sleepiness sleep pattern was more pronounced among individuals with a lower IOP at baseline (ie, <21 mmHg) or a history of diabetes. In the sensitivity analyses among individuals without night shift work (n=365 727), we observed comparable results to those of the main analyses (online supplemental table 6).

Table 2 Crude incidence rates and hazard ratios with 95% confidence intervals for glaucoma among participants with different sleep behaviours

Sleep behaviours	Any glaucoma		Primary open-angle glaucoma (POAG)		Primary angle-closure glaucoma (PACG)		Glaucoma excluding PACG	
	No. of cases (incidence rate *)	Hazard ratio† (95% CI)	No. of cases (incidence rate*)	Hazard ratio† (95% CI)	No. of cases (incidence rate*)	Hazard ratio† (95% CI)	No. of cases (incidence rate*)	Hazard ratio† (95% CI)
Sleep duration								
Normal‡	5663 (1.90)	Ref	1414 (0.47)	Ref	700 (0.24)	Ref	5262 (1.76)	Ref
Short or long sleep§	3027 (2.19)	1.08 (1.03 to 1.13)	700 (0.51)	1.01 (0.93 to 1.11)	398 (0.29)	1.14 (1.01 to 1.29)	2794 (2.02)	1.07 (1.02 to 1.12)
Chronotype								
Early¶	5622 (2.05)	Ref	1405 (0.51)	Ref	723 (0.26)	Ref	5201 (1.90)	Ref
Late**	3068 (1.89)	1.01 (0.97 to 1.06)	709 (0.44)	0.95 (0.87 to 1.04)	375 (0.23)	0.97 (0.85 to 1.10)	2855 (1.76)	1.02 (0.97 to 1.06)
Insomnia symptoms								
Never/sometimes	5922 (1.88)	Ref	1457 (0.46)	Ref	733 (0.23)	Ref	5500 (1.74)	Ref
Usually	2768 (2.29)	1.12 (1.07 to 1.17)	657 (0.54)	1.11 (1.01 to 1.22)	365 (0.30)	1.13 (0.99 to 1.28)	2556 (2.12	1.12 (1.07 to 1.17)
Snoring								
No	5334 (1.95)	Ref	1316 (0.48)	Ref	695 (0.25)	Ref	4942 (1.80)	Ref
Yes	3356 (2.07)	1.04 (1.00 to 1.09)	798 (0.49)	1.02 (0.93 to 1.12)	403 (0.25)	1.08 (0.95 to 1.23)	3114 (1.92)	1.03 (0.99 to 1.08)
Subjective daytime sleepiness								
Never/rarely	6143 (1.84)	Ref	1483 (0.44)	Ref	808 (0.24)	Ref	5654 (1.70)	Ref
Sometimes	2224 (2.44)	1.06 (1.01 to 1.11)	544 (0.60)	1.04 (0.95 to 1.15)	256 (0.28)	0.98 (0.85 to 1.13)	2100 (2.30)	1.08 (1.02 to 1.13)
Frequent††	323 (2.76)	1.20 (1.07 to 1.34)	87 (0.74)	1.33 (1.07 to 1.65)	34 (0.29)	1.04 (0.73 to 1.47)	302 (2.58)	1.21 (1.07 to 1.35)

*Per 1000 person-years.
†The Cox proportional hazards model was used to estimate hazard ratios, adjusted for birth year, sex, race/ethnicity, Townsend deprivation index, educational attainment, body mass index, alcohol status, smoking status, physical activity, history of hypertension, and history of diabetes.
‡7-<9 h/day.
§<7h/day or≥9 h/day.
¶Definitely a "morning" person or more a "morning" than "evening" person.
**More an "evening" than "morning" person, or definitely an "evening" person.
††often, or all of the time.

