The Ocular Surface

Association of Dry Eye Disease and Sun Exposure in Geographically Diverse Adult (> 40 years) Populations of India: The SEED (Sun Exposure, Environment and Dry eye disease) Study - Second Report of the ICMR-EYE SEE Study Group

--Manuscript Draft--

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Abstract:	Purpose To estimate the prevalence and determine risk factors for dry eye disease (DED) in geographically diverse regions. Method A population based cross-sectional study was conducted on people aged > 40 years in plain, hilly and coastal areas. Dry eye assessment by objective [tear film break-up time (TBUT), Schirmer I, corneal staining] and subjective [Ocular surface disease Index (OSDI)] parameters was performed with questionnaire-based assessment of exposure to sunlight, cigarette smoke, indoor smoke. The prevalence of DED with age, sex, occupation, location, smoking, exposure to sunlight, indoor smoke, diabetes, hypertension, BMI was subjected to logistic regression analysis. Results 9,735 people (age 54.5±0.1 years; range 40-99, males 45.5%) were included. The prevalence of DED was 26.2%, was higher in plains (41.3%) compared to hilly (24.0%) and coastal area (9.9%) (p<0.001) and increased with age (p<0.001), female gender (p<0.001), smoking (p<0.001), indoor smoke (p<0.001), diabetes (p-0.02), hypertension (0.001), occupations with predominant outdoor activity (p-0.013) and increasing exposure to sunlight (trend). Multi-logistic regression showed a positive association with female sex (OR-1.2, CI-1.01, 1.4), exposure to indoor smoke (OR-1.3, CI-1.1, 1.5), smoking (OR-1.2; CI-1.03, 1.3), prolonged exposure to sunlight (OR-1.8, CI-1.5, 2.2), hypertension (OR 1.3, CI-1.2, 1.4), diabetes (OR-1.2, CI-1, 1.5) and negative association with region - hilly (OR-0.5, CI-0.4, 0.6) and coastal (OR-0.2; CI-0.1, 0.2), and BMI (OR-0.8, CI-0.7, 0.9). Conclusion DED is common in population ≥40 years of age. Its prevalence is affected by extrinsic (geographic location, exposure to sunlight, smoking, indoor smoke) and intrinsic (age, sex, hypertension, diabetes, BMI) factors.
Suggested Reviewers:	James Chodosh, MD, MPH

	Professor, Massachusetts Eye and Ear Infirmary james_chodosh@meei.harvard.edu Prof Chodosh is a renowned ophthalmologist and corneal surgeon. He has a public health background and a global perspective of Ophthalmology.
	Madan Deshpande, MS Director, H V Desai Eye Hospital, Eye Hospital, Pune, India col.md@hvdeh.org Senior Ophthalmologist, Teacher, Academician with special interest and extensive experience in public health, preventive ophthalmology and health promotive policies.
Opposed Reviewers:	
Response to Reviewers:	

12 July 2020

To
The Editor-in-Chief
The Ocular Surface.

Subject: Submission of Revision of Manuscript of Original Research for Publication in the Journal The Ocular Surface

Dear Dr Djalilian,

I am submitting a revised version of our manuscript titled '**Association of Dry Eye Disease and Sun Exposure in Geographically Diverse Populations of India: The SEED (Sun Exposure, Environment and Dry eye disease) Study -Second Report of the ICMR-EYE SEE Study Group'** in response to your kind consideration for publication in your esteemed journal.

The work is original and has not been submitted to any other journal. The manuscript was been prepared in accordance with the instructions to authors and all authors have contributed substantially to the work for publication and approved the final manuscript and its revised version. We have attended to the comments and suggestion provided by the Editor and Reviewers and are indeed grateful for the opportunity to improve the quality of the work.

On behalf of all the co-authors, I do hope you find the revised manuscript worthy for publication.

With regards,

Dr Radhika Tandon, MD, DNB, FRCOphth, FRCSEd

Professor of Ophthalmology,

Dr Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi.

Detailed Point by Point Summary of Revisions and Responses by the Authors

Editor's letter

Manuscript Number: THEOCULARSURFACE-D-20-00172

Association of Dry Eye Disease and Sun Exposure in Geographically Diverse Populations of India: The SEED (Sun Exposure, Environment and Dry eye disease) Study - Second Report of the ICMR-EYE SEE Study Group

Dear Dr Tandon,

Thank you for submitting your manuscript to The Ocular Surface.

I have completed my evaluation of your manuscript. The reviewers recommend reconsideration of your manuscript following major revisions and modifications. I invite you to resubmit your manuscript after addressing the comments below. Please resubmit your revised manuscript by Jul 16, 2020.

When revising your manuscript, please consider all issues mentioned in the reviewers' comments carefully: please outline every change made in response to their comments and provide suitable rebuttals for any comments not addressed. Please note that your revised submission may need to be re-reviewed.

To submit your revised manuscript, please log in as an author at https://www.editorialmanager.com/theocularsurface/, and navigate to the "Submissions Needing Revision" folder under the Author Main Menu.

The Ocular Surface values your contribution and I look forward to receiving your revised manuscript.

Kind regards,

Ali Djalilian, MD

Editor-in-Chief

The Ocular Surface

Authors' response

Dear Dr Djalilian,

Thank you for giving us the opportunity to revise and resubmit our manuscript. We appreciate the considerable time and effort spent by the Editor and the Reviewers in evaluating our paper and providing valuable feedback for improvement. The detailed comments have been carefully processed and major revisions undertaken accordingly. The point by point explanation of the changes is indicated in the reply along with indications of how the manuscript has been corrected.

We sincerely hope the manuscript is now acceptable for publication in the prestigious journal The Ocular Surface.

With regards,

Dr Radhika Tandon

Corresponding author

AUTHORS REPLY

We would like to thank the editor for giving us the opportunity to revise and resubmit our manuscript and our grateful to the editor and reviewers for the helpful feedback which we found very useful and constructive in improving the reporting of our work. We are indeed grateful for this kind consideration and have revised the manuscript accordingly. We hope you find all the aspects put forth have been covered satisfactorily.

We have tried to address all the issues raised and concerns expressed and our responses to each is summarized in a point to point reply as follows:

Reviewer #1:

This is an interesting study conducted in India which looked into several associated factors of dry eye focusing on environmental variables. The sample size is large (close to 1000) and results are valuable. The magnitude of the dry eye problem is consistent with other studies.

1. The main study findings on the importance of UV exposure and smoking support the oxidative stress hypothesis in dry eye, which is not emphasized enough in the research in the dry eye field. Perhaps the authors can comment more on that in the discussion.

Authors: We thank the reviewer for the encouraging remarks and appreciation of our work. The observation to comment about the hypothesis and mechanisms of etio-pathogenesis in the discussion has been addressed by adding a brief note about it in the discussion. A paragraph highlighting the oxidative stress hypothesis has been added to the discussion-

"Oxidative stress is known to result in ocular surface changes and DED.[31,32] Both smoking and ultraviolet radiation are risk factors for increased oxidative stress and as a corollary can be considered as contributory risk factors for DED; as observed in our study. The role of smoking in oxidative damage to ocular structures resulting in dry eye, lenticular changes and retinal pigment epithelial cell changes has been reported in few studies.[31–34] Ocular exposure with ultraviolet radiation resulting in oxidative stress has been extensively

explored in relation to corneal collagen crosslinking.[35] However, its direct impact on the ocular surface is relatively unexplored. The rise of inflammatory mediators as a consequence of oxidative stress can result in goblet cell damage and DED. Future studies evaluating changes in tear film inflammatory markers with levels of UV radiation exposure and conjunctival impression cytology can be performed to quantitatively test this hypothesis." (Page 19-20; Line 439-450)

2. These are my comments, which mainly refer to clarifying some points.

Authors: The various comments referring to clarifying some points are indeed pertinent and were very interesting to consider. Most or all of the information has been provided and incorporated as best possible to add clarity and is shown point wise below.

Results

3. Since gender is a big factor, I suggest performing additional analysis for males and females separately for see the effects of the outdoor variables (and show as supplementary tables). It is also required for harmonizing study reporting as recommended by human studies involving both sexes.

Authors: We thank the reviewer for the suggestion and for emphasizing the requirement for harmonizing study reporting as recommended by human studies involving both sexes. A supplementary table has been added showing a gender-wise multivariate analysis. The association is the same for both for most of the risk factors except indoor smoke in males and diabetes in females. (Supplementary Table 2)

Supplementary Table 2: A gender wise multi-logistic regression analysis showing association of DED with various risk factors

The results section has also been updated to reflect the salient results

"On performing additional analysis for males and females separately, gender wise multi-logistic regression analysis, smoking was non-significant for both males and females, indoor smoke had a positive association in males (OR 1.7; CI-1.4, 2.0) only, and diabetes showed a positive association in females (OR 1.3; CI - 1.0, 1.6) only. (Supplementary Table 2). Additional

sub-analysis of hypertension as systolic and diastolic showed that only systolic hypertension had association with DED on multiple-logistic regression analysis. (Supplementary Table 3)."
(Page 15-16; Line 326-337)

4. Separately, since the prevalence of dry eye varies between the 3 centers, I think it is good to stratify the multivariate regression using each center (stratified by area) and show in supplementary tables and comment whether the relationships of sun exposure and smoking still hold.

Authors: The results of centre wise multivariate analysis are provided in Table 5. A positive correlation of DED with sun-exposure was observed in all the three centres; however, smoking showed a positive correlation with DED in the overall population and only in Delhi-NCR when assessed separately for individual centres.

Table 5: Centre-wise and overall multiple logistic regression analyses showing association of dry eye disease with various risk factors (included as Table 5 in original submission)

5. The study is sampled from clusters of about 500. If the participation rate is 81% it is quite reasonable. Is it possible to show a table of comparison between participants and non-participants in terms of age, sex, and location of address? There is always the possibility that older and more morbid cases avoid participation, so under estimating the prevalence.

Authors: It is nice that the reviewer drew attention to this aspect. An additional table has been provided below to show the age and gender composition of the participant and nonparticipant population. Also a study site wise proportion of participant and non-participant population is included. As can be seen in the table, an adequate proportion of recruited population in $\geq$ 70 years age group participated in the study and there is nothing to suggest that older and more morbid cases were left out; hence ruling out the possibility of an underestimated prevalence. Home visits were conducted in special situations like a bed bound or moribund patient and this could perhaps be partly responsible for the good response rate observed even in the elderly group.

"Home visits were conducted in special situations like a bed bound or moribund patient." (Page 7; Line 125-126)

"The participation was similar across age groups. (Supplementary Table 1)"

(Page 10; Line 198)

Supplementary Table 1: Demographic profile of the participant and non-participant population of the study

6. In the multiple regression, did you explore potential interaction terms such as sun exposure and pollution, or age and sun exposure, instead of using them as purely separate variables?

Authors: This is an important and interesting line of investigation. In the multivariate regression analysis, the effect of sun exposure was evaluated after adjusting for age and a positive correlation was obtained between DED and sun-exposure in the overall population as well as the individual study centres. We agree with the reviewer that exploring the interaction of pollution variables with DED could have added valuable information; however, the pollution variables were not individual specific as the data was collected at the site level and hence could not be assessed in the multivariate analysis. This point has been added in the discussion.

"Exploring the interaction of pollution variables with DED in multi-logistic regression analysis could have added valuable information. However, the pollution variables were not individual specific as the data was collected at the city level and hence could not be assessed in multi-logistic regression analysis. For the sake of scientific rigor, further validation of this aspect may be considered in future studies with long term monitoring of indoor air quality parameters of the participants using portable devices." (Page 21-22; Line 477-481)

7. The humidity readings in the Table 2 did not have SD or confidence intervals. Are these only taken once in each location? If so is it taken during the morning, mid afternoon or evening?

Authors: The table has now been revised to include standard deviations of the humidity data. The humidity data is generally recorded every 3 hours and the daily average value is then calculated. What has been reported in the table is the annual average value obtained from the monthly averaged data and the standard deviations represent those calculated from the monthly average values. (Refer revised Table 2)

8. In the last table multivariate regression, please indicate the list of independent variables in the model.

Authors: The list of independent variables in the last table (Table 5) have been added in the table footnote as advised.

Methodology

9. Since OSDI is symptom based, I wonder if there is a questionnaire used that monitored the frequency of use of artificial tears? If there is under-usage of such eyedrops, it will increase the severity levels obtained by OSDI

Authors: It is true that the assessment of artificial tear usage could have provided additional baseline information about the population and usage or under-usage of artificial tears would affect the severity levels obtained by OSDI which is a symptom based questionnaire. The idea of this study was to primarily assess the prevalence of dry eye disease in the population studied and it was not designed to estimate disease severity. OSDI was used as a screening tool and not applied as a diagnostic criterion. Recording of usage of lubricant eye drops and exact dosage etc. are not a part of the standard OSDI questionnaire nor has been mentioned as an essential criteria to be evaluated for diagnosis of DED by the TFOS study, hence, we did not formally capture these details. Based on the clinical noting in the records less than 10% participants were using artificial tears.

"Based on the clinical noting in the records, <10% participants were using artificial tears."

(Page 13 ; Line 258-9)

10. Are there features of meibomian gland dysfunction on slit lamp examination? This may be a confounding or contributing factor to symptoms.

Authors: We agree that meibomian gland dysfunction could be a contributing factor to symptoms and a confounding factor for etiology of dry eye disease. Features of Meibomian gland dysfunction on slit lamp examination were evaluated clinically but the nature, pattern and extent were not however assessed in this study. This has been mentioned as a short fall in the discussion.

"Similarly, the nature, pattern and extent of Meibomian gland dysfunction (MGD) which could be a contributing factor for symptoms of DED, though evaluated clinically on slit lamp examination, was not analysed. Also, hyperlipidaemia which has been reported to be associated with MGD and DED was not assessed as part of this study. These aspects have been included in the ongoing phase 2 of the study." (Page 23; Line 516-520)

11. What are the frequencies of allergies such as sinusitis, eczema and asthma in this study? Most of the symptoms of OSDI are not specific and can be contributed by other OSD. Please discuss this

Authors: Although specific questions were not asked for sinusitis, eczema and asthma; a separate question was asked for presence of any known systemic illness for which 51 participants reported a history of asthma, 3 participants reported having skin allergy and 1 reported for sinusitis. This has been added to the text as follows:

"Allergic conditions like asthma, skin allergy and sinusitis were observed in 0.56% of the participants (n-55/9,735). Asthma was the most common condition noted in the participants with allergic conditions (n-51/55)." (Page 11; Line 206-208)

We concur with the reviewer's concern regarding occurrence of OSDI symptoms from ocular surface disorders other than DED, hence we used both TBUT and OSDI for diagnosis of DED in the current study. As advised we have added this in the discussion.

"However, as symptoms of OSDI are non-specific and can occur due to any ocular surface disorder, it can be fallacious to rely on OSDI as a sole criterion for diagnosis of DED; hence

the TFOS DEWS II criteria were applied that take into consideration clinical signs in addition to symptoms for DED diagnosis.**”** (Page 16-17; Line 352-359)

12. Are there any questions related to sleep quality? This has been shown to be associated with symptoms of dry eye even after adjusting for hypertension, etc.

Authors: Regrettably there were no questions for sleep quality included in the study. The concept has recently come to the fore with few studies having shown an association between sleep disorder and dry eye disease. A proper assessment of sleep disorder would require use of validated sleep questionnaire like Pittsburgh Sleep Quality Index (27 questions) or the Epworth Sleepiness Scale (8 questions). As this was a large population based survey with 4 independent forms to be filled for each participant taking over one hour per participant for complete evaluation, hence its incorporation was not feasible as it was considerably increasing the time required for evaluation per participant. This has been added in the discussion for completeness.

“Recently, an association between sleep disorder, physical activity, stress factors and depression with DED has come to fore. Additional data on sleep parameters could have added to the study; however a proper assessment of sleep disorder requires use of validated sleep questionnaire like Pittsburgh Sleep Quality Index (27 questions) or the Epworth Sleepiness Scale (8 questions).[54,55] As this was a large population based survey with 4 independent forms to be filled requiring over one hour per participant for complete evaluation, hence its incorporation was not considered feasible.”(Page 22-23;Line 495-505)

13. Similarly are there data here on the use of CNS drugs like opioid drugs and antidepressants?

Authors: We regret to inform, there is no detailed information available on the use of CNS drugs like opioid drugs and antidepressants. There were very few patients who had a positive history for CNS or neuropsychiatric disorders like stroke (n-9), seizure (n-4), and Parkinson’s disease (n-3), anxiety disorder (n-2) and depression (n-1).

The cases with Parkinson's disease were on treatment while the rest of them were not on any therapy at the time of examination, hence to make an inference from the above is difficult. This information has been added in results.

"A detailed individual drug history for central nervous system (CNS) drugs like opioids and anti-depressants was not obtained separately in this study. However, a positive history for CNS or neuropsychiatric disorders was obtained in participants as follows: stroke (n-9), seizure (n-4), Parkinson's disease (n-3), anxiety disorder (n-2) and depression (n-1) of whom only those with Parkinson's disease were on treatment at the time of examination." (Page 14-15; Line 296-301)

Just to clarify:

14. Lifetime Effective Sun Exposure = Σ [Daily hours of sun exposure without head gear + (Daily 136 hours of sun exposure using head gear x protection factor)] x 365 x Number of years. Is the number of years referring to the age? If not how is the participant able to estimate the number of years?

Authors: The assessment was based on the Melbourne visual impairment project model. The number of years refers to the years after the person crossed the age of 15 till the time of examination (so effectively current age in years-15). The average hours of exposure per day was enquired about along with use of any sun protection. In case, there was a change of occupation or lifestyle resulting in an increase or decrease of sun exposure in the past, it was separately documented with the number of years and was summed up to calculate the lifetime effective sun exposure.

