PEER REVIEW HISTORY

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ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Association of sleep behavior and pattern with the risk of glaucoma: a prospective cohort study in the UK Biobank</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUTHORS</td>
<td>Sun, Cun; Yang, Huazhen; Hu, Yihan; Qu, Yuanyuan; Hu, Yao; Sun, Yajing; Ying, Zhiye; Song, Huan</td>
</tr>
</tbody>
</table>

VERSION 1 – REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>De Gregorio, Alessandra</th>
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<tbody>
<tr>
<td></td>
<td>San Bassiano Hospital, Ophthalmology</td>
</tr>
<tr>
<td>REVIEW RETURNED</td>
<td>19-May-2022</td>
</tr>
</tbody>
</table>

GENERAL COMMENTS

Dear authors I really appreciated the statistical work carried out on such a large sample. The large sample is always a guarantee of accuracy and scientific correctness. The subdivision of unhealthy sleep into various patterns is also quite interesting even if it is based on a simple questionnaire of a few questions and this greatly reduces the reliability of the research. Even the ascertainment of glaucoma is a simple data reported and does not exclude the lack of diagnosis in the rest of the sample. There are also too many neglected elements that would change the identity of the sample. Just to give an example: the use of drugs (such as anxiolytics and or any sleeping pills) to manage sleep disorders, this variable, like many others increases the risk of IOP increase in narrow angle glaucoma. This manuscript is an example of how well-used statistical analysis can still guarantee results but the starting data must be absolutely scientifically verifiable.

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Anujuo, Kenneth</th>
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<tr>
<td></td>
<td>London School of Hygiene &amp; Tropical Medicine, Population Health</td>
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<tr>
<td>REVIEW RETURNED</td>
<td>25-May-2022</td>
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</tbody>
</table>

GENERAL COMMENTS

This manuscript discussed an important and often-neglected topic in sleep health using a reliable data source with high power sample size. Results of the study is relevant to literature and sleep medicine, and in ophthalmology. The manuscript can be further improved if authors consider the comments below:

1. There is no study background information in the abstract
2. Methods for key outcome measures ought to be briefly indicated in the abstract
3. Authors may consider discussing the bi-directionality of the association between sleep behaviour OSA and glaucoma; also reflect on this in the discussion.
4. Page 7 line 8-17, Authors have not discussed the literature for the association between other sleep behaviour and glaucoma.
Methods/Results

5. Were these sleep behaviour and its subordinates defined? But for sleep duration, what are the contents of the questionnaire for other behaviour?
6. No information was given on the use of sleep medication, depression/anxiety which are relevant elements in sleep health/study.
7. Although mentioned as a limitation, what differences in the obtained results would you have anticipated had you used objective sleep measures (actigraphy, polysomnography)?
8. It was mentioned that ethnicity was extracted (evidenced in table 1), but no further information on its role/impact was highlighted in the entire study. UK Biobank is rich enough to reflect ethnic variation in this study. Also why was ethnicity omitted as a possible confounder in the adjusted models?
9. Could authors consider MCA as the gold-standard for measuring sleep behaviour? Obtained results may differ if alternative method was used. Please comment.
10. Mechanism of action for the observed association of sleep behaviour and glaucoma risk needs further explanation to clearly demonstrate the linkage.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Alessandra De Gregorio, San Bassiano Hospital

Comments to the Author:

Dear authors I really appreciated the statistical work carried out on such a large sample. The large sample is always a guarantee of accuracy and scientific correctness. The subdivision of unhealthy sleep into various patterns is also quite interesting even if it is based on a simple questionnaire of a few questions and this greatly reduces the reliability of the research. Even the ascertainment of glaucoma is a simple data reported and does not exclude the lack of diagnosis in the rest of the sample. There are also too many neglected elements that would change the identity of the sample. Just to give an example: the use of drugs (such as anxiolytics and or any sleeping pills) to manage sleep disorders, this variable, like many others increases the risk of IOP increase in narrow angle glaucoma. This manuscript is an example of how well-used statistical analysis can still guarantee results but the starting data must be absolutely scientifically verifiable.

