

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	THE PREVALENCE AND RISK FACTORS OF EYE DISEASES IN ADULT PATIENTS WITH OBSTRUCTIVE SLEEP APNOEA: RESULTS FROM THE SLE.E.P.Y COHORT STUDY
AUTHORS	Pedrotti, Emilio; Demasi, Christian Luigi; Bruni, Enrico; Bosello, Francesca; Di Sarro, Paolo Plinio; Passilongo, Mattia; Fasolo, Adriano; Gennaro, Nicola; De Gregorio, Alessandra; Ferrari, Marcello; Marchini, Giorgio

VERSION 1 – REVIEW

REVIEWER	Mutlu Acar Ankara Diskapi Yildirim Beyazit Training and Research Hospital Department of Ophthalmology Turkey
REVIEW RETURNED	13-Mar-2017

GENERAL COMMENTS	It's ok for me. Good job on ophthalmic diseases of OSA Patients.
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REVIEWER	Gorkem Bilgin,MD Hacettepe University Beytepe Hospital
REVIEW RETURNED	27-Mar-2017

GENERAL COMMENTS	The manuscript is well-written. However, references are not up-to-date. There are lots of studies about NOION and glaucoma association with sleep apnes. You should compare your results with the other recent studies.
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REVIEWER	Sophie west Newcastle upon Tyne Hospitals UK
REVIEW RETURNED	30-Mar-2017

GENERAL COMMENTS	This is an ambitious study with interesting results. This manuscript would benefit from editing by someone with English as a first language. Please advise on how the patients were selected for PSG/other sleep study - were they referred to sleep clinic for suspected OSA? or advert? ?ethics committee approval- please state
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	<p>Table 1 not very useful - it would be better to have baseline characteristics of participants divided by OSA severity. It is sufficient to say in text participants did not differ significantly from non participants.</p> <p>Need a flow chart of participants/drop outs eg CONSORT diagram</p> <p>Tables 3 and 4 are difficult to follow containing a lot of data.</p> <p>I would like to see a table with OD in terms of groups of mild/moderate/severe OSA and whether there is a significant difference between these groups in terms of OD frequency</p>
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REVIEWER	Jian Guan Department of Otolaryngology Head and Neck Surgery & Center of Sleep Medicine, Shanghai Jiao Tong University Affiliated Sixth People's Hospital
REVIEW RETURNED	04-May-2017

GENERAL COMMENTS	<p>The authors performed a clinical study and try to explore the relationship between eye diseases and obstructive sleep apnea, though this is an interesting topic, several comments should be answered.</p> <p>1) The lost rate was high in this prospective study;</p> <p>2) a portable device is an obvious limitation and should be added to the limitation part;</p> <p>3) This study seems to be a cross-sectional study not a prospective study; If it is a prospective study, follow-up time?</p> <p>4) The definition of eye diseases should be clearly stated, How do the authors examine the eye diseases? Does there any objective indicators? If have, please listed.</p>
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REVIEWER	Catey Bunce Kings College London, UK
REVIEW RETURNED	25-May-2017

GENERAL COMMENTS	<p>This paper presents what appear to be novel findings in relation to eye disease and obstructive sleep apnoea that has been diagnosed by overnight polysomnography. Table 2 presents findings using patients as the unit of analysis. Please clarify whether this has been created by defining a patient as having macular disease if one or both eyes had macular disease. Tables 3 & 4 present findings using eyes as the unit of analysis and given that the focus is on the association between OD within a person and OSA, my recommendation would be that they present Tables 3 and 4 at the patient level also. If they were to decide to include both eyes of each patient, the analysis would need to deal with clustering which currently it does not. The analysis needs to be focussed more upon what is novel within this study. It would be of interest to see how OD findings relate to the severity of OSA as assessed by AHI after adjustment for confounders. It would be interesting to see how AHI and ODI relate to each other. This is not currently presented. The analyses conducted need to be explained in a little more detail as it is not clear whether or not the authors conducted multivariate analysis or multivariable analysis. If there was a single outcome variable, then it is multivariable rather than multivariate analysis. It is not the focus of this paper to assess whether age, BMI etc are associated with specific eye disease as this information has been assessed by larger epidemiological studies.</p>
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	The focus here is whether there is an association between OD and OSA after adjustment for known confounders. Please clarify how BMI, age and AHI have been analysed. Were they introduced into the model as continuous variables to increase power?
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Reviewer Name: Mutlu Acar

It's ok for me. Good job on ophthalmic diseases of OSA patients Many thanks for your appreciation

Reviewer 2

Reviewer Name: Gorkem Bilgin,MD

Comment: The manuscript is well-written. However, references are not up-to-date. There are lots of studies about NAION and glaucoma association with sleep apnoea. You should compare your results with the other recent studies.