> "The number of years refers to the duration from the time respondent crossed the age of 15 years and the time of examination (current age - 15)." (Page 9; Line 160, 163-4)

This is the format in which the sun exposure details were obtained:

PRESENT ACTIVITY

1. What type of work are you mainly involved in throughout the day?

(Multiple responses possible)

आप की प्रत्येक दिन की दिनचर्या क्या है? **(एक से अधिक उत्तर संभव)**

1. Agricultural work (खेती का कार्य) ☐
2. Outdoor Non Agricultural Work (घर के बाहर अन्य कार्य) ☐
3. Indoor work (घर के अन्दर का कार्य) ☐

2. For how many years have you been doing this kind of work?
आप यह कार्य कितने वर्षो से कर रहे हैं?

_____ years (वर्ष)

3. How many hours do you usually spend outdoor after sunrise and before sunset? (9:00 AM to 5:00 PM) **Record in decimal form (eg: 1:30hr = 1.5hr)**
आप सूरज निकलने से सूरज डूबने तक प्रायः कितने घंटे घर से बाहर बिताते हैं ?
(सुबह 9:00 बजे से शाम 5:00 बजे तक) 0 = Nil (कुछ नही)

_____ hours (घंटे)

4. For how many hours are you usually outdoors in the middle of the day?
(From 11:00 AM to 3:00 PM)
आमतौर पर आप दोपहर में कितने घंटे घर से बाहर बिताते है? (सुबह 11:00 बजे से दोपहर 3:00 बजे तक)

_____ hours (घंटे)

5. What type of head gear or eye gear do you normally wear when outside b/w 9 AM to 5 PM?
आमतौर पर आप जब धूप में जाते है तो सुबह 9:00 बजे से 5:00 बजे तक सिर व आँख ढ़कने के लिए क्या इस्तेमाल करते है ? **Record in decimal form (eg: 1:30hr = 1.5hr)**

	घंटे प्रति दिन
0. None (कुछ नही)	.....
1. Veil/ Dupatta/Saree pallu/ Ghunghat(बूरका / दूपट्टा / साड़ी पल्लू / घूँघट)	.....
2. Pagdi/saroopa/ mundas /towel(पगड़ी / सरूपा / मुंडास / तौलीया)	.....
3. Umbrella(छाता)	.....
4. Cap (टोपी)	.....
5. Sunglasses/prescription glasses (धूप का चश्मा / नम्बर वाला चश्मा)	.....
66. Others अन्य (उल्लेख करें) _____	.....

PAST ACTIVITY

6. Were you doing some other work in the past? **(Multiple responses possible)**

क्या आप इसके पहले दूसरा काम करते थे? **(एक से अधिक उत्तर संभव)**

0 . Not applicable (लागू नही) ☐
1. Agricultural work (खेती का कार्य) ☐
2. Outdoor Non Agricultural Work (घर के बाहर अन्य कार्य) ☐
3. Indoor work (घर के अन्दर का कार्य) ☐

7. For how many years did you follow this routine?
आप ने यह कार्य कितने वर्षो तक किया था?

_____ years (वर्ष)

8. How many hours did you usually spend outdoor after sunrise and before sunset? (9.00am to 5.00PM) **Record in decimal form (eg: 1:30hr = 1.5hr)**
आप सूरज निकलने से सूरज डूबने तक प्रायः कितने घंटे घर से बाहर बिताते थे?
(सुबह 9:00 बजे से शाम 5:00 बजे तक) 0 = Nil (कुछ नही)

_____ hours (घंटे)

9. For how many hours were you usually outdoors in the middle of the day.
(From 11:00 AM to 3:00 PM)
आमतौर पर आप दोपहर में कितने घंटे घर से बाहर बिताते थे? (सुबह 11:00 बजे से दोपहर 3:00 बजे तक)

_____ hours (घंटे)

10. What type of head gear or eye gear did you normally wear when outside b/w 9:00 AM to 5:00 PM ?
आमतौर पर आप जब धूप में जाते थे तो सुबह 9:00 बजे से शाम 5:00 बजे तक सिर व आँख ढ़कने के लिए क्या इस्तेमाल करते थे? **Record in decimal form (eg: 1:30hr = 1.5hr)**

	घंटे प्रति दिन
0. None (कुछ नही)	.....
1. Veil/ Dupatta/Saree pallu/ Ghunghat(बूरका / दूपट्टा / साड़ी पल्लू / घूँघट)	.....
2. Pagdi/saroopa/ mundas /towel(पगड़ी / सरूपा / मुंडास / तौलीया)	.....
3. Umbrella (छाता)	.....
4. Cap (टोपी)	.....
5. Sunglasses/prescription glasses (धूप का चश्मा / नम्बर वाला चश्मा)	.....
66. Others अन्य (उल्लेख करें) _____	.....

REMOTE PAST ACTIVITY

11. Were you doing some other work in the past? **(Multiple responses possible)**

क्या आप इसके पहले दूसरा काम करते थे? **(एक से अधिक उत्तर संभव)**

0 . Not applicable (लागू नही) ☐
1. Agricultural work (खेती का कार्य) ☐
2. Outdoor Non Agricultural Work (घर के बाहर अन्य कार्य) ☐
3. Indoor work (घर के अन्दर का कार्य) ☐

12. For how many years did you follow this routine?
आप ने यह कार्य कितने वर्षो तक किया था ?

_____ years (वर्ष)

13. How many hours did you usually spend outdoor after sunrise and before sunset? (9.00AM to 5.00PM) **Record in decimal form (eg: 1:30hr = 1.5hr)**
आप सूरज निकलने से सूरज डूबने तक प्रायः कितने घंटे घर से बाहर बिताते थे?
(सुबह 9:00 बजे से शाम 5:00 बजे तक) 0 = Nil (कुछ नही)

_____ hours (घंटे)

14. For how many hours were you usually outdoors in the middle of the day.
(From 11:00 AM to 3:00 PM)
आमतौर पर आप दोपहर में कितने घंटे घर से बाहर बिताते थे? (सुबह 11:00 बजे से दोपहर 3:00 बजे तक)

_____ hours (घंटे)

15. What type of head gear or eye gear did you normally wear when outside b/w 9AM to5PM?

आमतौर पर आप जब धूप में जाते थे तो सुबह 9:00 बजे से शाम 5:00 बजे तक सिर व आँख ढ़कने के लिए क्या इस्तेमाल करते थे?

	घंटे प्रति दिन
0. None (कुछ नही)	.....
1. Veil/ Dupatta/Saree pallu/ Ghunghat(बूरका / दूपट्टा / साड़ी पल्लू / घूँघट)	.....
2. Pagdi/saroopa/ mundas /towel(पगड़ी / सरूपा / मुंडास / तौलीया)	.....
3. Umbrella (छाता)	.....
4. Cap (टोपी)	.....
5. Sunglasses/prescription glasses (धूप का चश्मा / नम्बर वाला चश्मा)	.....
66. Others अन्य (उल्लेख करें) _____	.....

15. Is type of occupation one of the questions? (for example indoor factory workers vs indoor secretaries? Some exposure to chemical is possible in specific occupations.) Since 82.2% of participants have outdoor occupations, it should be mentioned in the discussion that this study may not be optimal to evaluate indoor pollution and other similar factors

Authors: Yes, type of occupation was part of the questionnaire. The following was the list of occupations into which the participants were classified-

1. House work
2. Cultivator
3. Agricultural labourer
4. Non Agricultural labourer
5. Skilled worker
6. Office Job (Class I)
7. Office Job(Class II/III)
8. Office Job(Class IV)
9. Business
10. Professional (Doctor, Engineer, Lawyer etc.)
11. Unemployed
12. Retired/ Not working because of old age
13. Not working because of handicap/ sickness
14. Student
15. Not applicable
16. Others (specify)

Further the activity was divided based on their responses into primarily indoor or outdoor. There was no obvious history of occupational exposure to chemicals reported by the participants though details were not specifically obtained.

"Occupation was classified as primarily indoors or outdoors" (Page 7; Line 115)

"No definitive history of occupational exposure to chemicals was reported by any of the participants." (Page 10; Line – 201-202)

16. Are ozone and hydrocarbon levels measured in the study locations?

Authors: The ozone and hydrocarbon values were not measured at these locations during the study period.

17. Are there any measures of air flow rate? If there is a higher flow in coastal and hilly areas, may explain a reduced exposure of the ocular surface to some air pollutants.

Authors: Yes, measures of the air flow rates are available and have been mentioned as average wind speed in the table. The average wind speed is highest in the coastal region (8.4 Km/h) followed by the plain region in Delhi (6.5 Km/h) and minimum in hilly region Guwahati (3.4 Km/h). This may explain a reduced exposure of the ocular surface to some air pollutants and this has been added in the discussion.

"Also, the average wind speed was highest in Prakasam (Southern coastal). This may explain a reduced exposure of the ocular surface to some air pollutants and resultant low prevalence of DED. " (Page 21; Line 460-462)

18. Are there data on second hand smoke versus smoking, or current smokers vs past smokers, or heavy smokers vs lighter smokers?

Authors: Yes, the data for past and current smokers as well as light and heavy smokers is available. Participants with current smoking constituted 80.9% while 19.1% of the participants had history of smoking in the past.

In our study, smoking was defined as use of any smoked tobacco product like cigarette, bidi, hukkah etc. and hence classifying all of them into heavy and light smokers is difficult. However, among the participants using cigarettes, 59.5% of the participants were heavy smokers (>=5 cigarettes per day) while 40.5% were light smokers (<5 cigarettes per day).

"Smoking was reported by 36.8% of the participants with 80.9% participants being current smokers. Among the participants with history of cigarette smoking, 59.5% participants were heavy smokers (≥5 cigarettes/day)." (Page 11; Line – 208-210)

19. Is cosmetic use or contact lens wear documented in the women?

Authors: Since the study was planned for rural Indian population aged ≥40 years, contact lens use was not a part of our questionnaire as it is not routinely used in this section of the population. Based on the clinical records, none of the patients reported use of contact lenses. Use of cosmetics in women is again not common in rural populations above 40 though it was not specifically documented. This aspect has been listed as a short fall.

"In addition, data on usage of contact lens, eye cosmetics and visual display unit would have been of additional interest; however they are not commonly used in the rural Indian population aged ≥ 40 years studied, hence could not be separately assessed as a part of this study" (page 23, line 496-499)

20. I agree it is useful to know the type of anti-hypertensive medications in those with and without dry eye.

Authors: We thank the reviewer for understanding our concern.

21.The study is conducted in three different regions from 2010 to 2016. Are the three regions performed at the same time or one after another?

Authors: Yes, the study was conducted simultaneously at the same time in the three different regions between 2010 and 2016.

22. In multivariate regression, are height, weight and blood pressure entered into covariates?

Authors: Blood pressure has been added as a covariate in multiple regression analysis and was found to have a positive association with DED (Table 5). As height and weight are continuous variables and it is difficult to categorise the patients on its basis, BMI, a composite measure has been added as a covariate in the univariate analysis as well as

multiple logistic regression analysis for assessing its association with DED (Tables 4 and 5). It was observed that high BMI had a negative association with DED.

"The prevalence of DED was higher in participants with BMI<25 (27.8%) when compared to those with BMI ≥25 (22.4%) (p <0.001)." (Page 14; Line 294-5)

23. Are the questionnaires participant or interviewer administered? Are there cases where translation of the questionnaires are required? If so are there more than one language version of the questionnaire?

Authors: The questionnaires were interviewer administered. Yes, translation of questionnaire was required into Hindi, Telugu and Assamese for the convenience of comprehension of both the interviewer as well as the participants in the three study centre. The interviewers were initially trained following which a pilot study was conducted at each centre. Kappa value was calculated to assess the inter-observer variation and was found to be within the normal range.

"The questionnaire was translated into the three local languages (Assamese, Hindi and Telugu) and piloted to confirm that the items were comprehensible. These versions were then back translated into English by independent sets of translators conversant with the respective languages. The initial and back-translated versions were compared to assess linguistic validity. As it was a validated questionnaire, face validation with experts was done. The questionnaire was administered by trained interviewers. Kappa values were calculated to assess the inter-observer variation and were found to be within the acceptable range."

(Page 8; Line 144-151)

Discussion

24. Are there any data on BMI or amount of physical exercise, which may be proxies for general state of health? It is now believed that dry eye is a chronic holistic disease, so people who outdoor and more sun exposure could have more physical exercise (or less sedentary lifestyle) and therefore less dry eye? Refer to studies related to BDNF and stress

hormones. Currently it is not known whether behavioral modification is purely for the sun exposure or for more physical exercise, more balanced diet, etc.

Authors: Yes, data for BMI is available and details regarding the same have been added to the manuscript in table 4, table 5, and supplementary tables 2 and 3.

"Body mass index (BMI) was calculated as weight in kg divided by the square of height in metres." (Page 8; Line 133-134)

"The BMI was ≥ 25 in 24.9% of the participants (n-2425/9,735)"

(Page 11; Line 207-208)

"The prevalence of DED was higher in participants with BMI<25 (27.8%) when compared to those with BMI >= 25 (22.4%) (p <0.001)." (Page 15; Line – 294-295)

We agree with the reviewer that recently DED is being considered a chronic holistic disease with emphasis on stress factors and depression as a risk factor. In our study only one case suffered from depression and data for physical activity was not collected. However, as data for BMI and occupation involving predominant outdoor activity was available, we tried to correlate both these factors. A lower proportion of participants engaged in outdoor activity had BMI >25 which maybe an indirect indicator of better physical fitness in these cases. But the prevalence of DED was higher in participants with outdoor activity. Hence, in the absence of direct data for physical activity, it is difficult to conclusively comment on the same from our study. We have added the following discussion to the manuscript:

"Recently, an association between sleep disorder, physical activity, stress factors and depression with DED has come to fore. Additional data on sleep parameters could have been added to the study; however a proper assessment of sleep disorder requires use of validated sleep questionnaire like Pittsburgh Sleep Quality Index (27 questions) or the Epworth Sleepiness Scale (8 questions).[54,55] As this was a large population based survey with 4 independent forms to be filled requiring over one hour per participant for complete evaluation, sleep assessment was not considered feasible. In the current study, only one case suffered from depression. Detailed data for physical activity *per se* was not collected, hence it is not possible to comment on the relationship from our study. In addition, data on

usage of contact lens, eye cosmetics and visual display units would have been of additional interest; however as these are not commonly used in the rural Indian population aged ≥40 years studied, hence they could not be separately assessed." (Page 22-23; Line 487-499)

25. The current discussion is mainly on sex and age. There should be more discussion on the other factors, since the strength of this study is on outdoor factors.

Authors: We thank the reviewer for the suggestion. More discussion on the other factors has been incorporated in the discussion

- Oxidative stress, smoking, ultraviolet radiation: line 415
- Wind speed: line 461
- Pollution: line 462
- Physical Activity: Line 488, 494

26. Is systolic or diastolic hypertension significant on multivariate after adjusting for other diseases? If not this could be confounded by hyperlipidemia. Since the hypertensive may have more lipidemia which than be associated with MGD or other unknown variables.

Authors: Both systolic and diastolic hypertension were found to be significantly correlated with DED in single variate analysis and hence added to the multivariate analysis in addition to other factors. Only systolic blood pressure was positively associated with DED in multivariate regression analysis.

"Additional sub-analysis of hypertension as systolic and diastolic showed that only systolic hypertension had association with DED on multiple-logistic regression analysis. (Supplementary Table 3)." (Page 16; Line 326-328)

Supplementary Table 3- Multivariate regression analysis showing correlation of Dry eye disease with various risk factors including systolic and diastolic hypertension

We agree with the reviewer that hyperlipidaemia could be associated with MGD that could precipitate dry eye. However, data for the same was not collected, hence it is difficult to

comment on this association on the basis of our data. This element has been added in the discussion

"Also, hyperlipidaemia which has been reported to be associated with MGD and DED was not assessed as part of this study." (Page 23; Line – 501-502)

REVIEWER #2:

The study titled "Association of Dry Eye Disease and Sun Exposure in Geographically Diverse Populations of India: The SEED (Sun Exposure, Environment and Dry eye disease) Study - Second Report of the ICMR-EYE SEE Study Group" is a very interesting read. The authors can address the following issues to improve the quality of the manuscript:

Authors: We are grateful to the reviewer for taking interest in our paper and providing a list of issues to address to improve the quality of the manuscript. The action taken is explained point by point as follows-

1.If the OSDI questionnaires were administered in the local language, were the translated questionnaires validated? Was any Rasch analysis done for the translated questionnaires, that has been published previously? The OSDI is one of the main pillars of the diagnostic criteria, and there should be no uncertainty regarding its reliability.

Authors: The OSDI was translated into Hindi, Telegu and Assamese and then back translated into English. No discrepancy was observed in the process of translation and back translation. Both forward and backward translation was done and reviewed by experts in these language. Since only the translated original validated OSDI questionnaire was used, Rasch analysis was not performed. Also, various studies have previously reported the use of validated OSDI questionnaire in Indian population. These details have been added in the manuscript as follows:

"The questionnaire was interviewer administered and was translated into local language for convenience of comprehension to both the interviewer as well as participants in the three study centres. The questionnaire was translated into three Indian languages (Assamese, Hindi and Telugu) and then back translated into English by independent sets of translators

conversant with the respective languages. As it was a validated questionnaire, face validation with experts was done. The interviewers were initially trained following which a pilot study was conducted at each centre. Kappa values were calculated to assess the inter-observer variation and were found to be within the acceptable range." (Page 8; Line 144-51)

2. In the Abstract, Schirmer I is mentioned but in the definition of Dry Eye Disease in the text, there is no mention of whether Schirmer was done or if it was used for diagnosis? "OSDI was used as a screening test and participants with OSDI score ≥13 with either TBUT<10 seconds or evidence of ocular surface staining were defined as having DED."

Authors: Schirmer I test was done for all cases and this has now been added in the text in methods. Schirmer I was not used for diagnosis. The diagnosis of DED was based on diagnostic criteria of TFOS DWES II which uses Dry eye questionnaire as a screening tool and TBUT, corneal staining or tear osmolarity for diagnosis. Tear osmolarity was not performed in this study so the objective criteria used were either TBUT<10s or evidence of ocular surface staining. This has now been explained more clearly.