Response:
Thank you for the positive comments on our manuscript. We do also agree with the reviewer that there are multiple limitations in the study, including problems related to the ascertainment of sleep pattern and glaucoma as well as alternative explanations of the findings, including the use of the drugs to manage sleep disorders. Unfortunately, as the reviewer very correctly pointed out, these are inherent problems of the UK Biobank data and there is indeed a trade-off between detailedness and breadth of data collection, especially in studies of very large sample size like the UK Biobank. Regardless, we have now elaborated these limitations in the Discussion and call for validation studies.

Discussion (page 15):
“This study also has limitations. First, sleep behaviors 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 behaviors, preferably using objective measurement of sleep patterns (e.g., 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 generalizability of our findings to glaucoma never attended in inpatient care. Further, the ascertainment of glaucoma subtypes (i.e., POAG and PACG) was incomplete as a large proportion of the identified glaucoma cases had unknown subtype. 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.”

Reviewer: 2
Dr. Kenneth Anujuo, London School of Hygiene & Tropical Medicine

Comments to the Author:
This manuscript discussed an important and often-neglected topic in sleep health using a reliable data source with high power sample size. Results of the study is relevant to literature and sleep medicine, and in ophthalmology. The manuscript can be further improved if authors consider the comments below:

Response:
Thank you for the encouraging comments. We have now responded to all your comments and made corresponding changes to the manuscript. Please see below.

1. There is no study background information in the abstract

Response:
Thank you and we have now added background information in the Abstract (page 2):

“Because of the role of intraocular pressure in glaucoma, sleeping pattern might contribute to the development and progression of glaucoma. We therefore performed a study to understand the association between sleep behaviors and glaucoma.”

2. Methods for key outcome measures ought to be briefly indicated in the abstract

Response:
Thank you and we have now added such information in the Abstract (page 2):

“We identified glaucoma as any hospital admission with a diagnosis of glaucoma, based on UK Biobank inpatient hospital data.”

Introduction
3. Authors may consider discussing the bi-directionality of the association between sleep behaviour OSA and glaucoma; also reflect on this in the discussion.

Response:
We agree and have now added such information in Introduction (pages 4-5) as well as Discussion.

Introduction (pages 4-5):
“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, 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 however yet conclusive. For instance, some studies have shown a higher prevalence of OSA among patients with glaucoma than the general population, 17 whereas other studies failed to do so 18,19.”
Discussion (page 15):
"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."

4. Page 7 line 8-17, Authors have not discussed the literature for the association between other sleep behaviour and glaucoma.

Response:
Thank you for the suggestion. We have now discussed previous studies on sleep duration and glaucoma in Introduction (page 4):

"For instance, the National Health and Nutrition Examination Survey (NHANES) 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 h per night. A cross-sectional study of 9410 Koreans showed that the prevalence of glaucoma was highest among individuals who slept for <5 hours or ≥9 hours per night."

Methods/Results
5. Were these sleep behaviour and its subordinates defined? But for sleep duration, what are the contents of the questionnaire for other behaviour?

Response:
Thank you for the comment. In the UK Biobank, information on five sleep behaviours (i.e., sleep duration, chronotype, insomnia symptoms, subjective daytime sleepiness, and snoring) was collected at baseline through touchscreen questionnaire. Details about the questions and answers related to sleep behaviours have been shown in Supplementary Table 1 in the original manuscript. We have now added such information in Methods (page 6):

‘In the analyses, we categorized the sleep duration by sleep hours per day, as normal (7 to <9h/day) or short or long (<7h/day or ≥9h/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 (e.g., have trouble falling asleep at night or wake up in the middle of the night) was classified as never/sometimes (i.e., never/rarely or sometimes) or usually, whereas subjective daytime sleepiness was categorized as never/rarely, sometimes, or frequent (i.e., often, or all of the time). Snoring was labelled as yes or no, according to the original variable from questionnaire. Details about the original questions and used variables in the analyses are shown in Supplementary Table 1.'