Response: We have revised the Discussion following the suggestion, as follows:

Line 271: "A large multicentre prospective cohort study in France failed to show a significant influence of OSA diagnosis on the risk to develop glaucoma, while age > 61.4 years, female gender, BMI < 30kg/m², hypertension, high triglyceride levels, and thyroid dysfunction, were significantly associated to the increased risk of glaucoma.³⁴ In contrast, a meta-analysis involving 2,288,701 participants showed that OSA is a risk factor for glaucoma, higher in Chinese population, female and younger.³⁵ "

Line 297: "This is also supported by a relative risk of 3.34 to have OSA in NTG patients compared to systemic risk factors-matched subjects.⁴⁰ "

Line 305: "Several studies have investigate the increase prevalence of OSA in patients with NAION, some showing OSA as a risk factor, other as a contributing factor to established vascular endothelium defects that can damage autoregulation of optic nerve head blood flow.⁴²⁻⁴⁴ "

Reviewer 3

Reviewer Name: Sophie west

Comments:

- This is an ambitious study with interesting results. This manuscript would benefit from editing by someone with English as a first language.
- Please advise on how the patients were selected for PSG/other sleep study - were they referred to sleep clinic for suspected OSA? or advert??ethics committee approval- please state
- Table 1 not very useful - it would be better to have baseline characteristics of participants divided by OSA severity. It is sufficient to say in text participants did not differ significantly from non participants. Need a flow chart of participants/drop outs eg CONSORT diagram

Response: Tables 3 and 4 are difficult to follow containing a lot of data.

I would like to see a table with OD in terms of groups of mild/moderate/severe OSA and whether there is a significant difference between these groups in terms of OD frequency

The English language has been revised by an English mother tongue.

We have revised the Method section as follows:

Lines 95: "SLE.E.P.Y is a cross-sectional cohort study on adult patients with OSA assessed for eye diseases (eyelid disorders, corneal disorders, glaucoma, macular and optic nerve disorders) at the Eye Clinic of the Verona University between 2014 and 2015. All patients were previously diagnosed with OSA at the University Sleep Clinic following overnight PSG because of breathing disorders during sleep and/or suspected OSA."

Lines 104: "Our Institutional Review Board that is an ethics committee approved the study."

We replaced the original Table 1 with a new Table 1 showing baseline characteristic per eye according to the levels of AHI. We have revised the Results section as follows:

Line 180: Participants did not differ significantly from non-participants. The main reason for exclusion was refusing to participate. The majority of the patients justified due to deambulation difficulties and/or need of parents' assistance.

A flow chart of participants/drop outs was included (Figure 1) and the text revised accordingly.

We replaced the original Tables 3 and 4 by a single new Table 3 that shows the frequency of ED in terms of AHI. We changed Results and Discussion accordingly.

Reviewer 4

Reviewer Name: Jian Guan

The authors performed a clinical study and try to explore the relationship between eye diseases and obstructive sleep apnoea, though this is an interesting topic, several comments should be answered.

- 1) The lost rate was high in this prospective study;
- 2) a portable device is an obvious limitation and should be added to the limitation part
- 3) This study seems to be a cross-sectional study not a prospective study; If it is a prospective study, follow-up time?
- 4) The definition of eye diseases should be clearly stated, How do the authors examine the eye diseases? Does there any objective indicators? If have, please listed.