"Diagnosis of dry eye disease (DED) was based on the guidelines defined by TFOS DEWS II which uses Dry eye questionnaire as a screening tool and TBUT, corneal staining or tear osmolarity for diagnosis. [1] OSDI was used as a screening test and participants with OSDI score ≥13 were further assessed with objective tests that included TBUT and ocular surface staining. Tear osmolarity was not performed in this study. Hence, cases with OSDI >13 and either TBUT<10s or evidence of ocular surface staining were defined as having DED."

(Page 8; Line 137-142)

3. The authors should also elaborate on how TBUT was done. Is this Fluorescein break-up time? Or Non-invasive break-up time? How was this done in the community, using a hand-help slit lamp? If fluorescein break up was done with a cobalt blue light was it done in low-light conditions or done outdoors (is it possible to be done outdoors in daylight

with the blue light?) Because of this criteria used, it is impossible to differentiate between evaporative, mixed or aqueous deficiency dry eyes. This is very crucial missing data.

Authors: It is good that the reviewer noted that this was not adequately explained. The details of TBUT examination have now been added in the methodology section:

"All cases underwent a detailed ophthalmic evaluation including uncorrected visual acuity (UCVA) and corrected distance visual acuity (CDVA) on ETDRS chart, intraocular pressure, Schirmer I, slit lamp examination, tear film break-up time (TBUT), ocular surface staining, anterior segment examination and indirect ophthalmoscopy for fundus evaluation in a local indoor clinic set-up at the study site. TBUT was assessed the help of a hand-held slit lamp using cobalt blue filter after instillation of fluorescein stain. Home visits were conducted in special situations like a bed bound or moribund patient." (Page 7; Line 120-126)

"TBUT <10 seconds was noted in 34.5% of cases, Schirmer I < 5 mm in 27.5% and fluorescein staining in 1.7% of the population." (Page 12; Line 245-247)

4. Is it possible to have OSDI more than 13, TBUT less than 10 and no corneal staining? TFOS DEWS II recommends both symptoms and signs have to be present to be classified as DED, symptoms without signs is possible neuropathic pain and not DED. The statement in the results that "Considering an abnormal OSDI score (≥13) as a sole criterion, the prevalence of dry eye symptoms was observed in 66.4% (95% CI: 65.4% - 67.3%) of the population" is not justified, this cannot be considered dry eyes.

Authors: Yes, it is possible to have TBUT<10 and OSDI >13 in the absence of corneal staining. In fact only 1.7% of the participants in the current study showed corneal staining. We agree with the reviewer that OSDI cannot be used as a sole diagnostic criteria for DED and that the symptoms can be due to other causes as well. The sentence was written to highlight that if one went by OSDI alone, a very large percentage of people has such symptoms in the study population. The statement has now been modified as it appears it was conveying an erroneous impression from what we intended to communicate.

"An abnormal OSDI score (≥13) was observed in 66.4% (95% CI: 65.4% - 67.3%) of the population." (Page 12; Line 246-247)

However, it should be noted that a lot of studies in the past have used OSDI as the only criteria and hence to provide a comparative view the statement of OSDI based results is felt to be necessary. But, considering the fallacy of using it as the only criteria, our study used the TFOS DEWS II for diagnosis of DED as it considers both symptoms as well as signs and therefore is more reliable. This has been made more clear now to avoid confusion.

5.The inclusion criteria clearly states that the patients were >40 years of age, but this is not mentioned in the title. In India >70% of the population is LESS than 40 years old. So it is unfair to say that this sample is representative of the Indian population, at most the authors can claim that they have sampled middle aged and older Indians. If DED has a bimodal distribution the authors would not be able to pick it up. The data derived a sample representative of less than 30% of the country's population cannot be extrapolated to a population that largely has the opposite age demographics. The title should be changed for accuracy and the authors should explain why they did not chose a sample representative of the population.

Authors: We agree with the reviewer, hence the title of the study has been revised to:

"Association of Dry Eye Disease and Sun Exposure in Geographically Diverse Adult (≥40 years) Populations of India: The SEED (Sun Exposure, Environment and Dry eye disease) Study - Second Report of the ICMR-EYE SEE Study Group"

While it is true that the population chosen was not representative of the entire country's population, however it is important to understand that an important objective of the study was to assess the impact of sunlight and pollution exposure on ocular health. Using a lower cut-off age for recruitment of participants would not have allowed us to explore the effect of these factors which are expected to affect the eye slowly and gradually over time. Also, this work and report is part of a wider study where the other ocular parameters assessed in included cataract (published as the first report).

6. A recent hospital-based study also looked at the association between the presence of dry eye and sociodemographic factors (Incidence, demographics, types and risk factors of dry eye disease in India: Electronic medical records driven big data analytics report I. Ocul

Surf. 2019;17(2):250-256.), many of the risk-factors identified were similar to the current study, but it has not been cited. Irrespective of the study design it deserves mention. Why did the authors not ask about screen time or use of VDUs?

Authors: We regret the error. The details of this study have been added in the manuscript.

"It is interesting that these findings are also reflected in a hospital based study from India where an age and gender stratification showed that males were more frequently affected during the 2nd and 3rd decade of life, while females were more affected during 4th and 5th decade of life, and the sex differences were insignificant beyond the age of 60 years. [22]" (Page 18; Line 375-379)

Regarding the assessment of VDUs, we agree with the reviewer that it is an important risk factor for DED in the current scenario; however it is also important to understand that this study was conducted in rural India wherein resources are limited and use of VDUs is rare. Hence, we presumed asking a separate question related to it may not yield any additional information. This has been mentioned in the discussion as a shortcoming.

"In addition, data on usage of contact lens, eye cosmetics and visual display unit could have provided additional results; however as they are not commonly used in rural Indian population aged ≥40 years, hence was not separately assessed as a part of this study." (Page 23; Line 495-498)

7. The presentation of the data is very text-heavy, there are no visualizations in the form of figures/charts that readers can glance at and quickly grasp the findings of the study.

Authors: We are grateful for this practical tip. Four figures have now been added to the manuscript for improving the readability and easy comprehension of the results.

Figure 1 Flowchart showing the study methodology

Figure 2 Bar-graph showing age-wise stratified prevalence of dry eye disease in males and females

Figure 3 Stratification of the overall participants and participants with dry eye disease based on gender, site of residence and occupation

Figure 4 Stratification of the overall participants and participants with dry eye disease based on risk factors of smoking, sun-exposure and exposure to indoor smoke.

8. How did the authors decide on the three geographical areas? What was the rationale used? India has close to 30 states, these three regions hardly represent 3 states that account for 10% of the country's population. The heterogeneity in the prevalence between the three areas itself points towards the selection bias. "Delhi NCR (Northern plains) had the highest prevalence (41.3%) followed by Guwahati (North-eastern hilly) (24%) and Prakasam (Southern coastal) (9.9%)." A range between 9.9% to 41.3% is very wide and the possible causes for this variation should be discussed.

Authors: One of the main objectives of the study was to assess ocular health in different geographical locations of varying latitude, altitude and distance from the sea. Hence, districts with different environmental and climatic conditions were selected. Also, consideration was given to sites where reliable environmental data was available to the investigators.

High altitude and coastal region have a high ultraviolet radiation exposure, hence they were required to check for its correlation. While it is true that these three regions are very limited and hardy represent a small fraction of the country, they were chosen specifically and selectively to represent three distinct geographical areas to test the hypothesis that different environments do have different effects. The wide range is noticeable and the possible causes for this variation have been added in discussion. This includes various factors including UV radiation, sunlight, pollution, humidity, temperature and wind velocity etc which all have been highlighted in the discussion in relation to the variable prevalence of DED in the three study locations.

9. Delhi NCR is a state, Guwahati is a city and Prakasam is a district. I cannot understand the logic behind selecting these 3 sites. Either 3 cities or three districts or three states should have been sampled.

Authors: We are thankful that the reviewer's suggestion corroborates with what has been done, that three districts would be appropriate and are sorry if the choice of study locations

was not clear enough as described. Three rural districts have been sampled. All the three study locations were individual districts, each in a different geographical location identified by name which was the most prominent locality . Districts were chose to have uniformity as correctly pointed out by the reviewer. Gurgaon district of Delhi NCR, is a district, and was the chosen study location as representative for northern plains and for convenience and easy understanding has been referred to as Delhi NCR (which it is a part of) as has been now more clearly mentioned in the methodology. The study in hills was done in Kamrup district of Guwahati considering that it is a part of the same district and a well-known place that can be easily related by readers. Prakasam district was chosen to represent the southern coastal region. Another very important consideration in choosing the regions was to have sites for which the physical and environmental data was reliably available.

"A multi-centric population based cross-sectional study was conducted at three geographically diverse places in rural settings of India between 2010 and 2016. Important considerations in choosing the study sites were, to have representation of plains, hilly and coastal areas, and sites should have readily available physical and environmental data. Gurgaon district of National Capital Region (NCR) Delhi, was chosen as representative for northern plains (henceforth referred to as Delhi NCR). The study in hills was done in Kamrup district located adjacent to Guwahati, capital city of the state of Assam (henceforth referred to as Guwahati). Prakasam district was chosen to represent the southern coastal region."
(Page 6; Line 90-97)

10. What is the authors hypothesis behind the association between sun exposure and dry eyes? Does sun exposure affect the lacrimal or meibomian glands?

Authors: We hypothesise that sun exposure and other environmental factors result in oxidative stress that causes release of various inflammatory markers. This in turn can damage the conjunctival goblet cells resulting in dry eye disease. Therefore, future studies with tear inflammatory markers and conjunctival impression cytology can be planned along with obtaining history for sun exposure for a better insight in this field. We are not sure of the impact of sun exposure on the meibomian or lacrimal glands and this would require

further study. These concepts have now been mentioned in the discussion for better understanding.

"Oxidative stress is known to result in ocular surface changes and DED.[31,32] Both smoking and ultraviolet radiation are risk factors for increased oxidative stress and as a corollary can be considered as contributory risk factors for DED; as observed in our study. The role of smoking in oxidative damage to ocular structures resulting in dry eye, lenticular changes and retinal pigment epithelial cell changes has been reported in few studies.[31–34] Ocular exposure with ultraviolet radiation resulting in oxidative stress has been extensively explored in relation to corneal collagen crosslinking. [35] However, its direct impact on the ocular surface is relatively unexplored. The rise of inflammatory mediators as a consequence of oxidative stress can result in goblet cell damage and DED. Future studies evaluating changes in tear film inflammatory markers with levels of UV radiation exposure and conjunctival impression cytology can be performed to quantitatively test this hypothesis and also explore any effects on the meibomian or lacrimal glands." (Page 19-20; Line 414-425)

Additional Corrections made by the authors

Incorporating the additional information (generated by further analysis) in the abstract exceeded the word limit. Hence some minor editorial corrections have been made to adjust the text to remain within 250 words.

Association of Dry Eye Disease and Sun Exposure in Geographically Diverse Adult (≥40 years) Populations of India: The SEED (Sun Exposure, Environment and Dry eye disease) Study -

Second Report of the ICMR-EYE SEE Study Group*

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Keywords: Epidemiology; Dry Eye; Risk Factors; Age; Sex; Sunlight exposure; Smoking; Indoor smoke exposure; Environment air pollution and geographic location; Systemic diseases hypertension and diabetes.

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Abstract (250 words)

Purpose

To estimate the prevalence and determine risk factors for dry eye disease (DED) in geographically diverse regions.

Method

A population based cross-sectional study was conducted on people aged ≥ 40 years in plain, hilly and coastal areas. Dry eye assessment by objective [tear film break-up time (TBUT), Schirmer I, corneal staining] and subjective [Ocular surface disease Index (OSDI)] parameters was performed with questionnaire-based assessment of exposure to sunlight, cigarette smoke, indoor smoke. The prevalence of DED with age, sex, occupation, location, smoking, exposure to sunlight, indoor smoke, diabetes, hypertension, BMI was subjected to logistic regression analysis.

Results

9,735 people (age 54.5±0.1 years; range 40-99, males 45.5%) were included. The prevalence of DED was 26.2%, was higher in plains (41.3%) compared to hilly (24.0%) and coastal area (9.9%) ($p<0.001$) and increased with age ($p<0.001$), female gender ($p<0.001$), smoking ($p<0.001$), indoor smoke ($p<0.001$), diabetes (p-0.02), hypertension (0.001), occupations with predominant outdoor activity (p-0.013) and increasing exposure to sunlight (trend). Multi-logistic regression showed a positive association with female sex (OR-1.2, CI-1.01, 1.4), exposure to indoor smoke (OR-1.3, CI-1.1, 1.5), smoking (OR-1.2; CI-1.03, 1.3), prolonged exposure to sunlight (OR-1.8, CI-1.5, 2.2), hypertension (OR 1.3, CI-1.2, 1.4), diabetes (OR-1.2, CI-1, 1.5) and negative association with region - hilly (OR-0.5, CI-0.4, 0.6) and coastal (OR-0.2; CI-0.1, 0.2), and BMI (OR-0.8, CI-0.7, 0.9).

Conclusion

58 DED is common in population ≥40 years of age. Its prevalence is affected by extrinsic

59 (geographic location, exposure to sunlight, smoking, indoor smoke) and intrinsic (age, sex,

60 hypertension, diabetes, BMI) factors.

61

Introduction

Dry eye disease has been defined by Tear Film Ocular Surface Society Dry eye workshop II (TFOS DEWS II) as a multi-factorial disorder of the ocular surface characterized by loss of ocular homeostasis resulting in various ocular symptoms.[1] It is a major cause of ocular morbidity which usually does not directly affect vision in most cases, but does affect the quality of life markedly. Its reported prevalence varies from 5%-75%.[2–12]

The TFOS DEWS II epidemiological report concluded that DED is more common in Asians compared to Caucasians.[3] While there are numerous studies from China[5,13,14], Japan[2], Korea[6,7] and Singapore[8], there are no similar reports from India, world's second most populated country.[3] Additionally, it is hypothesized that geographic location and climate can influence the occurrence of DED; however, this has not been validated by evaluating diverse environmental conditions in a single study.[3] With the geographic and climatic variation in India, we had an opportunity to explore the effect of the same in the prevalence of DED by conducting a multi-centric study with geographic mapping approach including populations from coastal, hilly and plain areas accounting for the effect of variations in humidity and air quality index on DED. Sunlight exposure and smoke are additional risk factors for DED for which, at present, reports are inconclusive. In the current study, their effect was assessed in addition to age, sex, education, job profile, and use of protective eye wear and head gear.

We present herein, the results of, to the best of our knowledge, the first population-based study on dry eye disease from India reporting its prevalence, associated risk factors, with

the evaluation of the effect of geographical variations, an arena that has not been extensively explored previously.

Methods

A multi-centric population based cross-sectional study was conducted at three geographically diverse places in rural settings of India between 2010 and 2016. Important considerations in choosing the study sites were, to have representation of plains, hilly and coastal areas, and sites should have readily available physical and environmental data. Gurgaon district of National Capital Region (NCR) Delhi, was chosen as representative for northern plains (henceforth referred to as Delhi NCR). The study in hills was done in Kamrup district located adjacent to Guwahati, capital city of the state of Assam (henceforth referred to as Guwahati). Prakasam district was chosen to represent the southern coastal region. The study adhered to the Declaration of Helsinki. The study was approved by Institutional Ethics Committee of All India Institute of Medical Sciences, New Delhi, India (P-16/04.08.2009); Indian Institute of Public Health, Hyderabad, India (33/2011- 08-08); and Regional Institute of Ophthalmology, Guwahati, India (MC/190/2007/1098-23.02.2010). Written informed consent was obtained from all participants prior to enrollment in the study. The detailed methodology of the study has been reported previously and is outlined in Figure 1.[15]

Population

A target of 3500 participants aged ≥ 40 years from each location was set. Using census village data, the population was divided into clusters of 400-600 population each having 100-150 eligible participants. Cluster random sampling was used to select 35 clusters at each study site.

Questionnaire Schedule

House visits were conducted by trained field workers and participants were interviewed using a structured questionnaire schedule. It included questions on socio-demographic information, smoking, indoor smoke exposure, sun exposure and systemic illness. Occupation was classified as primarily indoors or outdoors. Smoking was defined as lifetime history of use of any smoked tobacco product. Indoor smoke exposure was defined as lifetime history of use of biomass fuels (coal, dung-cakes, wood) in the kitchen.

Clinical examination

All cases underwent a detailed ophthalmic evaluation including uncorrected visual acuity (UCVA) and corrected distance visual acuity (CDVA) on ETDRS chart, intra-ocular pressure, Schirmer I, slit lamp examination, tear film break-up time (TBUT), ocular surface staining, anterior segment examination and indirect ophthalmoscopy for fundus evaluation in a local indoor clinic set-up at the study site. TBUT was assessed with the help of a hand-held slit lamp using cobalt blue filter after instillation of fluorescein stain. Home visits were conducted in special situations like a bed bound or moribund patient.

Systemic examination included measurement of height, weight, random blood sugar and blood pressure (two readings taken five minutes apart). Diabetes mellitus was diagnosed if the random blood sugar level was ≥200 mg/dl or the participant was an already diagnosed case of diabetes mellitus on medical treatment.[16] Hypertension was diagnosed if systolic blood pressure (SBP) was ≥140 mm of Hg or diastolic blood pressure (DBP) was ≥90 mm of Hg or a participant was a previously diagnosed case of hypertension on medical

treatment.[17] Body mass index (BMI) was calculated as weight in kg divided by the square of height in metres.