Table 3 Crude incidence rates and hazard ratios with 95% confidence intervals for glaucoma among participants with different sleep patterns

Derived sleep patterns	Any glaucoma		Primary open-angle glaucoma (POAG)		Primary angle-closure glaucoma (PACG)		Glaucoma excluding PACG	
	No. of cases (incidence rate*)	Hazard ratio† (95% CI)	No. of cases (incidence rate*)	Hazard ratio† (95% CI)	No. of cases (incidence rate*)	Hazard ratio† (95% CI)	No. of cases (incidence rate*)	Hazard ratio (95% CI)
Healthy sleep pattern	3853 (1.92)	Ref	942 (0.47)	Ref	486 (0.24)	Ref	3565 (1.77)	Ref
Late chronotype sleep pattern	2504 (1.81)	0.97 (0.93 to 1.03)	622 (0.45)	1.00 (0.90 to 1.10)	321 (0.23)	1.00 (0.87 to 1.15)	2320 (1.68)	0.98 (0.93 to 1.03)
Snoring and daytime sleepiness sleep pattern	937 (2.50)	1.10 (1.02 to 1.18)	243 (0.65)	1.16 (1.01 to 1.34)	101 (0.27)	1.06 (0.85 to 1.32)	882 (2.35)	1.11 (1.03 to 1.19)
Insomnia and short/long sleep duration sleep pattern	1396 (2.35)	1.13 (1.06 to 1.20)	307 (0.52)	1.05 (0.92 to 1.20)	190 (0.32)	1.16 (0.98 to 1.37)	1289 (2.17)	1.13 (1.06 to 1.20)
P_{trend}		<0.0001		0.15		0.092		<0.0001

*Per1000 person-years
†The Cox proportional hazards model was used to estimate hazard ratios, adjusted for birth year, sex, race/ethnicity, Townsend deprivation index, educational attainment, body mass index, alcohol status, smoking status, physical activity, history of hypertension, and history of diabetes.
CI, confidence interval.

DISCUSSION

Based on a large prospective cohort study of the UK Biobank data, we found that individuals with unfavourable sleep behaviours were at a higher risk of glaucoma. The analyses of sleep patterns, taking into consideration the correlations between individual sleep behaviours, indicated that both snoring and daytime sleepiness sleep pattern and insomnia and short/long sleep duration sleep pattern were associated with a higher risk of developing glaucoma, whereas late chronotype sleep pattern had little impact on the risk. Finally, we also showed that the results were similar for any glaucoma and for different types of glaucoma.

Although no previous study has to our knowledge explored the association between sleep pattern and risk of glaucoma, some studies have indeed reported an increased risk of glaucoma in relation to specific sleep-related behaviours – including snoring and daytime sleepiness, which are classic symptoms and predictors of OSA.[24 25] Patients with moderate or severe OSA have been shown to have a higher prevalence of glaucoma than individuals with no or mild OSA.[26] Several cohort studies have further shown that OSA is associated with a higher incidence of subsequent glaucoma.[16 26–28] Based on data from the Longitudinal Health Insurance Database, a retrospective cohort study conducted in Taiwan found that surgery for OSA could reduce the risk of glaucoma,[29] supporting a possible causal link between OSA and glaucoma. However, other studies have not shown the same results.[18 30–32] These inconsistent findings may be attributable to different factors including the control of confounding factors. With the consideration of a wide range of potential confounders, the present study demonstrated a positive association between the sleep pattern with snoring and daytime sleepiness as the predominant symptoms and a higher risk of glaucoma, using individuals with relatively healthy sleep pattern as a reference group. In addition, we also found a higher risk of glaucoma in relation to both short and long sleep duration, corroborating two earlier studies.[7 33]