We agree that the lost rate is high, and for this reason, we made the analyses comparing examined and withdrawn patients showing no differences. The main reason for exclusion was refusing to participate, that the majority of the patients justified due to deambulation difficulties and/or need of parents' assistance. See revision made on the Results section as requested also by Reviewer # 3

2) Line 313, we add: "To have performed portable monitoring PSG was the major limitation of our study. Portable PSG underestimates AHI compared to in-laboratory PSG. However, portable PSG is not inferior to in-laboratory PSG for a diagnosis of OSA and can be used in the majority of patients with suspected sleep apnoea with lower costs.⁴⁴"

3) We change in the Text 'prospective' with 'cross-sectional'

4) In Line 96 we add: "...assessed for ED (eyelid disorders, corneal disorders, glaucoma, macular and optic nerve disorders) at the Eye Clinic...". Details of the ophthalmic examination are reported from line 119 through line 158 in the Methods section.

Reviewer 5

Reviewer Name: Catey Bunce

This paper presents what appear to be novel findings in relation to eye disease and obstructive sleep apnoea that has been diagnosed by overnight polysomnography.

Comment:

- Table 2 presents findings using patients as the unit of analysis. Please clarify whether this has been created by defining a patient as having macular disease if one or both eyes had macular disease.
- Tables 3 & 4 present findings using eyes as the unit of analysis and given that the focus is on the association between OD within a person and OSA, my recommendation would be that they present Tables 3 and 4 at the patient level also. If they were to decide to include both eyes of each patient, the analysis would need to deal with clustering which currently it does not. The analysis needs to be focussed more upon what is novel within this study. It would be of interest to see how OD findings relate to the severity of OSA as assessed by AHI after adjustment for confounders.
- It would be interesting to see how AHI and ODI relate to each other. This is not currently presented.
- The analyses conducted need to be explained in a little more detail as it is not clear whether or not the authors conducted multivariate analysis or multivariable analysis. If there was a single outcome variable, then it is multivariable rather than multivariate analysis.
- It is not the focus of this paper to assess whether age, BMI etc are associated with specific eye disease as this information has been assessed by larger epidemiological studies. The focus here is whether there is an association between OD and OSA after adjustment for known confounders. Please clarify how BMI, age and AHI have been analysed. Were they introduced into the model as continuous variables to increase power?

Responses: We clarify this point in Methods as follows:

Line 164: "Each patient was considered prevalent in case of at least one eye was affected."

We maintained the analyses at the eye level and Table 1 was replaced by a new Table 1, and Tables 3 and 4 by a unique new Table 3 reporting the results of the clustering multivariable analysis showing how ED findings related to the severity of OSA in terms of AHI.

A new Table 1 shows the relation between AHI and ODI.

We agree to rename in the text multivariate with multivariable.

We introduced confounders into the model as categorical variables

VERSION 2 – REVIEW

REVIEWER	Gorkem Bilgin,MD Hacettepe University Beytepe Hospital
REVIEW RETURNED	11-Jul-2017

GENERAL COMMENTS	Congratulations. This is a well-designed study with results supporting the previous ones.
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REVIEWER	Jlan Guan Department of Otolaryngology Head and Neck Surgery and Center of Sleep Medicine, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, China
REVIEW RETURNED	18-Aug-2017

GENERAL COMMENTS	The authors have all addressed my questions
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REVIEWER	Catey Bunce Kings College London, UK No competing interests
REVIEW RETURNED	15-Aug-2017

GENERAL COMMENTS	This study finds evidence of an association between AHI and glaucoma. It does not provide evidence that AHI is a risk factor for glaucoma. This need amending in the abstract and on line 195. Line 195 also needs to state multivariable rather than multivariate.
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VERSION 2 – AUTHOR RESPONSE

Reviewer 2

Reviewer Name: Gorkem Bilgin,MD

Comment: Congratulations. This is a well-designed study with results supporting the previous ones.

Response: Many thanks for your appreciation

Reviewer 4

Reviewer Name: Jian Guan

Comment: The authors have all addressed my questions

Response: Many thanks for the constructive comments

Reviewer 5

Reviewer Name: Catey Bunce

Comment: This study finds evidence of an association between AHI and glaucoma. It does not provide evidence that AHI is a risk factor for glaucoma. This need amending in the abstract and on line 195. Line 195 also needs to state multivariable rather than multivariate.

Response: In the Abstract, line 33 was changed in: "Severe OSA was significantly associated to glaucoma (OR, 95% CI 1.05-5.93, P = 0.037)." In the text, line 166 was changed in: "The multivariable analysis demonstrated that a severe AHI level was associated to glaucoma." We agree to rename "multivariate" with "multivariable" in line 166 of the text.