Dry Eye Disease

Diagnosis of dry eye disease (DED) was based on the guidelines defined by TFOS DEWS II which uses dry eye questionnaire as a screening tool and TBUT, corneal staining or tear osmolarity for diagnosis. [1] OSDI was used as a screening test. Participants with OSDI score ≥13 were further assessed with objective tests that included TBUT and ocular surface staining. Tear osmolarity was not performed in this study. Cases with OSDI >13 and either TBUT< 10s or evidence of ocular surface staining were defined as having DED.

The Ocular Surface Disease Index (OSDI), a 12-item questionnaire, was used for assessment of severity of symptoms related to dry eye and its effect on vision. The questionnaire was translated into the three local languages (Assamese, Hindi and Telugu) and piloted to confirm that the items were comprehensible. These versions were then back translated into English by independent sets of translators conversant with the respective languages. The initial and back-translated versions were compared to assess linguistic validity. As it was a validated questionnaire, face validation with experts was done. The questionnaire was administered by trained interviewers. Kappa values were calculated to assess the inter-observer variation and were found to be within the acceptable range.

The response to each question in the OSDI questionnaire has a five-category Likert-type response option. The final OSDI score is calculated by the following formula:

$$\text{OSDI Score} = \frac{Total\ score}{Number\ of\ questions\ answered\ by\ the\ participants} * 25$$

Lifetime Effective Sun & Ultraviolet radiation exposure

The lifetime effective sun exposure was calculated for every individual using the following formula, based on the Melbourne visual impairment project model:

Lifetime Effective Sun Exposure = Σ [Daily hours of sun exposure without head gear + (Daily hours of sun exposure using head gear x protection factor)] x 365 x Number of years

The number of years refers to the duration from the time respondent crossed the age of 15 years and the time of examination (current age - 15). The sun-protection factors for hats, sunglasses, spectacles, and contact lenses were taken as 0.53, 0.07, 0.21 and 0.31 respectively.[18]

Climatic Parameters

The measurements of aerosol optical depth (AOD) data, total (direct + diffuse) UVA (315-400 nm) and UVB (280-315 nm) flux were noted at Delhi between October 2012 to September 2015 and compared with the satellite-based Clouds and Earth's Radiant Energy System (CERES) data products for UVA, UVB to validate the same. The measurements showed excellent agreement (r ~0.92 – 0.93) with satellite-retrieved CERES UV fluxes.[19] Hence, the satellite-based data was used for the long-term UVA, UVB and AOD values in the present study at the three locations. In addition, meteorological data for humidity, precipitation, temperature, wind speed, and air pollutants was also obtained for the three locations. Meteorological data for Prakasam (Southern coastal) was obtained from the nearest center at Vishakhapatnam (representing coastal region).

Statistical analysis

Double entry of all data was done in a Microsoft Access™ database to avoid transcription errors. Data was analyzed using Stata 13 (StataCorp, College Station, TX). Participants with incomplete information on sun exposure or ocular examination were excluded. All study participants were distributed into quintiles based on the lifetime effective sun exposure. Pearson chi-square test, t-test and Kruskal-Wallis tests were used for data that was categorical, continuous, and non-parametric continuous respectively. Risk factor comparisons were performed within-site and for combined data. P-value < 0.05 was considered statistically significant and 95% confidence intervals (CI) were calculated. Multi-variable logistic regression analysis was performed for all the factors that showed a significant association on simple logistic regression.

Results

Demographic and Basic Clinical Characteristics

A total of 12,021 individuals above 40 years of age were recruited in the study from the three locations (Delhi – 4,353; Guwahati – 4,140; Prakasam – 3,528). A comprehensive risk factor and clinical assessment for dry eye disease was completed in 81% of the recruited population (n=9,735/12,021; Delhi- 3,595; Guwahati- 3,231; Prakasam- 2,909). The participation was similar across age groups. (Supplementary Table 1) The characteristics of the participant population is shown in Table 1 and Figure 2. The mean age of the population was 54.5±0.1 years. Males constituted 45.5% and females 54.5%. The occupation included predominant outdoor activity in 82.2% of the population. No definitive history of occupational exposure to chemicals was reported by any of the participants. Diabetes mellitus was observed in 8.7% participants, with highest prevalence in Prakasam (Southern coastal) (16.2%). Hypertension was observed in 38.5% participants, with highest prevalence

in Prakasam (Southern coastal) (43.8%). Allergic conditions like asthma, skin allergy and sinusitis were observed in 0.56% of the participants (n-55/9,735). Asthma was the most common condition noted in the participants with allergic conditions (n-51/55). The BMI was ≥ 25 in 24.9% of the participants (n-2425/9,408). Smoking was reported by 36.8% of the participants with 80.9% participants being current smokers. Among the participants with history of cigarette smoking, 59.5% participants were heavy smokers (≥5 cigarettes/day). The presenting visual acuity of the better eye was ≥6/12 in 69.9% (95% CI-68.9%, 70.8%) of the participants. Mild visual impairment (<6/12-6/18) was observed in 7.8% (95% CI - 7.3%, 8.3%), moderate visual impairment (<6/18-6/60) in 17.7% (95% CI -16.9%, 18.4%), severe visual impairment (<6/60-3/60) in 1.2% (95% CI - 0.9%, 1.4%) and blindness (<3/60) in 3.5% (95% CI- 3.1%, 3.9%).

Climatic Parameters

The only available long-term data of UV is the erythemal UV irradiance data obtained from Nimbus-7 and Earth probe total ozone mapping spectrometer (TOMS) satellite during the period 1979-2005 over the entire Indian region. The study of these data over Delhi and other Indian stations show that though monthly or seasonal variations do existed but there was no significant change in the UV irradiance in the long-term.[20] In the present study, the data from ground observations as well as CERES products, as mentioned earlier, have been used. The mean values of UVA, UVB flux, aerosol optical depth (AOD) along with the major air pollutants at the mid-point of the study (2013) have been tabulated in Table 2 for all the three stations. The mean UVA and UVB exposure was higher in the coastal region as compared to the hilly region and plains.

The major air pollutants in these regions are surface SO_2, NO_2, PM_{10}, $PM_{2.5}$ and surface ozone. Concentrations of the gaseous pollutants are generally within the National Ambient Air Quality Standards (NAAQS) but particulate matter (PM_{10} and $PM_{2.5}$) is the major problem in all these areas which is significantly higher than the NAAQS values. Long-term observation suggests a rising trend of pollutants concentration at all the three centers. It was observed that the AOD, AQI, PM10 and atmospheric nitrogen oxide level was highest in Delhi NCR (Northern plains) among the three study locations while the humidity and precipitation level were lowest here highlighting that the environment in Delhi NCR (Northern plains) is relatively dry and polluted when compared to the other study sites. (Table 2) Maximum temperature and rainfall with lowest PM10 value and relatively high humidity was observed in Prakasam (Southern coastal) suggesting that it is hot and humid but the environment is relatively clean compared to other centers. Most of the parameters for air pollution for Guwahati (North-eastern hilly) were in between the two centers. The wind speed was noted to be highest in Prakasam (Southern coastal). (Table 2)

Dry Eye Disease & Socio-demographic Risk Factors

The overall prevalence of DED was 26.2% (95% CI: 25.3% - 27.1%; n=2,548/9,735) based on the TFOS DEWS II diagnostic criteria (OSDI≥13 and TBUT <10 seconds or ocular surface staining. (Table 3) TBUT < 10 seconds was noted in 34.5% of cases, Schirmer I < 5 mm in 27.5% and fluorescein staining in 1.7% of the population. An abnormal OSDI score (≥13) was observed in 66.4% (95% CI: 65.4% - 67.3%) of the population.

Analysis of OSDI questionnaire items among people with DED revealed that blurred vision was the most common symptom experienced by 94.5% (n=2,408/2,548) followed by poor vision (93.1%; n=2,371/2,548) and sensitivity to light (57.2%; n=1,458/2,548). Visual

function impairment was noted maximally while reading in 40.5% (n=1,033/2,548) followed by watching television (37.9%; n=965/2,548). The most common environmental trigger for dry eye was wind (41.2%; n=1051/2,548) followed by dry environment (36.7%; n=934/2,548). Of the cases identified to have DED, mild DED (OSDI score 13-22) was observed in 27.8% (707/2,548), moderate DED (OSDI score 23-32) in 27.9% (710/2,548) and severe DED (OSDI score >32) in 44.4% (1,131/2,548). Based on the clinical noting in the records, < 10% participants were using artificial tears.

A rising trend of prevalence of DED was observed with increasing age of the population in all the study centers as well as in the overall population (p <0.001). (Table 4) The prevalence of DED was highest in population aged ≥70 years (37.2%) and lowest in 40-49 years age group (20.7%). Females had a higher prevalence (28%) when compared to males (24%) (p <0.001) in the overall population. The difference in prevalence of DED between male and female were not statistically significant above the age of 70 years (35.6% vs. 38.8%; p-0.226). (Table 3 and Figure 3) A significant difference was observed between the prevalence of DED from the three study centers (p <0.001). Delhi NCR (Northern plains) had the highest prevalence (41.3%) followed by Guwahati (North-eastern hilly) (24%) and Prakasam (Southern coastal) (9.9%). Participants with occupation involving primarily outdoor activity (26.7%) showed a higher prevalence of DED compared to those who primarily spent time indoors (23.8%, p=0.013).

Health Behavior Risk Factors

The median life-time cumulative effective sun-exposure in the overall population was 95.6 thousand-hours (range; 7.3 thousand-hours – 314.1 thousand-hours). A rising trend of

prevalence of DED with increasing lifetime cumulative effective sun-exposure was observed. The participants with sun exposure in the fifth quintile had the highest prevalence (35.58%; 95% CI-33.5, 37.7) when compared to those in the other sub-groups, in the overall study population as well as in each of the three study centers (p <0.001). Also, participants with history of smoking and exposure to indoor smoke showed a higher prevalence (p <0.001, <0.001). (Figure 4) No difference was observed in participants with or without the use of protective eye or head gear (p=0.670). (Table 4)

Systemic Risk Factors

The prevalence of DED was higher in participants with hypertension in the overall study population (p=0.001), as well as in plains (p=0.234), hilly (p< 0.001) and coastal region (p=0.007). (Table 4) The prevalence of DED was similar in participants with newly detected hypertension not taking any treatment (28.0%) compared to those already diagnosed and on medication (28.3%) (p=0.887). The prevalence of DED was similar among diabetics and non-diabetics in each of the three sites: Delhi NCR (Northern plains) (p=0.112), Guwahati (North-eastern hilly) (p= 0.667) and Prakasam (Southern coastal) (p=0.234), but overall, it was higher among non-diabetics (p=0.023) (Table 4) The prevalence of DED was higher in participants with newly detected diabetes mellitus not taking any treatment (26.7%) compared to those previously diagnosed and already on treatment (21.5%), however the difference was not significant (p=0.105). The prevalence of DED was higher in participants with BMI < 25 (27.8%) when compared to those with BMI ≥ 25 (22.4%) (p <0.001). A detailed individual drug history for central nervous system (CNS) drugs like opioids and anti-depressants was not obtained separately in this study. However, a positive history for CNS or neuropsychiatric disorders was obtained in participants as follows: stroke (n-9), seizure

(n-4), Parkinson's disease (n-3), anxiety disorder (n-2) and depression (n-1) of whom only those with Parkinson's disease were on treatment at the time of examination.

Regression Analysis

Multiple logistic regression analysis comparing the association of DED with various risk factors for each center and the overall population is shown in Table 5. Female gender had a higher association with DED (OR-1.2; CI 1.01-1.4). Hypertension had a higher association with DED (OR 1.3; CI 1.2-1.4). People with history of smoking (OR-1.2; CI 1.03-1.3) and indoor smoke exposure (OR-1.3; CI 1.1-1.5) had a higher likelihood of having DED. Increasing lifetime cumulative effective sun exposure had a positive association with DED. However, a center wise variation was observed in the levels of these results. The population from Delhi-NCR (Northern plains) showed a positive association in the fifth quintile (OR-1.5; CI 1.2-1.9) while those from Prakasam (Southern coastal) showed a positive association in the fifth quintile (OR-2.1; CI 1.3-3.2). The participants from Guwahati (North-eastern hilly) showed a positive association in the second quintile (OR 1.3; CI- 1.0, 1.6), third quintile (OR-1.5; CI 1.1-1.9), fourth quintile (OR-1.8; CI 1.3-2.4) and fifth quintile (OR-2.8; CI 1.7-4.5) of lifetime cumulative effective sun exposure. In the overall population, a higher association was observed with fifth quintile of lifetime cumulative effective sun exposure (OR-1.8; CI 1.5-2.2) when compared to the fourth quintile (OR-1.4; CI 1.2-1.6) and third quintile (OR-1.3; CI 1.1-1.5). Assessment of study location showed that there was a lower likelihood of DED in populations from Guwahati (North-eastern hilly) (OR-0.5; CI 0.4-0.6) and Prakasam (Southern coastal) (OR-0.2; CI 0.1-0.2) when compared to Delhi-NCR (Northern plains). Analysis for BMI showed a negative association with DED (OR 0.8; CI-0.7-0.9) in the overall population. On performing additional analysis for males and females separately, gender

wise multi-logistic regression analysis, smoking was non-significant for both males and females, indoor smoke had a positive association in males (OR 1.7; CI-1.4, 2.0) only, and diabetes showed a positive association in females (OR 1.3; CI - 1.0, 1.6) only. (Supplementary table 2). Additional sub-analysis of hypertension as systolic and diastolic showed that only systolic hypertension had association with DED on multiple-logistic regression analysis. (Supplementary table 3).

Discussion

Dry eye disease is an important entity in clinical practice. It is a common reason for seeking medical help, especially in the elderly and can be quite debilitating when severe. The prevalence and associated risk factors for DED has been extensively studied. (Table 6) However, the lack of clarity in the definitive diagnostic criteria for DED prior to the TFOS DEWS II report, led to non-uniform diagnostic criteria being used in the reported studies making it difficult to make direct comparisons.[21, 22] It is difficult to assess the actual disease burden and the inter-play of risk factors in the population based on hospital based data alone and community based studies are hence much required.

The current study is the largest population-based study on dry eye disease from Asia founded on the diagnostic criteria suggested by the TFOS DEWS II. The prevalence of DED in the ≥40 years population in this study was observed as 26.2%. A previous study from North India reported a 32% prevalence of DED in a hospital based survey with OSDI questionnaire used for diagnosis.[9] However, as symptoms of OSDI are non-specific and can occur due to any ocular surface disorder, it can be fallacious to rely on OSDI as a sole criterion for diagnosis of DED; hence the TFOS DEWS II criteria were applied that take into consideration

clinical signs in addition to symptoms for DED diagnosis. Literature review suggests that the prevalence of symptomatic DED (both symptoms and signs used for diagnosis) in China is 30.1%, Korea is 8%, Spain is 11%, Iran is 8.7% and France is 10.7%.[3,5,7,10,11,23,24] The result of our study was close to that observed by Tian et al. in a study from China but higher than that reported from other parts of the world confirming a higher prevalence of DED in the south-east Asian population compared to others. [3,5,7,10,11,23,24] It is noteworthy that Shanti et al. recently reported an even higher 64% prevalence of DED in population based study from Palestine using the same diagnostic criteria as used in the current study (TFOS DEWS II).[25]

Analyzing the contributory factors, an increasing prevalence of DED was observed with increasing age in our study. The prevalence in ≥70 years population was 1.8 times higher than that observed in the 40-49 years age group. A similar trend was observed in the study by Viso et al. in a Spanish population, wherein the prevalence of DED in the 40-49-year age group was 3.6% while that in the ≥80 years age group was 20.5%.[10] Also, Vehof et al. observed a similar trend in the British population wherein the prevalence of DED increased from 2.7% in the third decade to 20.0% in the ninth decade.[26] A population based study from South Korea in participants aged 19-95 years found age to be a common risk factor for both clinically diagnosed dry eye syndrome and presence of dry eye symptoms. [7] Age related changes in the lacrimal functional unit and prolonged exposure to environmental triggers for ocular surface inflammation are some possible reasons for this age-related increase observed in prevalence of DED. The highest prevalence of DED observed in the >70 years population could be due to the cumulative impact of exposure to climatic factors and biomass fuels over the life span.

A gender wise difference was observed in the prevalence of DED in our study with a higher prevalence in females (27.7% vs. 23.6%). However, an age and gender wise stratification of prevalence of DED showed that the difference in prevalence of DED became insignificant after the age of 70 years, thus illustrating the complexity of interplay of these intrinsic factors.(Table 3) It is interesting that these findings are also reflected in a hospital based study from India where an age and gender stratification showed that males were more frequently affected during the 2nd and 3rd decade of life, while females were more affected during 4th and 5th decade of life, and the sex differences were insignificant beyond the age of 60 years. [22] Ahn et al. reported this similarly as noteworthy in their analysis of the above 40 years subset of population of the Korea National Health and Nutrition Examination Survey (2010–2012) wherein the females had a higher prevalence than males (13.6% vs. 4.9%), but females did not demonstrate an increasing prevalence with age as was seen in males in linear regression models and multivariate logistic regression analysis showed that ageing in females was protectively associated.[27] Tian et al. reported a prevalence of 33.8% in women and 24.1% in men in a Chinese population aged 20-95 years. While most of the studies report a higher prevalence of DED in females, Tong et al. reported a higher prevalence in males (8.2% vs. 4.9%) in a Malayan population.[28] However, as the study was based only on dry eye questionnaire in the absence of clinical grading, it is difficult to compare the results of this study with the present study.

Exposure to sunlight particularly ultraviolet radiation are hypothesized to be associated with the occurrence of DED with limited data available in literature. In the current study, the effect of sun exposure was evaluated and a positive association was observed with DED. A stronger association was observed between higher cumulative effective sun exposure and

the occurrence of DED (fifth quantile - OR 21.8; CI 1.5-2.2 vs second quantile- OR 1.2; CI 1.07-1.4). Um et al. in a population based study from South Korea similarly reported a positive association between DED and longer exposure to sunshine (OR 1.015; CI 1.006-1.023).[6] However, in this study average sunshine duration for the study location was used for analysis overlooking the inter-individual differences in the exposure to sunlight based on variation in the lifestyle and occupation of the individual. In the present study, an individualized approach was used for calculating the approximate cumulative lifetime effective sunlight exposure taking into account the effect of protective head gear and eye gear with the help of Melbourne formula.[18] This observed association between DED and ocular exposure to sunlight can have a strong clinical implication. Avoiding sunlight exposure to the eyes can be added to the list of factors included in the lifestyle modification which is core to the management of cases presenting with symptomatic DED.