6. No information was given on the use of sleep medication, depression/anxiety which are relevant elements in sleep health/study.

Response:
Thank you for the important comment. We did not assess the impact of sleep medication directly because of the lack of complete information in the UK Biobank. Sleep medication use was only self-reported at baseline, although for some 45% of the participants efforts could be made to update such information from primary care data. In the original manuscript, we instead conducted two sensitivity analyses by additionally adjusting for the presence of sleep disorder, as an indicator of sleep medication use, and by restricting the analysis to individuals without sleep disorder (see Table R1 below and Supplementary Table 5 in the original manuscript). As both analyses led to largely unchanged results, we consider the impact of sleep medication use relatively limited.

We agree with the reviewer that it is important to also consider depression and anxiety and have now conducted new sensitivity analyses where we additionally adjusted for the presence of either sleep or psychiatric disorder during follow-up and repeated the main analyses by restricting the analysis to individuals without a history of sleep or psychiatric disorder at baseline (n=397,993). These new analyses yielded again largely similar results as the main analysis (see Table R2 below
and Supplementary Table 5 in the revised manuscript). We have added these analyses to the manuscript and made corresponding changes in the tables/figures/text of the revised manuscript.

Table R1 Crude incidence rates and hazard ratios with 95% confidence intervals for glaucoma among participants with different sleep patterns when additionally adjusting for the diagnosis of sleep disorders during follow-up

<table>
<thead>
<tr>
<th>Derived sleep patterns</th>
<th>Any glaucoma</th>
<th>Primary open-angle glaucoma (POAG)</th>
<th>Primary angle-closure glaucoma (PACG)</th>
<th>Glaucoma excluding PACG</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>Hazard ratio (95% confidence interval)</td>
<td>No. of cases</td>
<td>Hazard ratio (95% confidence interval)</td>
<td>No. of cases</td>
</tr>
<tr>
<td>Healthy sleep pattern</td>
<td>3853 (1.92)</td>
<td>Ref</td>
<td>942 (0.47)</td>
<td>Ref</td>
</tr>
<tr>
<td>Late chronotype sleep</td>
<td>2504 (1.81)</td>
<td>0.98 (0.93-1.03)</td>
<td>622 (0.45)</td>
<td>1.00 (0.90-1.11)</td>
</tr>
<tr>
<td>Snoring and daytime</td>
<td>937 (2.50)</td>
<td>1.11 (1.03-1.19)</td>
<td>243 (0.65)</td>
<td>1.18 (1.02-1.36)</td>
</tr>
<tr>
<td>Insomnia and short/lon</td>
<td>1396 (2.35)</td>
<td>1.12 (1.05-1.19)</td>
<td>307 (0.52)</td>
<td>1.04 (0.91-1.19)</td>
</tr>
<tr>
<td>P_trend &lt;0.0001</td>
<td>0.17</td>
<td>0.12</td>
<td>&lt;0.0001</td>
<td>3774 (1.90)</td>
</tr>
<tr>
<td>Restricting to</td>
<td></td>
<td></td>
<td></td>
<td>3493 (1.76)</td>
</tr>
<tr>
<td>participants without</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sleep disorder</td>
<td></td>
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</tbody>
</table>
and daytime sleepiness sleep pattern
Insomnia and short/long sleep duration sleep pattern