The association between sleep disturbance and glaucoma is biologically plausible. The proposed hypotheses concern mainly mechanical and vascular factors.[34] The mechanical hypothesis of glaucoma development emphasises the importance of increased IOP, which is related to a supine position[35]and altered sleep hormone balance (ie, nocturnal serum melatonin peak, which is associated with lowered IOP during sleep).[36 37] Mood disorders, such as anxiety and depression, co-occur often with insomnia and may also lead to elevated IOP, possibly through dysregulation of cortisol hormone.[38 39] The vascular hypothesis proposes that repetitive or prolonged episodes of hypoxia might cause direct damage to the optic nerve. This is supported by studies reporting changes in the optic disc and visual field defects in patients with OSA.[26 40] Further, insomnia and its related stress response may stimulate neurotransmitter secretion and the autonomic nervous system, influencing the regulation of IOP and blood flow.[41] Decreased ocular blood flow is a well-known risk factor for the development and progression of glaucoma.[42] Studies have shown thinner retinal nerve fibre layers and glaucoma structural deterioration among patients with OSA, compared with individuals free of OSA.[28 43] Finally, changes of pupillary reflex and polysomnography parameters have also been reported among individuals with daytime sleepiness,[9] possibly leading to altered RGC function. The loss of ipRGCs compromise circadian rhythms and regulation of sleep.[44]

The strengths of our study include the large sample size, the prospective cohort design, and the rich information on sleep-related behaviours which allowed us to not only analyse the five individual sleep behaviours separately but also to identify five sleep patterns to understand the joint impact of different sleep behaviours. Importantly, the application of cluster analyses (ie, MCA and the k-means clustering algorithm) enabled us to extract the most informative sleep patterns among the study population. Consequently, the exposed and reference groups in our analyses are realistic and mutually exclusive, leading to meaningful comparisons. Finally, we were able to consider a wide range of important confounders in the analyses due to the availability of detailed information on sociodemographic factors, lifestyle, and somatic comorbidities.

Our study is not without some limitations. First, sleep behaviours were measured by self-reported data using five questions asked at baseline. We had therefore little information on the accuracy of this measurement and no update of such information during follow-up, leading to a concern of potential information bias due to misclassification of exposure. However, as such misclassification, especially concerning the measurement at baseline, is unlikely to differ between individuals who would later develop glaucoma and those who would not, it most likely has led to an underestimated estimate of the studied associations. Studies with repeated measurement of sleep behaviours, preferably using objective measurement of sleep patterns (eg, actigraphy and polysomnography) are regardless warranted to validate or refute our findings. Second, the ascertainment of glaucoma was based on inpatient data, restricting therefore the generalisability of our findings to glaucoma never attended in inpatient care. Further, the ascertainment of glaucoma subtypes (ie, POAG and PACG) was incomplete as a large proportion of the identified glaucoma cases had unknown subtypes. Another concern is potential alternative explanations of the findings. For instance, use of sleep medications in relation to sleep problems might have contributed to the observed associations. However, our sensitivity analyses adjusting for sleep disorders or excluding individuals with sleep disorders rendered largely similar results, suggesting that such impact is likely negligible. Further, given the observational nature of the study, the associations observed cannot be directly interpreted as causal, as glaucoma might also influence sleep quality and pattern. More research is therefore needed to better understand

the potentially bi-directional relationship between sleep and glaucoma. Finally, as participants of the UK Biobank are not a representative sample of the entire UK population,[45] the generalisation of our findings to the entire UK or other populations needs further assessment.

CONCLUSION

In conclusion, this community-based cohort study demonstrated that individuals with suboptimal sleep patterns, that is, characterised by snoring and daytime sleepiness or insomnia and short/long sleep duration, were at increased risk of glaucoma. As sleep behaviours are modifiable, these findings underscore the necessity of sleep intervention for individuals at high risk of glaucoma and potential ophthalmologic screening among individuals with chronic sleep problems to help prevent glaucoma.

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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 the UK Biobank, has full ethical approval from the NHS National Research Ethics Service (16/NW/0274) and informed consent was obtained before data collection from each participant. The present study was also approved by the biomedical research ethics committee of West China Hospital (reference number: 2019-1171). Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data may be obtained from a third party and are not publicly available. Data from the UK Biobank (http://www.ukbiobank.ac.uk/) are available to all researchers upon making an application.

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