In the present study history of smoking was found to have a positive association with DED. Previous studies have shown variable results for smoking as a risk factor for DED and a meta-analysis of available literature indicated that smoking may be associated with the risk of DED in the normal population.[29] Similarly, Moss et al. in a population based study from USA reported a positive association between smoking and DED (OR -1.44; CI 1.13-1.83) in the participants aged 43-84 years after adjusting for age and gender.[30]Hence, avoidance and cessation of smoking are worthwhile preventative and ameliorative measures to suggest in this regard.

Oxidative stress is known to result in ocular surface changes and DED.[31,32] Both smoking and ultraviolet radiation are risk factors for increased oxidative stress and as a corollary can be considered as contributory risk factors for DED; as observed in our study. The role of smoking in oxidative damage to ocular structures resulting in dry eye, lenticular changes and

retinal pigment epithelial cell changes has been reported in few studies.[31–34] Ocular exposure with ultraviolet radiation resulting in oxidative stress has been extensively explored in relation to corneal collagen crosslinking.[35] However, its direct impact on the ocular surface is relatively unexplored. The rise of inflammatory mediators as a consequence of oxidative stress can result in goblet cell damage and DED. Future studies evaluating changes in tear film inflammatory markers with levels of UV radiation exposure and conjunctival impression cytology can be performed to quantitatively test this hypothesis and also explore any effects on the meibomian or lacrimal glands.

As far as exposure to indoor smoke is concerned, as wood, biomass fuel and coal is still used by large proportion of the rural population in the world for the purpose of cooking and heating, it still remains a tangible problem.[36–39] Respiratory disorders and increased risk of cardiovascular events are the known complications of increased exposure to indoor smoke.[36–41] In the present study, a positive association was observed between exposure to indoor smoke and presence of DED. Hence, the proven associated health hazards highlight a real need to sensitize the population and step-up supportive policies to switch to smokeless fuel alternatives.

Regarding the effect of systemic diseases of hypertension and DM, both were found to be risk factors for DED in our study. Some population based studies have shown similar results while other have not. [2,42–44] Several factors can account for such variations such as inherent differences in populations studied, other linked complex factors, limitations of accuracy of determining the proper diagnosis, particularly exact duration of the illness along with full details of nature and duration of treatment in epidemiological surveys in rural

areas. However, the results do confirm that underlying presence of both hypertension and diabetes can affect the occurrence of DED and should be accounted for if needed.

As for the effect of geographic location, the prevalence of DED showed a distinct variation in our study with the highest observed prevalence in Delhi NCR (Northern plains) (41.3%) compared to Guwahati (North-eastern hilly) (24%) and Prakasam (Southern coastal) (9.9%). Various climatic and environmental factors like sun-exposure, humidity and air pollution may be responsible for the observed difference in the three study locations. Literature review suggests that studies performed in controlled environment chambers report a more stable tear film in high humidity and low ambient temperatures.[45–47] In the current study, it was observed that Prakasam (Southern coastal), the center with highest humidity, had the lowest prevalence of DED while Delhi NCR (Northern plains), the center with the lowest humidity, had the highest prevalence of DED. This highlights the inverse relation of humidity as a risk factor for DED.

Delhi NCR (Northern plains), the location with highest air pollution level had the highest prevalence of DED in the population residing in this location. Similarly, Prakasam (Southern coastal), the location with lowest air pollution level had the lowest prevalence of DED. This observation supports the notion that air pollution is a risk factor for DED. Also, the average wind speed was highest in Prakasam (Southern coastal). This may explain a reduced exposure of the ocular surface to some air pollutants and resultant low prevalence of DED. Literature review also suggests a positive association between air pollution and prevalence of DED.[6,38,48–51] Exploring the interaction of pollution variables with DED in multi-logistic regression analysis could have added valuable information. However, the pollution

variables were not individual specific as the data was collected at the city level and hence could not be assessed in multi-logistic regression analysis. For the sake of scientific rigor, further validation of this aspect may be considered in future studies with long term monitoring of indoor air quality parameters of the participants using portable devices.

As for effect of altitude, in the current study, comparatively low prevalence of DED was observed in the population from the hilly region of Guwahati. Generally, literature suggests a high prevalence of DED in natives residing in very high altitudes.[2,12–14] This difference can be because the hills of Guwahati do not have a very high altitude. Moreover, the people residing there are also exposed to riverine and char environments. Therefore, the effect of altitude could not be conclusively determined in our study and needs to be further explored by assessing populations residing in extremely high altitude.

The study has strengths of providing a large population-based dataset with evaluation of both intrinsic and extrinsic risk factors following the guidelines of TFOS DEWS II in definitions and analysis, but may be considered to have some lacunae . Lack of individualized data for the air quality parameters and absence of detailed drug history for participants with history of hypertension on medication make it difficult to ascertain the exact impact of different air quality parameters or specific environmental pollutants and if the higher observed prevalence of DED in hypertensives was due to the hypertension *per se* or an adverse effect of particular anti-hypertensive agents such as beta blockers and diuretics as is currently believed.[52,53] Recently, an association between sleep disorder, physical activity, stress factors and depression with DED has come to fore. Additional data on sleep parameters could have been added to the study; however a proper assessment of

sleep disorder requires use of validated sleep questionnaire like Pittsburgh Sleep Quality Index (27 questions) or the Epworth Sleepiness Scale (8 questions).[54,55] As this was a large population based survey with 4 independent forms to be filled requiring over one hour per participant for complete evaluation, sleep assessment was not considered feasible. In the current study, only one case suffered from depression. Detailed data for physical activity *per se* was not collected, hence it is not possible to comment on the relationship from our study. In addition, data on usage of contact lens, eye cosmetics and visual display units would have been of additional interest; however as these are not commonly used in the rural Indian population aged ≥40 years studied, hence they could not be separately assessed. Similarly, the nature, pattern and extent of Meibomian gland dysfunction (MGD) which could be a contributing factor for symptoms of DED, though evaluated clinically on slit lamp examination, was not analysed. Also, hyperlipidaemia which has been reported to be associated with MGD and DED was not assessed as part of this study. These aspects have been included in the ongoing phase 2 of the study.

Conclusion

To conclude, this study has provided reliable new information on the prevalence of dry eye in India in populations residing in geographically diverse regions and evaluated the various known risk factors for DED and sun exposure. The study has confirmed the association of DED with intrinsic factors like increasing age, female gender, BMI, hypertension and diabetes mellitus, and extrinsic factors like exposure to sunlight, smoking and indoor smoke. The place of residence and livelihood influenced the prevalence of DED which had the highest prevalence in plains when compared to hills and coastal region for which air pollution and humidity could have had important influences as the prevalence of DED was

highest in the location with highest air pollution and lowest humidity. The study highlights the importance of various extrinsic risk factors for DED which are often missed out while counselling patients presenting with DED. This information can help in advocacy, guide policy making and allocation of resources for preventive and therapeutic measures and these factors can be added to the list of lifestyle modification which is an essential component in the management of all patients of DED. It makes a strong case for counselling to minimize direct sun-exposure of eye, cease smoking, reduce indoor air pollution by using smokeless fuels and if necessary for patients severely affected, greater measures to improve living environments with avoidance of high pollution and low humidity levels. Lastly, the study has highlighted the complex interplay of a multitude of factors involved in the genesis and manifestations of DED and indicates the care needed to interpret and apply information generated by various studies.

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Conflict of Interest

The authors have no conflict of interest.

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Figure Legends

Figure 1: Flowchart showing the study methodology

Figure 2: Bar-graph showing age-wise stratified prevalence of dry eye disease in males and females

Figure 3: Stratification of the overall participants and participants with dry eye disease based on gender, site of residence and occupation

Figure 4: Stratification of the overall participants and participants with dry eye disease based on risk factors of smoking, sun-exposure and exposure to indoor smoke.

Table legends

Table 1: Demographic characteristics of participants examined for the SEED (Sun Exposure, Environment and Dry eye disease) study

Table 2: Climatic parameters at the three locations during mid-point of the study (2013)

Table 3: Prevalence (95% Confidence Intervals, CI) of Dry Eye Disease (DED) in three geographical locations of India, among population aged ≥40 years

Table 4: Site-specific prevalence of dry eye disease (DED) and its association with various risk factors

Table 5: Multiple logistic regression showing association of dry eye disease with various risk factors

Table 6: Review of literature of studies evaluating environmental risk factors for Dry Eye Disease (DED)

Supplementary Table 1: Demographic profile of the participant and non-participant population of the study

Supplementary Table 2: A gender wise multi-logistic regression analysis showing association of DED with various risk factors

Supplementary Table 3: Multivariate regression analysis showing correlation of Dry eye disease with various risk factors including systolic and diastolic hypertension

Table 1: Demographic characteristics of participants examined for the SEED (Sun Exposure, Environment and Dry eye disease) study

	Delhi-NCR (Northern Plains) n (%)	**Guwahati (North-eastern Hilly)** n (%)	**Prakasam (Southern Coastal)** n (%)	**All Centers** n (%)
Age (Years)				
Mean age (±SE)	55.3 (0.20)	53.4 (0.20)	54.6 (0.21)	54.5 (0.12)
Gender				
Male	1,614 (44.9)	1,491 (46.2)	1,321 (45.4)	4,426 (45.5)
Female	1,981 (55.1)	1,740 (53.9)	1,588 (54.6)	5,309 (54.5)
Education n (%)				
Illiterate	1,769 (49.2)	1,306 (40.4)	1,924 (66.2)	5,000 (51.4)
Studied up to primary	532 (14.8)	779 (24.1)	487 (16.7)	1,798 (18.5)
Middle School (class 6-8)	471 (13.1)	294 (9.1)	169 (5.8)	934 (9.6)
High School (class 9-12)	721 (20.1)	742 (23.0)	262 (9.0)	1,725 (17.7)
Graduation	102 (2.8)	101 (3.1)	65 (2.2)	268 (2.8)
Occupation (%)				
Primarily Indoor	569 (15.9)	102 (3.2)	1,062 (36.5)	1,733 (17.8)
Primarily Outdoor	3,021 (84.2)	3,121 (96.8)	1,847 (63.5)	7,989 (82.2)
Diabetes Mellitus (%)	206 (5.8)	166 (5.3)	460 (16.2)	832 (8.7)
Hypertension (%)	1,309 (36.7)	1,140 (35.6)	1,247 (43.8)	3,696 (38.5)
Body Mass Index (%)				
<25 kg/m^2	2554 (71.8)	2686 (85.5)	1743 (64.3)	6983 (74.2)
≥25 kg/m^2	1002 (28.1)	456 (14.5)	967 (35.7)	2425 (25.8)
Lifetime cumulative effective sun exposure (Thousand hours)				
Median	114.14	72.76	109.89	96.067
Range (min.-max.)	7.30-314.10	7.30-223.76	7.30-252.18	7.305-314.10

Table 2: Climatic parameters at the three locations in India during the mid-point of the study (2013)

Region Parameters	Delhi-NCR (Northern Plains)	Guwahati (North-eastern Hilly)	Prakasam (Southern Coastal)
UVA (mean ± SD) (Wm^{-2})	10.92 ± 3.87	11.23± 3.33	13.05 ± 3.48
UVB (mean ± SD) (Wm^{-2})	0.25 ± 0.11	0.28 ± 0.11	0.35 ± 0.10
AOD (mean ± SD)	0.64 ± 0.38	0.49 ± 0.36	0.46 + 0.19
AQI	179	127	68
Humidity (mean ± SD) (%)	65.24 ± 21.70	80.57 ± 9.09	73.94 ± 4.86
Precipitation (mm)	1085.4	1650.5	1219.2
Temperature (°C)			
Mean ± SD	24.51 ± 7.41	24.91 ± 4.77	28.03 ±2.10
Minimum	19.0	19.4	24.2
Maximum	31.8	31.1	31.8
Average Wind Speed (km/hr)	6.5	3.4	8.4
Air pollutants ($\mu g/m^3$)			
Sulfur dioxide			
Mean	4.1	7	13.4
Maximum	10.5	12	56.1
Minimum	3.4	3.2	4
Nitrogen dioxide			
Mean	63.7	15.7	18
Maximum	108.2	22.7	81.3
Minimum	31.7	9.8	8.9
PM10			
Mean	218.8	141.2	67.8
Maximum	473.5	325.7	198.4
Minimum	60.2	38	19

Footnote

NCR- National capital region; UVA- Ultraviolet-A; UVB- Ultraviolet-B; AOD- Aerosol optical depth; AQI- Air quality index; PM10- Particulate matter ≤10µm.

Table 3: Age-wise Prevalence (95% Confidence Intervals, CI) of Dry Eye Disease (DED) in three geographical locations of India, among population aged ≥40 years

	Overall		Gender				
			Male		Female		
	n	DED % (CI)	n	DED % (CI)	n	DED % (CI)	*p†*
All participants	9733	26.2 (25.3-27.1)	4,426	24.0 (22.7-25.2)	5,307	28.0 (26.8-29.2)	***<0.001***
Age Group							
40-49 years	3,998	20.7 (19.5-22.0)	1727	18.9 (17.0-20.7)	2271	22.1 (20.4-23.9)	0.011
50-59 years	2,438	26.8 (25.1-28.6)	1138	22.8 (20.4-25.3)	1300	30.3 (27.8-32.8)	0.000
60-69 years	1,981	29.1 (27.1-31.1)	900	26.8 (23.9-29.7)	1081	31.0 (28.2-33.8)	0.040
>70 years	1,316	37.2 (34.5-39.8)	661	35.6 (31.9-39.2)	655	38.8 (35-42.5)	0.226
p value*		***<0.001***		**<0.001**		**<0.001**	

Footnote

* represents p-value of comparison of prevalence across age-groups, calculated using Chi-square tests

† represents p-value of comparison of prevalence across males and females, calculated using Chi-square tests

Table 4: Site-specific prevalence of dry eye disease (DED) and its association with various risk factors

Risk Factor	Delhi NCR (Northern Plains)		Guwahati (North-eastern Hilly)		Prakasam (Southern Coastal)		Overall	
	n	DED *	N	DED *	n	DED	n	DED*
SOCIO-DEMOGRAPHIC FACTORS								
Age Group								
40-49 years	1427	461 (32.3)	1454	279 (19.2)	1117	89 (8.0)	3,998	829 (20.7)
50-59 years	881	374 (42.5)	802	200 (24.9)	755	80 (10.6)	2,438	654 (26.8)
60-69 years	746	345 (46.3)	603	162 (26.9)	632	69 (10.9)	1,981	576 (29.1)
70+ years	540	304 (56.3)	371	135 (36.4)	405	50 (12.4)	1,316	489 (37.2)
p value†		***<0.001***		***<0.001***		***0.036***		***<0.001***
Gender								
Male	1614	645 (40.0)	1491	298 (20.0)	1321	119 (9.0)	4,426	1062 (24.0)
Female	1980	839 (42.4)	1739	478 (27.5)	1588	169 (10.6)	5,307	1486 (28.0)
p value†		*0.144*		***<0.001***		*0.142*		***<0.001***
Site								
Delhi NCR/Plain	-	-	-	-	-	-	3,594	1484 (41.3)
Guwahati/Hilly	-	-	-	-	-	-	3,230	776 (24.0)
Prakasam/Coastal	-	-	-	-	-	-	2,909	288 (9.9)
p value†	-	-	-	-	-	-		***<0.001***
Occupation								
Primarily Indoor	569	259 (45.5)	101	37 (36.6)	1062	116 (10.9)	1732	412 (23.8)
Primarily Outdoor	3020	1223 (40.5)	3121	737 (23.6)	1847	172 (9.3)	7988	2132 (26.7)
p value†		***0.026***		***0.003***		*0.160*		***0.013***
HEALTH BEHAVIOR RISK FACTORS								
Smoking								
Yes	1993	874 (43.9)	723	153 (21.2)	868	71 (8.2)	3584	1098 (30.6)
No	1601	610 (38.1)	2501	622 (24.9)	2041	217 (10.6)	6143	1449 (23.6)
p value†		***<0.001***		***0.040***		***0.043***		***<0.001***
Indoor smoke exposure								
Yes	2323	997 (42.9)	2958	748 (25.3)	1651	175 (10.6)	6932	1920 (27.7)
No	1271	487 (38.3)	272	28 (10.3)	1258	113 (9.0)	2801	628 (22.4)
p value†		***0.007***		***<0.001***		*0.148*		***<0.001***
Lifetime cumulative effective sun exposure								
1st quintile	468	166 (35.5)	912	180 (19.7)	567	38 (6.7)	1947	384 (19.7)
2nd quintile	506	188 (37.2)	1186	277 (23.4)	253	15 (5.9)	1945	480 (24.7)
3rd quintile	649	248 (38.2)	682	179 (26.3)	616	50 (8.1)	1947	477 (24.5)
4th quintile	840	334 (39.8)	347	102 (29.4)	760	79 (10.4)	1947	515 (26.5)
5th quintile	1131	548 (48.5)	100	37 (37.0)	711	106 (14.9)	1942	691 (35.6)
p value†		***<0.001***		***<0.001***		***<0.001***		***<0.001***
Protective eye gear/ head gear use								
Yes	3533	1461 (41.4)	3015	728 (24.2)	2900	288 (9.9)	9448	2477 (26.2)
No	61	23 (37.7)	214	48 (22.4)	8	0 (0.0)	283	71 (25.1)
p value†		*0.566*		*0.570*		*0.348*		*0.670*