<table>
<thead>
<tr>
<th>Derived sleep patterns</th>
<th>Any glaucoma</th>
<th>Primary open-angle glaucoma (POAG)</th>
<th>Primary angle-closure glaucoma (PACG)</th>
<th>Glaucoma excluding PACG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases (incidence rate&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>Hazard ratio&lt;sup&gt;b&lt;/sup&gt; (95% confidence interval)</td>
<td>No. of cases (incidence rate&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>Hazard ratio&lt;sup&gt;b&lt;/sup&gt; (95% confidence interval)</td>
</tr>
<tr>
<td>Healthy sleep pattern</td>
<td>3853 (1.92)</td>
<td>Ref</td>
<td>942 (0.47)</td>
<td>Ref</td>
</tr>
<tr>
<td>Late chronotype sleep pattern</td>
<td>2504 (1.81)</td>
<td>0.96 (0.91-1.01)</td>
<td>622 (0.45)</td>
<td>1.00 (0.90-1.10)</td>
</tr>
<tr>
<td>Snoring and daytime sleepiness sleep pattern</td>
<td>937 (2.50)</td>
<td>1.07 (1.00-1.15)</td>
<td>243 (0.65)</td>
<td>1.16 (1.01-1.34)</td>
</tr>
<tr>
<td>Insomnia and short/long sleep duration sleep pattern</td>
<td>1396 (2.35)</td>
<td>1.09 (1.02-1.16)</td>
<td>307 (0.52)</td>
<td>1.05 (0.92-1.20)</td>
</tr>
</tbody>
</table>

P<sub>trend</sub> = 0.0011 0.41 0.22 0.0012

Restricting to participants without sleep or psychiatric disorder at baseline (N=397,993)

<table>
<thead>
<tr>
<th>Derived sleep patterns</th>
<th>Any glaucoma</th>
<th>Primary open-angle glaucoma (POAG)</th>
<th>Primary angle-closure glaucoma (PACG)</th>
<th>Glaucoma excluding PACG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy sleep pattern</td>
<td>3767 (1.91)</td>
<td>Ref</td>
<td>927 (0.47)</td>
<td>Ref</td>
</tr>
<tr>
<td>Late chronotype sleep pattern</td>
<td>2422 (1.79)</td>
<td>0.97 (0.92-1.02)</td>
<td>608 (0.45)</td>
<td>0.99 (0.90-1.10)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Per 1000 person-years

<sup>b</sup> Cox model was used to estimate hazard ratios, adjusted for birth year, sex, Townsend deprivation index, educational attainment, body mass index, alcohol status, smoking status, physical activity, history of hypertension, history of diabetes, and sleep disorder during follow-up.

Table R2: Crude incidence rates and hazard ratios with 95% confidence intervals for glaucoma among participants with different sleep patterns when additionally adjusting for the diagnosis of sleep or psychiatric disorders during follow-up.

P<sub>trend</sub> = 0.0011 0.41 0.22 0.0012

Restricting to participants without sleep or psychiatric disorder at baseline (N=397,993)
In the revised manuscript, we made the following changes:

Methods (page 8):
"Also, the role of sleep and psychiatric disorders on the studied association was detected by either additionally adjusting for the presence of such a diagnosis (yes or no) during follow-up or restricting the analysis to individuals without this condition at baseline (n=397,993)."

Results (pages 12-13):
"Neither additional adjustment for the diagnosis of sleep or psychiatric disorders during follow-up nor restricting the analysis to participants without such conditions substantially modified the estimates (Supplementary Table 5)."

7. Although mentioned as a limitation, what differences in the obtained results would you have anticipated had you used objective sleep measures (actigraphy, polysomnography)?

Response:
Thank you for the good suggestion. We have now added discussion about this in Discussion (page 15):

"First, sleep behaviors 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 behaviors, preferably using objective measurement of sleep patterns (e.g., actigraphy and polysomnography) are regardless warranted to validate or refute our findings."

8. It was mentioned that ethnicity was extracted (evidenced in table 1), but no further information on its role/impact was highlighted in the entire study. UK Biobank is rich enough to reflect ethnic variation in this study. Also why was ethnicity omitted as a possible confounder in the adjusted models?

Response:
Thank you for the good comment. Race/ethnicity was indeed adjusted for as a covariate in the analyses. Please see Methods (page 7) in the original manuscript:

"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, ≥30.0kg/m2, 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 diabetes (yes or no).”