SYSTEMIC RISK FACTORS								
Diabetes Mellitus								
Yes	206	96 (46.6)	166	42 (25.3)	460	53 (11.5)	832	191 (23.0)
No	3365	1379 (41.0)	2995	714 (23.8)	2381	231 (9.7)	8741	2324 (26.6)
p value†		*0.112*		*0.667*		*0.234*		***0.023***
Hypertension								
Yes	1309	625 (47.4)	1139	311 (28.5)	1247	102 (8.2)	3695	1038 (28.1)
No	2254	849 (38.0)	2061	459 (21.7)	1599	183 (11.4)	5914	1484 (25.1)
p value†		***<0.001***		***<0.001***		***0.004***		**0.001**
Body Mass Index								
<25 kg / m^2	2553	1087 (42.6)	2686	635 (23.6)	1743	220 (12.6)	6974	1942 (27.8)
≥25 kg / m^2	1002	378 (37.7)	456	113 (24.8)	*967*	51 (5.2)	2423	542 (22.4)
p value †		***0.008***		*0.597*		**<0.001**		**<0.001**

*Note: * values represent number of participants with DED and row %; † p-value calculated using chi-square test*

Table 5: Centre-wise and overall multiple logistic regression analyses showing association of dry eye disease with various risk factors

	Delhi-NCR (Northern Plains) n= 3595		Guwahati (North-eastern Hilly) n= 3231		Prakasam (Southern Coastal) n= 2909		All Centers n= 9735	
	OR (95% CI)	**p value**	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**
Gender								
Male	1	-	1	-	1	-	1	-
Female	1.0 (0.8, 1.3)	0.889	1.4 (1.1, 1.7)	0.001	0.8 (0.4, 1.5)	0.462	1.2 (1.0, 1.4)	**0.017**
Smoking								
No	1	-	1	-	1	-	1	-
Yes	1.3 (1.1, 1.6)	**<0.001**	1.0 (0.8, 1.3)	0.739	0.7 (0.5, 1.1)	0.107	1.2 (1.0, 1.3)	**0.019**
Indoor Smoke								
No	1	-	1	-	1	-	1	-
Yes	1.4 (1.1, 1.7)	**0.014**	2.7 (1.8, 4.2)	**<0.001**	1.6 (0.8, 3.1)	0.144	1.3 (1.1, 1.5)	**0.006**
Lifetime Cumulative Effective Sun Exposure								
1st quintile	1	-	1	-	1	-	1	-
2nd quintile	1.1 (0.8, 1.4)	0.640	1.3 (1.0, 1.6)	**0.043**	0.8 (0.4, 1.6)	0.603	1.2 (1.0, 1.4)	0.056
3rd quintile	1.1 (0.9, 1.4)	0.459	1.5 (1.1, 1.9)	**0.002**	1.0 (0.7, 1.7)	0.861	1.3 (1.1, 1.5)	**0.005**
4th quintile	1.1 (0.9, 1.4)	0.382	1.8 (1.3, 2.4)	**<0.001**	1.5 (1.0, 2.3)	0.072	1.4 (1.2, 1.6)	**<0.001**
5th quintile	1.5 (1.2, 1.9)	**0.001**	2.8 (1.7, 4.5)	**<0.001**	2.1 (1.3, 3.2)	**0.001**	1.8 (1.5, 2.2)	**<0.001**
Diabetes Mellitus								
No	1	-	1	-	1	-	1	-
Yes	1.2 (0.9, 1.6)	0.205	1.0 (0.7, 1.5)	0.980	1.8 (1.3, 2.6)	**0.001**	1.2 (1.0, 1.5)	**0.031**
Hypertension								
No	1	-	1	-	1	-	1	-
Yes	1.5 (1.3, 1.7)	**<0.001**	1.3 (1.1, 1.5)	**0.009**	0.7 (0.5, 0.9)	**0.003**	1.3 (1.2, 1.4)	**<0.001**
BMI								
<25 kg/ m^2	1		1		1		1	
≥25 kg/ m^2	0.8 (0.7, 0.9)	**0.009**	1.0 (0.8, 1.3)	0.923	0.4 (0.3, 0.6)	**<0.001**	0.8 (0.7, 0.9)	**<0.001**
Site								
Delhi NCR/Plain	-		-		-		1	-
Guwahati/Hilly	-		-		-		0.5 (0.4, 0.6)	**<0.001**
Prakasam/Coastal	-		-		-		0.2 (0.1, 0.2)	**<0.001**

Footnotes

Note: Only participants with dry eye disease on clinical evaluation were assessed and participants with no dry eye disease were included as controls. OR=Odd Ratio; CI=Confidence Interval; NCR-National capital region.

The values of OR and CI have been rounded off to first decimal place.

Independent variables include: Gender, Smoking, Indoor Smoke, Lifetime cumulative effective sun exposure, diabetes mellitus, hypertension and site of study

778 **Table 6: Review of literature of studies evaluating environmental risk factors for Dry Eye Disease (DED)**

Author	Type of Study	Sample Size	Site of Study	Study population	Age (mean)	Gender (M/F)	Diagnostic criteria	Prevalence	Risk Factors Assessed	Results
Um et al.[6], 2014	Population based Cross-sectional study	16,431	South Korea	>30 years age of the 5th KNHANES	NA	43:57	Previously diagnosed by ophthalmologist with presence of symptoms	10.4% (Diagnosed cases) 17.7% (Symptoms only)	Age, gender, sunshine exposure, region (urban/rural), city size, temperature, wind speed, humidity, sunshine duration, precipitation, air pollutants (SO_2, NO_2, CO, Ozone, PM10)	**Positive association** Age Female gender Urban area Higher temperature Longer sunshine Air pollutant- SO_2 **Negative association** Humidity
Galor et al.[48], 2014	Retrospective study	3,410,000	USA	Patients with ICD-9 code for DED in Veterans Administration eye between 2006-2011	NA	NA	NA	19.6%	AOD, Atmospheric pressure, Humidity, temperature	**Positive association** Air pollution Air pressure Longitude Latitude **Negative association** Wind speed Humidity
Zhong et al.[49], 2018	Retrospective study	25,818	Taiwan	Patients with ICD-9 code for DED at National Health Insurance of Taiwan from 2004 to 2013	51.1±17.7 years	31:69	NA	-	Air pollutants - CO, NO_2, Ozone, PM2.5, PM10, and SO_2, and meteorological data, Relative humidity and temperature	**Positive association** Age Female gender Air pollution – CO, NO_2 Temperature **Negative association** Relative humidity
Yu et al.[50]A, 2019	Hospital based cross sectional study	23,922	China	Cases presenting to ophthalmology clinics in China between July to December 2013	NA	49:51	Chinese dry-eye diagnostic criteria*	61.6%	Age, gender, history of kerato-refractive surgery, history of diseases (DM, arthritis and thyroid diseases), medication history, air	**Positive association** Age Female gender History of kerato-refractive surgery Arthritis, thyroid disease

									pollutant data (CO, NO_2, Ozone, PM10, PM2.5, SO_2), relative humidity, mean air pressure, and air temperature	Antihistaminic, diuretic, duodenal ulcer drug, diazepam Air Pollutants-Ozone, PM2.5, SO_2
Current study	Population based Cross-sectional study (part of ICMR-EYE SEE Study)	9,735	India-Plain/ Delhi NCR, Hilly/Guwahati, Coastal/Prakasam	Population with age ≥40 years	54.5±0.1 years	46:54	TFOS-DEWS II diagnostic criteria (OSDI≥13 and TBUT<10 or ocular surface staining> 5 corneal spots/>9 conjunctival spots)	26.2% (TBUT <10-34.5%; Schirmer I <5 -27.5%; Ocular surface staining - 1.7%; OSDI ≥ 13 - 65.4%)	Age, Gender, Occupation, DM, HTN, life-time cumulative effective sun-exposure, smoking, indoor smoke, ultra-violet radiation, humidity, temperature, air pollution (AOD, AQI, PM10, SO_2, NO_2),	**Positive association** Age Female gender HTN Lifetime cumulative effective sun-exposure Smoking Indoor smoke **Negative association** Site of residence (hills & coastal region) **Possible positive association** Air pollution – NO_2, PM10, AQI, AOD **Possible negative association** Humidity Temperature Wind speed

* (1) presence of at least one of the six symptoms: dry sensation, foreign body sensation, burning sensation, eyesight fatigue, discomfort and vision fluctuation; (2) TBUT≤5 s or Schirmer I test ≤5 mm/5 min; (3) a positive diagnosis of fluorescein staining accompanied by one of the results: 5 s<TBUT≤10 s or 5 mm/5 min < Schirmer I test ≤10 mm/5 min. The presence of (1) was essential for disease diagnosis. Subjects showing the presence of a combination of (1) and (2), or (1) and (3) were diagnosed with DED.

Footnotes: KNHANES - Korea National Health and Nutrition Examination Survey; SO_2 - Sulphur dioxide; NO_2 - Nitrogen dioxide; CO - Carbon mono-oxide; PM10 - Particulate matter 10 µm; ICD - International classification of disease; DED - Dry eye disease; AOD- aerosol optical depth; PM2.5 - Particulate matter 2.5 µm; NCR- National capital region; DM - Diabetes mellitus; OSDI- Ocular Surface Disease Index; TBUT- Tear break up time; HTN –Hypertension; AQI-Air quality index.

Supplementary Table 1: Demographic profile of the participant and non-participant population of the study

	Non-Participant n (%)	Participant n (%)	Overall n (%)
Age group			
40-49	1,169 (22.6)	3,998 (77.4)	5,167 (100)
50-59	610 (20)	2,437 (80)	3,047 (100)
60-69	320 (13.9)	1,981 (86.1)	2,301 (100)
≥70	189 (12.5)	1,317 (87.5)	1,506 (100)
Gender			
Male	1614 (26.7)	4426 (73.3)	6040 (100)
Female	674 (11.3)	5307 (88.7)	5981 (100)
Study Site			
Delhi	758 (17.4)	3595 (84.6)	4353 (100)
Guwahati	911 (22)	3229 (78)	4140 (100)
Prakasam	619 (17.5)	2909 (82.5)	3528 (100)

Supplementary Table 2: A gender wise multi-logistic regression analysis showing association of DED with various risk factors

	Male n= 4314		Female n= 5143	
	OR (95% CI)	**p value**	**OR (95% CI)**	**p value**
Smoking				
No	1	-	1	-
Yes	1.2 (1.0, 1.4)	0.112	1.1 (0.9, 1.4)	0.16
Indoor Smoke				
No	1		1	
Yes	1.7 (1.4, 2.0)	**<0.001**	1.1 (0.3, 1.4)	0.294
Lifetime Cumulative Effective Sun Exposure				
1st quintile	1	-	1	-
2nd quintile	1.2 (0.9, 1.5)	0.172	1.2 (0.9, 1.4)	0.168
3rd quintile	1.6 (1.3, 2.1)	**<0.001**	1.1 (0.9, 1.4)	0.420
4th quintile	1.6 (1.3, 2.0)	**<0.001**	1.3 (1.1, 1.7)	**0.013**
5th quintile	2.1 (1.3, 268)	**<0.001**	1.8 (1.4, 2.3)	**<0.001**
Diabetes Mellitus				
No	1	-	1	-
Yes	1.2 (0.9, 1.6)	0.226	1.3 (1.0, 1.6)	0.06
Hypertension				
No	1	-	1	-
Yes	1.3 (1.1, 1.6)	**0.001**	1.2 (1.1, 1.4)	**0.002**
BMI				
< 25	1	-	1	-
>= 25	.7 (0.5-0.8)	**<0.001**	0.8 (0.7-0.97)	**0.021**
Site				
Delhi NCR/Plain	1	-	1	-
Guwahati/Hilly	0.3 (0.3, 0.4)	**<0.001**	0.6 (0.5, 0.7)	**<0.001**
Prakasam/Coastal	0.2 (0.1, 0.2)	**<0.001**	0.2 (0.1, 0.2)	**<0.001**

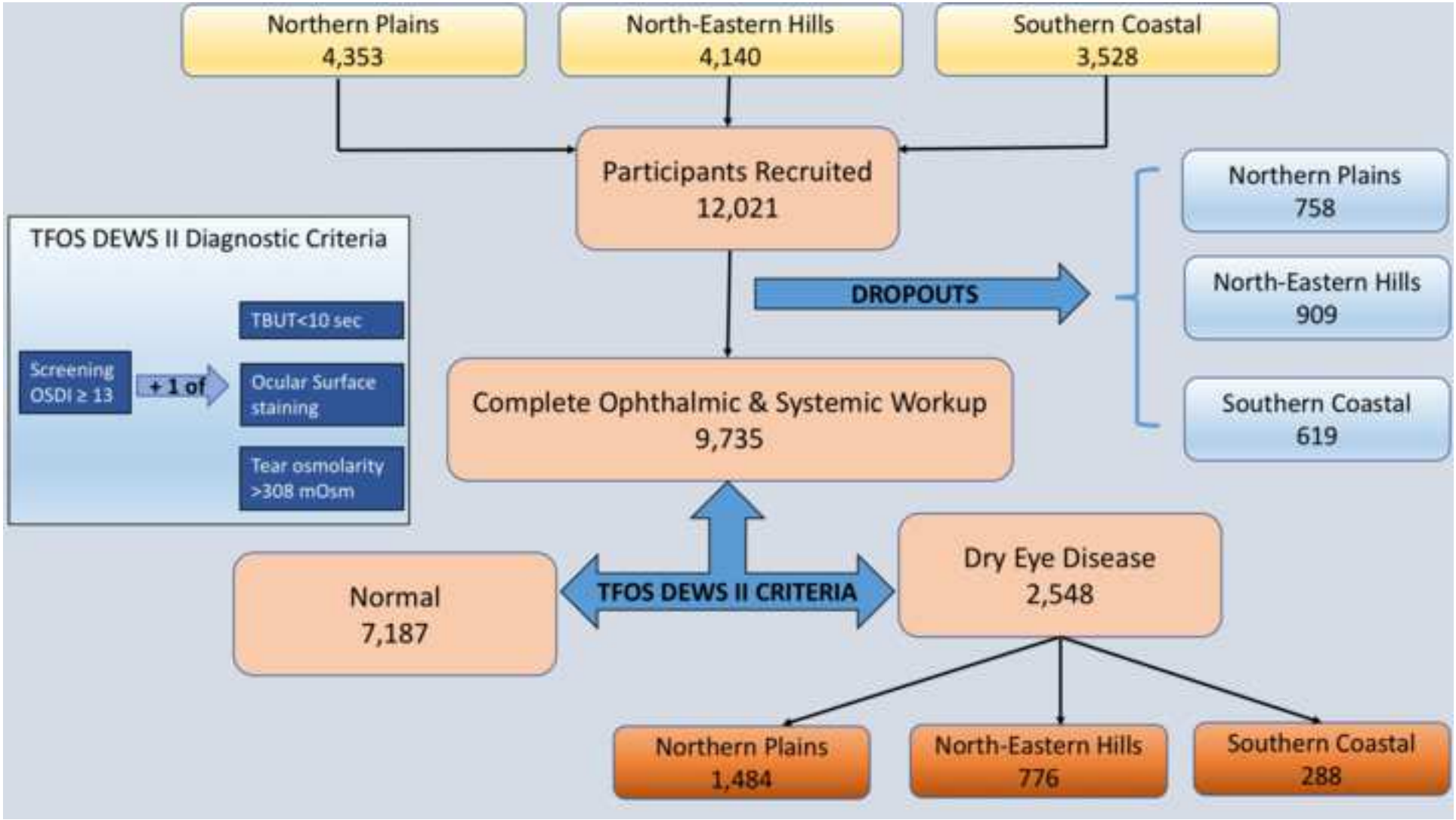
Footnotes

OR- Odd's ratio; CI- Confidence interval; NCR- National capital region

Supplementary Table 3: Multivariate regression analysis showing association of dry eye disease with various risk factors including systolic and diastolic hypertension

	Delhi n= 3534		Guwahati n= 3065		Prakasam n= 2620		Overall Population n= 9219	
	OR (95% CI)	**p value**	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**
Gender								
Male	1		1		1		1	
Female	1.0 (0.8, 1.3)	0.860	1.4 (1.1, 1.7)	**0.001**	0.8 (0.4, 1.5)	0.446	1.2 (1.0,1.4)	**0.014**
Smoking								
No	1		1		1		1	
Yes	1.3 (1.1, 1.6)	**<0.001**	1.0 (0.8, 1.3)	0.811	0.7 (0.5, 1.1)	0.092	1.2 (1.0, 1.3)	**0.022**
Indoor Smoke								
No	1		1		1		1	
Yes	1.4 (1.1, 1.7)	**0.012**	2.7 (1.8, 4.2)	**<0.001**	1.6 (0.9, 3.1)	0.141	1.3 (1.1, 1.5)	**0.004**
Lifetime Cumulative Effective Sun Exposure								
1st quintile	1		1		1		1	
2nd quintile	1.1 (0.8, 1.4)	0.524	1.2 (1.0, 1.6)	**0.047**	0.8 (0.4, 1.6)	0.595	1.2 (1.0, 1.4)	**0.056**
3rd quintile	1.1 (0.9, 1.4)	0.368	1.5 (1.1, 1.9)	**0.003**	1.0 (0.7, 1.7)	0.861	1.3 (1.1, 1.5)	**0.005**
4th quintile	1.1 (0.9, 1.5)	0.280	1.8 (1.4, 2.5)	**<0.001**	1.5 (1.0, 2.3)	0.061	1.4 (1.2, 1.7)	**<0.001**
5th quintile	1.5 (1.2, 1.9)	**<0.001**	2.9 (1.8, 4.6)	**<0.001**	2.1 (1.4, 3.3)	0.001	1.9 (1.6, 2.2)	**<0.001**
Diabetes Mellitus								
No	1		1		1		1	
Yes	1.2 (0.9, 1.7)	0.161	1.0 (0.7, 1.5)	0.984	1.7 (1.2, 2.5)	**0.002**	1.3 (1.0, 1.5)	**0.017**
Systolic Hypertension								
No	1		1		1		1	
Yes	1.4 (1.2, 1.6)	**<0.001**	1.1 (0.9, 1.4)	0.243	0.6 (0.5, 0.9)	**0.009**	1.2 (1.0, 1.3)	**0.010**
Diastolic Hypertension								
No	1		1		1		1	
Yes	1.1 (0.9, 1.4)	0.305	1.2 (0.9, 1.6)	0.290	1.0 (0.6, 1.6)	0.990	1.1 (1.0, 1.3)	0.111
BMI								
<25 kg/ m^2	1		1		1		1	
≥25 kg/ m^2	0.8 (0.7, 0.9)	**0.007**	1.0 (0.8, 1.3)	0.789	0.4 (0.3, 0.5)	**<0.001**	0.8 (0.7, 0.9)	**<0.001**
Site								
Delhi NCR/Plain	-	-	-	-	-	-	-	
Guwahati/Hilly	-	-	-	-	-	-	0.5 (0.5,0.6)	**<0.001**
Prakasam/Coastal	-	-	-	-	-	-	0.2 (0.1, 0.2)	**<0.001**

Figure



Figure

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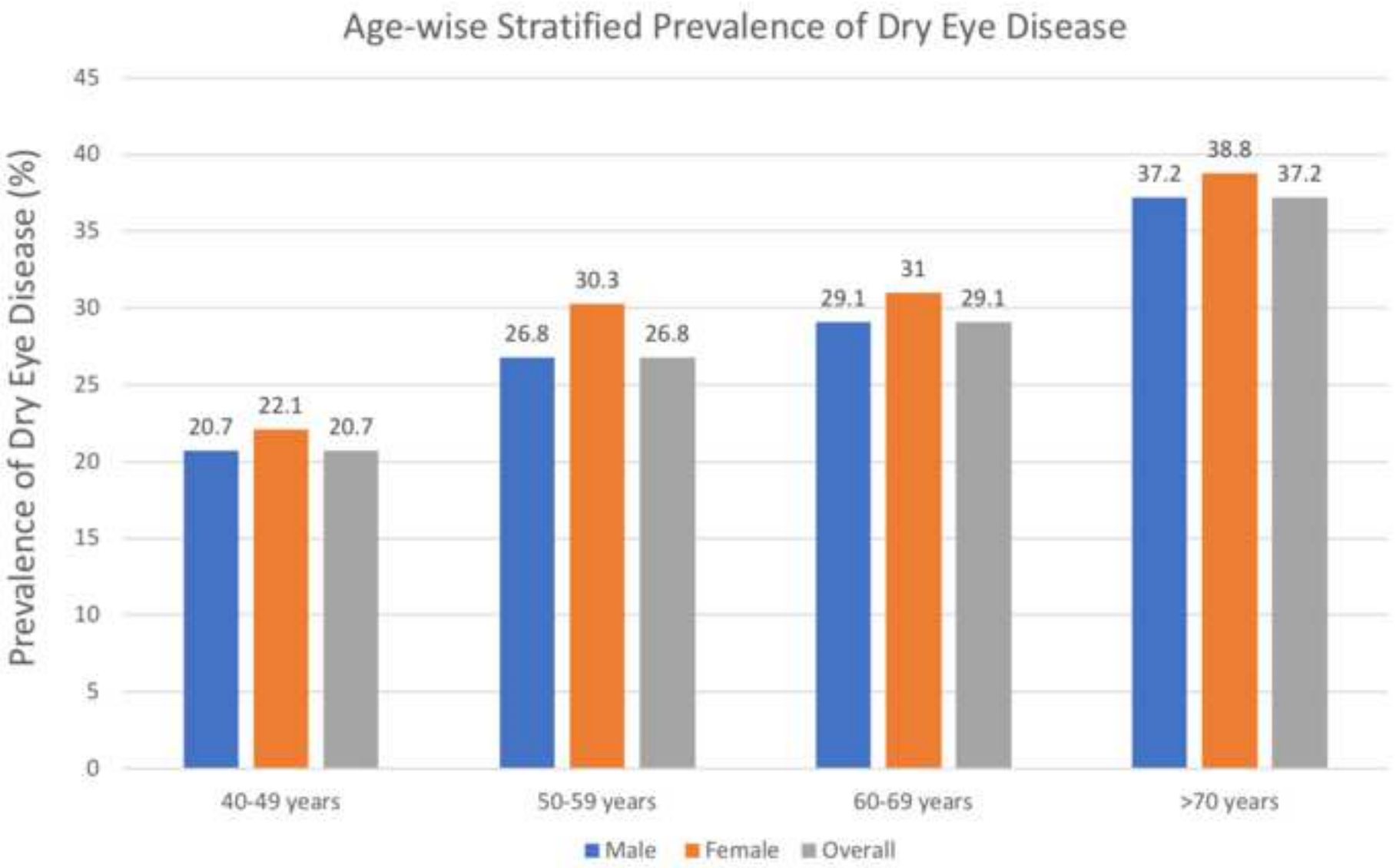

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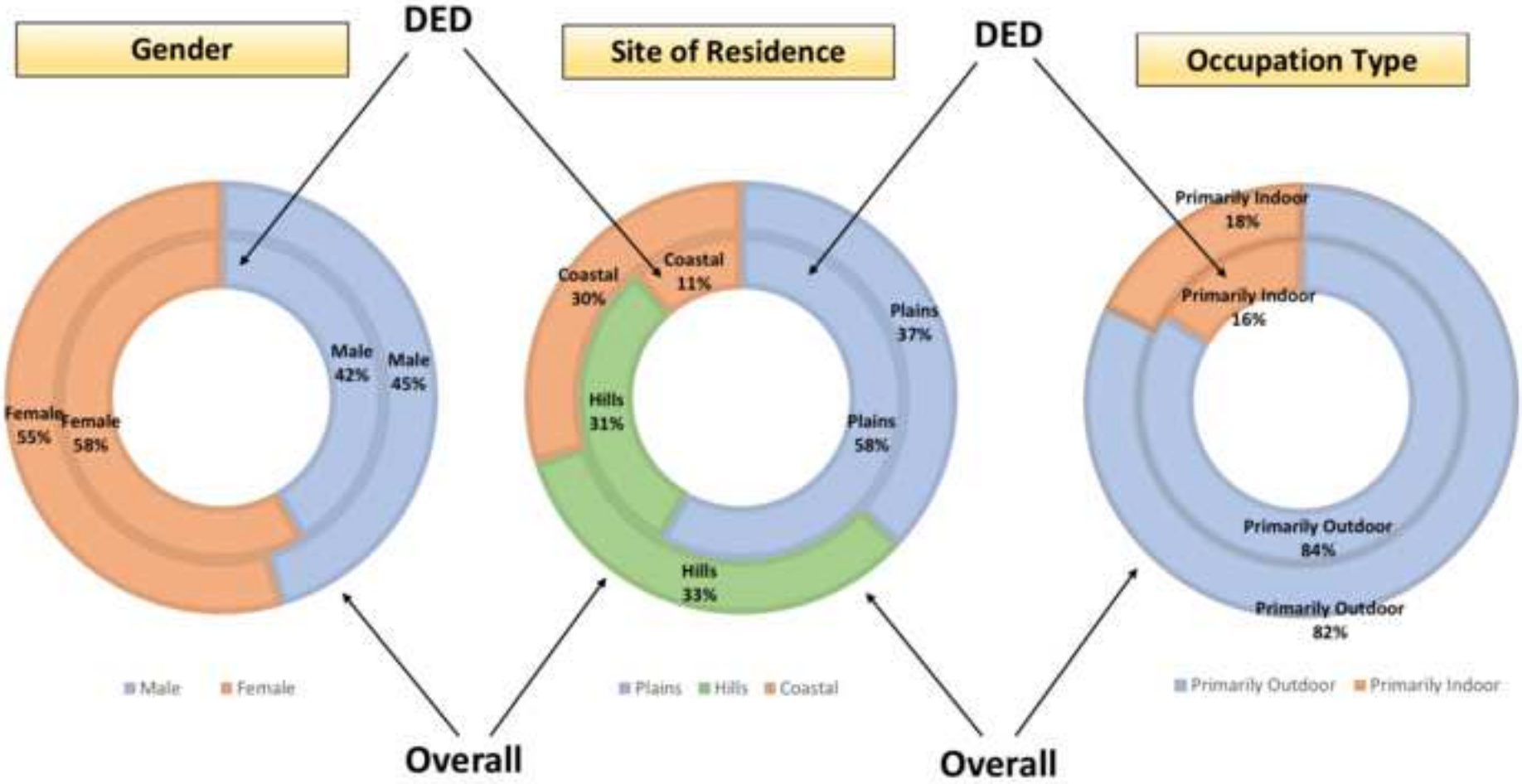

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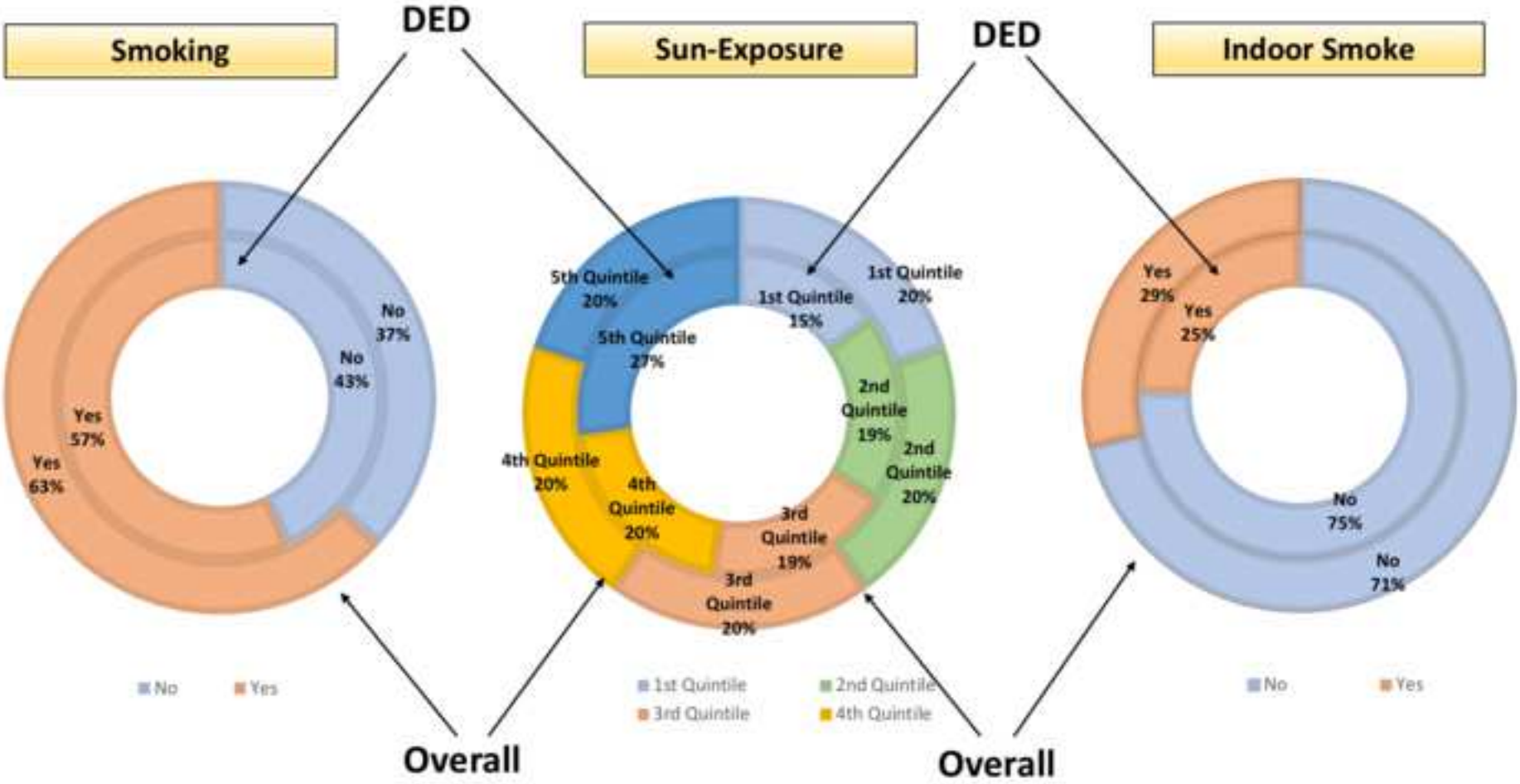

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Association of Dry Eye Disease and Sun Exposure in Geographically Diverse Adult (≥40 years) Populations of India: The SEED (Sun Exposure, Environment and Dry eye disease) Study -

Second Report of the ICMR-EYE SEE Study Group*

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Keywords: Epidemiology; Dry Eye; Risk Factors; Age; Sex; Sunlight exposure; Smoking; Indoor smoke exposure; Environment air pollution and geographic location; Systemic diseases hypertension and diabetes.

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Abstract (250 words)

Purpose

To estimate the prevalence and determine risk factors for dry eye disease (DED) in geographically diverse regions of India.

Method

A population based cross-sectional study was conducted on people aged ≥ 40 years in plain, hilly and coastal areas. Dry eye assessment by objective [tear film break-up time (TBUT), Schirmer I, corneal staining] and subjective [Ocular surface disease Index (OSDI)] parameters was performed with questionnaire-based assessment of exposure to sunlight, cigarette smoke, indoor smoke. The prevalence of DED with age, sex, occupation, location, smoking, exposure to sunlight, indoor smoke, diabetes, hypertension, was subjected to logistic regression analysis.

Results

9,735 people (age 54.5±0.1 years; range 40-99, males 45.5%) were included. The prevalence of DED was 26.2%, was higher in plains (41.3%) compared to hilly (24.0%) and coastal area (9.9%) ($p<0.001$) and increased with age ($p<0.001$), female gender ($p<0.001$), smoking ($p<0.001$), indoor smoke ($p<0.001$), diabetes (p-0.02), hypertension (0.001), occupations with predominant outdoor activity (p-0.013) and increasing exposure to sunlight (trend). Multi-logistic regression showed a positive association with female sex (OR-1.2, CI-1.01, 1.4), exposure to indoor smoke (OR-1.3, CI-1.1, 1.5), smoking (OR-1.2; CI-1.03, 1.3), prolonged exposure to sunlight (OR-1.8, CI-1.5, 2.2), hypertension (OR 1.3, CI-1.2, 1.4), diabetes (OR-1.2, CI-1, 1.5) and negative association with region - hilly (OR-0.5, CI-0.4, 0.6) and coastal (OR-0.2; CI-0.1, 0.2), and BMI (OR-0.8, CI-0.7, 0.9).

Conclusion

DED is common in population ≥40 years of age. Its prevalence is affected by extrinsic (geographic location, exposure to sunlight, smoking, indoor smoke) and intrinsic (age, sex, hypertension, diabetes, BMI) factors.

Introduction

Dry eye disease has been defined by Tear Film Ocular Surface Society Dry eye workshop II (TFOS DEWS II) as a multi-factorial disorder of the ocular surface characterized by loss of ocular homeostasis resulting in various ocular symptoms.[1] It is a major cause of ocular morbidity which usually does not directly affect vision in most cases, but does affect the quality of life markedly. Its reported prevalence varies from 5%-75%.[2–12]

The TFOS DEWS II epidemiological report concluded that DED is more common in Asians compared to Caucasians.[3] While there are numerous studies from China[5,13,14], Japan[2], Korea[6,7] and Singapore[8], there are no similar reports from India, world's second most populated country.[3] Additionally, it is hypothesized that geographic location and climate can influence the occurrence of DED; however, this has not been validated by evaluating diverse environmental conditions in a single study.[3] With the geographic and climatic variation in India, we had an opportunity to explore the effect of the same in the prevalence of DED by conducting a multi-centric study with geographic mapping approach including populations from coastal, hilly and plain areas accounting for the effect of variations in humidity and air quality index on DED. Sunlight exposure and smoke are additional risk factors for DED for which, at present, reports are inconclusive. In the current study, their effect was assessed in addition to age, sex, education, job profile, and use of protective eye wear and head gear.

We present herein, the results of, to the best of our knowledge, the first population-based study on dry eye disease from India reporting its prevalence, associated risk factors, with

the evaluation of the effect of geographical variations, an arena that has not been extensively explored previously.

Methods

A multi-centric population based cross-sectional study was conducted at three geographically diverse places in rural settings of India between 2010 and 2016. Important considerations in choosing the study sites were, to have representation of plains, hilly and coastal areas, and sites should have readily available physical and environmental data. Gurgaon district of National Capital Region (NCR) Delhi, was chosen as representative for northern plains (henceforth referred to as Delhi NCR). The study in hills was done in Kamrup district located adjacent to Guwahati, capital city of the state of Assam (henceforth referred to as Guwahati). Prakasam district was chosen to represent the southern coastal region. The study adhered to the Declaration of Helsinki. The study was approved by Institutional Ethics Committee of All India Institute of Medical Sciences, New Delhi, India (P-16/04.08.2009); Indian Institute of Public Health, Hyderabad, India (33/2011- 08-08); and Regional Institute of Ophthalmology, Guwahati, India (MC/190/2007/1098-23.02.2010). Written informed consent was obtained from all participants prior to enrollment in the study. The detailed methodology of the study has been reported previously and is outlined in Figure 1.[15]

Population

A target of 3500 participants aged ≥ 40 years from each location was set. Using census village data, the population was divided into clusters of 400-600 population each having 100-150 eligible participants. Cluster random sampling was used to select 35 clusters at each study site.