We have now clarified this in the footnotes of Tables 2-3 and Supplementary Tables 4-6.

We also conducted a subgroup analysis by race/ethnicity (see Table R3 below and Supplementary Table 4 in the revised manuscript) and added this new analysis to the revised manuscript.

**Table R3** Crude incidence rates and hazard ratios with 95% confidence intervals for glaucoma among participants with different sleep patterns, subgroup analysis by race/ethnicity, compared with individuals with healthy sleep pattern

<table>
<thead>
<tr>
<th>By race/ethnicity</th>
<th>Late chronotype sleep pattern</th>
<th>Snoring and daytime sleepiness sleep pattern</th>
<th>Insomnia and short/long sleep duration sleep pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of glaucoma in the studied pattern (incidence ratea)/healthy sleep pattern</td>
<td>Hazard ratio (95% confidence interval)</td>
<td>No. of glaucoma in the studied pattern (incidence ratea)/healthy sleep pattern</td>
</tr>
<tr>
<td>White</td>
<td>2349 (1.79)/3 645 (1.9)</td>
<td>0.98 (0.93-1.03)</td>
<td>819 (2.38)/3 645 (1.9)</td>
</tr>
<tr>
<td>Others</td>
<td>155 (2.21)/2 08 (2.25)</td>
<td>0.98 (0.80-1.21)</td>
<td>118 (3.79)/2 08 (2.25)</td>
</tr>
</tbody>
</table>

*a* 1000 person-years

*b* Cox 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.

In the revised manuscript, we made the following changes:

**Method (page 8):**

“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.”

**Result (page 12):**

“Subgroup analyses indicated that the associations of sleep patterns with glaucoma did not differ by age at recruitment, sex, race/ethnicity, BMI, lifestyle factors (i.e., smoking status and physical activity), and history of hypertension (Supplementary Table 4).”

9. Could authors consider MCA as the gold-standard for measuring sleep behaviour? Obtained results may differ if alternative method was used. Please comment.

**Response:**

Thank you for your comment. We agree with the reviewer that the results of clustering analyses may differ according to different approaches used. However, the MCA, a principal component method, is the most widely used one for categorical variables. In our analyses, we first separately estimated the association between each sleep behaviour and risk of glaucoma, and then use the MCA-based
analyses as a complement to consider the co-occurrence of different sleep behaviours with individuals. As these two methods rendered largely similar results, we believe our choice of methods is robust. We are certainly happy to reconsider our position if the reviewer would disagree with us.

10. Mechanism of action for the observed association of sleep behaviour and glaucoma risk needs further explanation to clearly demonstrate the linkage.

Response:
Thank you for the suggestion. We have now discussed the biological plausibility of the observed association in the Discussion (page 14):

“The association between sleep disturbance and glaucoma is biologically plausible. The proposed hypotheses concern mainly mechanical and vascular factors. The mechanical hypothesis of glaucoma development emphasizes the importance of increased IOP, which is related to supine position and altered sleep hormone balance (i.e., nocturnal serum melatonin peak, which is associated with lowered IOP during sleep). 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. The vascular hypothesis proposes that repetitive or prolonged episodes of hypoxia might cause direct damage to the optic nerve, supported by studies reporting changes in the optic disc and visual field defects in patients with OSA. Further, insomnia and its related stress response may stimulate neurotransmitter secretion and the autonomic nervous system, influencing the regulation of IOP and blood flow. Decreased ocular blood flow is a well-known risk factor for the development and progression of glaucoma. Studies have shown thinner retinal nerve fiber layers and glaucoma structural deterioration among patients with OSA, compared with individuals free of OSA. Finally, changes of pupillary reflex and polysomnography parameters have also been reported among individuals with daytime sleepiness, possibly leading to altered RGC function. The loss of ipRGCs compromise circadian rhythms and regulation of sleep.”