Questionnaire Schedule

House visits were conducted by trained field workers and participants were interviewed using a structured questionnaire schedule. It included questions on socio-demographic information, smoking, indoor smoke exposure, sun exposure and systemic illness. Occupation was classified as primarily indoors or outdoors. Smoking was defined as lifetime history of use of any smoked tobacco product. Indoor smoke exposure was defined as lifetime history of use of biomass fuels (coal, dung-cakes, wood) in the kitchen.

Clinical examination

All cases underwent a detailed ophthalmic evaluation including uncorrected visual acuity (UCVA) and corrected distance visual acuity (CDVA) on ETDRS chart, intra-ocular pressure, Schirmer I, slit lamp examination, tear film break-up time (TBUT), ocular surface staining, anterior segment examination and indirect ophthalmoscopy for fundus evaluation in a local indoor clinic set-up at the study site. TBUT was assessed with the help of a hand-held slit lamp using cobalt blue filter after instillation of fluorescein stain. Home visits were conducted in special situations like a bed bound or moribund patient.

Systemic examination included measurement of height, weight, random blood sugar and blood pressure (two readings taken five minutes apart). Diabetes mellitus was diagnosed if the random blood sugar level was ≥200 mg/dl or the participant was an already diagnosed case of diabetes mellitus on medical treatment.[16] Hypertension was diagnosed if systolic blood pressure (SBP) was ≥140 mm of Hg or diastolic blood pressure (DBP) was ≥90 mm of Hg or a participant was a previously diagnosed case of hypertension on medical

treatment.[17] Body mass index (BMI) was calculated as weight in kg divided by the square of height in metres.

Dry Eye Disease

Diagnosis of dry eye disease (DED) was based on the guidelines defined by TFOS DEWS II which uses dry eye questionnaire as a screening tool and TBUT, corneal staining or tear osmolarity for diagnosis. [1] OSDI was used as a screening test. Participants with OSDI score ≥13 were further assessed with objective tests that included TBUT and ocular surface staining. Tear osmolarity was not performed in this study. Cases with OSDI >13 and either TBUT< 10s or evidence of ocular surface staining were defined as having DED.

The Ocular Surface Disease Index (OSDI), a 12-item questionnaire, was used for assessment of severity of symptoms related to dry eye and its effect on vision. The questionnaire was translated into the three local languages (Assamese, Hindi and Telugu) and piloted to confirm that the items were comprehensible. These versions were then back translated into English by independent sets of translators conversant with the respective languages. The initial and back-translated versions were compared to assess linguistic validity. As it was a validated questionnaire, face validation with experts was done. The questionnaire was administered by trained interviewers. Kappa values were calculated to assess the inter-observer variation and were found to be within the acceptable range.

The response to each question in the OSDI questionnaire has a five-category Likert-type response option. The final OSDI score is calculated by the following formula:

OSDI Score = $\frac{Total\ score}{Number\ of\ questions\ answered\ by\ the\ participants} * 25$

Lifetime Effective Sun & Ultraviolet radiation exposure

The lifetime effective sun exposure was calculated for every individual using the following formula, based on the Melbourne visual impairment project model:

Lifetime Effective Sun Exposure = Σ [Daily hours of sun exposure without head gear + (Daily hours of sun exposure using head gear x protection factor)] x 365 x Number of years

The number of years refers to the duration from the time respondent crossed the age of 15 years and the time of examination (current age - 15). The sun-protection factors for hats, sunglasses, spectacles, and contact lenses were taken as 0.53, 0.07, 0.21 and 0.31 respectively.[18]

Climatic Parameters

The measurements of aerosol optical depth (AOD) data, total (direct + diffuse) UVA (315-400 nm) and UVB (280-315 nm) flux were noted at Delhi between October 2012 to September 2015 and compared with the satellite-based Clouds and Earth's Radiant Energy System (CERES) data products for UVA, UVB to validate the same. The measurements showed excellent agreement (r ~0.92 – 0.93) with satellite-retrieved CERES UV fluxes.[19] Hence, the satellite-based data was used for the long-term UVA, UVB and AOD values in the present study at the three locations. In addition, meteorological data for humidity, precipitation, temperature, wind speed, and air pollutants was also obtained for the three locations. Meteorological data for Prakasam (Southern coastal) was obtained from the nearest center at Vishakhapatnam (representing coastal region).

Statistical analysis

Double entry of all data was done in a Microsoft Access™ database to avoid transcription errors. Data was analyzed using Stata 13 (StataCorp, College Station, TX). Participants with incomplete information on sun exposure or ocular examination were excluded. All study participants were distributed into quintiles based on the lifetime effective sun exposure. Pearson chi-square test, t-test and Kruskal-Wallis tests were used for data that was categorical, continuous, and non-parametric continuous respectively. Risk factor comparisons were performed within-site and for combined data. P-value < 0.05 was considered statistically significant and 95% confidence intervals (CI) were calculated. Multi-variable logistic regression analysis was performed for all the factors that showed a significant association on simple logistic regression.

Results

Demographic and Basic Clinical Characteristics

A total of 12,021 individuals above 40 years of age were recruited in the study from the three locations (Delhi – 4,353; Guwahati – 4,140; Prakasam – 3,528). A comprehensive risk factor and clinical assessment for dry eye disease was completed in 81% of the recruited population (n=9,735/12,021; Delhi- 3,595; Guwahati- 3,231; Prakasam- 2,909). The participation was similar across age groups. (Supplementary Table 1) The characteristics of the participant population is shown in Table 1 and Figure 2. The mean age of the population was 54.5±0.1 years. Males constituted 45.5% and females 54.5%. The occupation included predominant outdoor activity in 82.2% of the population. No definitive history of occupational exposure to chemicals was reported by any of the participants. Diabetes mellitus was observed in 8.7% participants, with highest prevalence in Prakasam (Southern coastal) (16.2%). Hypertension was observed in 38.5% participants, with highest prevalence

in Prakasam (Southern coastal) (43.8%). Allergic conditions like asthma, skin allergy and sinusitis were observed in 0.56% of the participants (n-55/9,735). Asthma was the most common condition noted in the participants with allergic conditions (n-51/55). The BMI was ≥ 25 in 24.9% of the participants (n-2425/9,408). Smoking was reported by 36.8% of the participants with 80.9% participants being current smokers. Among the participants with history of cigarette smoking, 59.5% participants were heavy smokers (≥5 cigarettes/day). The presenting visual acuity of the better eye was ≥6/12 in 69.9% (95% CI-68.9%, 70.8%) of the participants. Mild visual impairment (<6/12-6/18) was observed in 7.8% (95% CI - 7.3%, 8.3%), moderate visual impairment (<6/18-6/60) in 17.7% (95% CI -16.9%, 18.4%), severe visual impairment (<6/60-3/60) in 1.2% (95% CI - 0.9%, 1.4%) and blindness (<3/60) in 3.5% (95% CI- 3.1%, 3.9%).

Climatic Parameters

The only available long-term data of UV is the erythemal UV irradiance data obtained from Nimbus-7 and Earth probe total ozone mapping spectrometer (TOMS) satellite during the period 1979-2005 over the entire Indian region. The study of these data over Delhi and other Indian stations show that though monthly or seasonal variations do existed but there was no significant change in the UV irradiance in the long-term.[20] In the present study, the data from ground observations as well as CERES products, as mentioned earlier, have been used. The mean values of UVA, UVB flux, aerosol optical depth (AOD) along with the major air pollutants at the mid-point of the study (2013) have been tabulated in Table 2 for all the three stations. The mean UVA and UVB exposure was higher in the coastal region as compared to the hilly region and plains.

The major air pollutants in these regions are surface SO_2, NO_2, PM_{10}, $PM_{2.5}$ and surface ozone. Concentrations of the gaseous pollutants are generally within the National Ambient Air Quality Standards (NAAQS) but particulate matter (PM_{10} and $PM_{2.5}$) is the major problem in all these areas which is significantly higher than the NAAQS values. Long-term observation suggests a rising trend of pollutants concentration at all the three centers. It was observed that the AOD, AQI, PM10 and atmospheric nitrogen oxide level was highest in Delhi NCR (Northern plains) among the three study locations while the humidity and precipitation level were lowest here highlighting that the environment in Delhi NCR (Northern plains) is relatively dry and polluted when compared to the other study sites. (Table 2) Maximum temperature and rainfall with lowest PM10 value and relatively high humidity was observed in Prakasam (Southern coastal) suggesting that it is hot and humid but the environment is relatively clean compared to other centers. Most of the parameters for air pollution for Guwahati (North-eastern hilly) were in between the two centers. The wind speed was noted to be highest in Prakasam (Southern coastal). (Table 2)

Dry Eye Disease & Socio-demographic Risk Factors

The overall prevalence of DED was 26.2% (95% CI: 25.3% - 27.1%; n=2,548/9,735) based on the TFOS DEWS II diagnostic criteria (OSDI≥13 and TBUT <10 seconds or ocular surface staining. (Table 3) TBUT < 10 seconds was noted in 34.5% of cases, Schirmer I < 5 mm in 27.5% and fluorescein staining in 1.7% of the population. An abnormal OSDI score (≥13) was observed in 66.4% (95% CI: 65.4% - 67.3%) of the population.

Analysis of OSDI questionnaire items among people with DED revealed that blurred vision was the most common symptom experienced by 94.5% (n=2,408/2,548) followed by poor vision (93.1%; n=2,371/2,548) and sensitivity to light (57.2%; n=1,458/2,548). Visual

function impairment was noted maximally while reading in 40.5% (n=1,033/2,548) followed by watching television (37.9%; n=965/2,548). The most common environmental trigger for dry eye was wind (41.2%; n=1051/2,548) followed by dry environment (36.7%; n=934/2,548). Of the cases identified to have DED, mild DED (OSDI score 13-22) was observed in 27.8% (707/2,548), moderate DED (OSDI score 23-32) in 27.9% (710/2,548) and severe DED (OSDI score >32) in 44.4% (1,131/2,548). Based on the clinical noting in the records, < 10% participants were using artificial tears.

A rising trend of prevalence of DED was observed with increasing age of the population in all the study centers as well as in the overall population (p <0.001). (Table 4) The prevalence of DED was highest in population aged ≥70 years (37.2%) and lowest in 40-49 years age group (20.7%). Females had a higher prevalence (28%) when compared to males (24%) (p <0.001) in the overall population. The difference in prevalence of DED between male and female were not statistically significant above the age of 70 years (35.6% vs. 38.8%; p-0.226). (Table 3 and Figure 3) A significant difference was observed between the prevalence of DED from the three study centers (p <0.001). Delhi NCR (Northern plains) had the highest prevalence (41.3%) followed by Guwahati (North-eastern hilly) (24%) and Prakasam (Southern coastal) (9.9%). Participants with occupation involving primarily outdoor activity (26.7%) showed a higher prevalence of DED compared to those who primarily spent time indoors (23.8%, p=0.013).

Health Behavior Risk Factors

The median life-time cumulative effective sun-exposure in the overall population was 95.6 thousand-hours (range; 7.3 thousand-hours – 314.1 thousand-hours). A rising trend of

prevalence of DED with increasing lifetime cumulative effective sun-exposure was observed. The participants with sun exposure in the fifth quintile had the highest prevalence (35.58%; 95% CI-33.5, 37.7) when compared to those in the other sub-groups, in the overall study population as well as in each of the three study centers (p <0.001). Also, participants with history of smoking and exposure to indoor smoke showed a higher prevalence (p <0.001, <0.001). (Figure 4) No difference was observed in participants with or without the use of protective eye or head gear (p=0.670). (Table 4)

Systemic Risk Factors

The prevalence of DED was higher in participants with hypertension in the overall study population (p=0.001), as well as in plains (p=0.234), hilly (p< 0.001) and coastal region (p=0.007). (Table 4) The prevalence of DED was similar in participants with newly detected hypertension not taking any treatment (28.0%) compared to those already diagnosed and on medication (28.3%) (p=0.887). The prevalence of DED was similar among diabetics and non-diabetics in each of the three sites: Delhi NCR (Northern plains) (p=0.112), Guwahati (North-eastern hilly) (p= 0.667) and Prakasam (Southern coastal) (p=0.234), but overall, it was higher among non-diabetics (p=0.023) (Table 4) The prevalence of DED was higher in participants with newly detected diabetes mellitus not taking any treatment (26.7%) compared to those previously diagnosed and already on treatment (21.5%), however the difference was not significant (p=0.105). The prevalence of DED was higher in participants with BMI < 25 (27.8%) when compared to those with BMI $\geq$ 25 (22.4%) (p <0.001). A detailed individual drug history for central nervous system (CNS) drugs like opioids and anti-depressants was not obtained separately in this study. However, a positive history for CNS or neuropsychiatric disorders was obtained in participants as follows: stroke (n-9), seizure

298 (n-4), Parkinson's disease (n-3), anxiety disorder (n-2) and depression (n-1) of whom only
299 those with Parkinson's disease were on treatment at the time of examination.
300
301 *Regression Analysis*
302 Multiple logistic regression analysis comparing the association of DED with various risk
303 factors for each center and the overall population is shown in Table 5. Female gender had a
304 higher association with DED (OR-1.2; CI 1.01-1.4). Hypertension had a higher association
305 with DED (OR 1.3; CI 1.2-1.4). People with history of smoking (OR-1.2; CI 1.03-1.3) and
306 indoor smoke exposure (OR-1.3; CI 1.1-1.5) had a higher likelihood of having DED. Increasing
307 lifetime cumulative effective sun exposure had a positive association with DED. However, a
308 center wise variation was observed in the levels of these results. The population from Delhi-
309 NCR (Northern plains) showed a positive association in the fifth quintile (OR-1.5; CI 1.2-1.9)
310 while those from Prakasam (Southern coastal) showed a positive association in the fifth
311 quintile (OR-2.1; CI 1.3-3.2). The participants from Guwahati (North-eastern hilly) showed a
312 positive association in the second quintile (OR 1.3; CI- 1.0, 1.6), third quintile (OR-1.5; CI 1.1-
313 1.9), fourth quintile (OR-1.8; CI 1.3-2.4) and fifth quintile (OR-2.8; CI 1.7-4.5) of lifetime
314 cumulative effective sun exposure. In the overall population, a higher association was
315 observed with fifth quintile of lifetime cumulative effective sun exposure (OR-1.8; CI 1.5-2.2)
316 when compared to the fourth quintile (OR-1.4; CI 1.2-1.6) and third quintile (OR-1.3; CI 1.1-
317 1.5). Assessment of study location showed that there was a lower likelihood of DED in
318 populations from Guwahati (North-eastern hilly) (OR-0.5; CI 0.4-0.6) and Prakasam
319 (Southern coastal) (OR-0.2; CI 0.1-0.2) when compared to Delhi-NCR (Northern plains).
320 Analysis for BMI showed a negative association with DED (OR 0.8; CI-0.7-0.9) in the overall
321 population. On performing additional analysis for males and females separately, gender

wise multi-logistic regression analysis, smoking was non-significant for both males and females, indoor smoke had a positive association in males (OR 1.7; CI-1.4, 2.0) only, and diabetes showed a positive association in females (OR 1.3; CI - 1.0, 1.6) only. (Supplementary table 2). Additional sub-analysis of hypertension as systolic and diastolic showed that only systolic hypertension had association with DED on multiple-logistic regression analysis. (Supplementary table 3).

Discussion

Dry eye disease is an important entity in clinical practice. It is a common reason for seeking medical help, especially in the elderly and can be quite debilitating when severe. The prevalence and associated risk factors for DED has been extensively studied. (Table 6) However, the lack of clarity in the definitive diagnostic criteria for DED prior to the TFOS DEWS II report, led to non-uniform diagnostic criteria being used in the reported studies making it difficult to make direct comparisons.[21, 22] It is difficult to assess the actual disease burden and the inter-play of risk factors in the population based on hospital based data alone and community based studies are hence much required.

The current study is the largest population-based study on dry eye disease from Asia founded on the diagnostic criteria suggested by the TFOS DEWS II. The prevalence of DED in the ≥40 years population in this study was observed as 26.2%. A previous study from North India reported a 32% prevalence of DED in a hospital based survey with OSDI questionnaire used for diagnosis.[9] However, as symptoms of OSDI are non-specific and can occur due to any ocular surface disorder, it can be fallacious to rely on OSDI as a sole criterion for diagnosis of DED; hence the TFOS DEWS II criteria were applied that take into consideration

clinical signs in addition to symptoms for DED diagnosis. Literature review suggests that the prevalence of symptomatic DED (both symptoms and signs used for diagnosis) in China is 30.1%, Korea is 8%, Spain is 11%, Iran is 8.7% and France is 10.7%.[3,5,7,10,11,23,24] The result of our study was close to that observed by Tian et al. in a study from China but higher than that reported from other parts of the world confirming a higher prevalence of DED in the south-east Asian population compared to others. [3,5,7,10,11,23,24] It is noteworthy that Shanti et al. recently reported an even higher 64% prevalence of DED in population based study from Palestine using the same diagnostic criteria as used in the current study (TFOS DEWS II).[25]

Analyzing the contributory factors, an increasing prevalence of DED was observed with increasing age in our study. The prevalence in ≥70 years population was 1.8 times higher than that observed in the 40-49 years age group. A similar trend was observed in the study by Viso et al. in a Spanish population, wherein the prevalence of DED in the 40-49-year age group was 3.6% while that in the ≥80 years age group was 20.5%.[10] Also, Vehof et al. observed a similar trend in the British population wherein the prevalence of DED increased from 2.7% in the third decade to 20.0% in the ninth decade.[26] A population based study from South Korea in participants aged 19-95 years found age to be a common risk factor for both clinically diagnosed dry eye syndrome and presence of dry eye symptoms. [7] Age related changes in the lacrimal functional unit and prolonged exposure to environmental triggers for ocular surface inflammation are some possible reasons for this age-related increase observed in prevalence of DED. The highest prevalence of DED observed in the >70 years population could be due to the cumulative impact of exposure to climatic factors and biomass fuels over the life span.

A gender wise difference was observed in the prevalence of DED in our study with a higher prevalence in females (27.7% vs. 23.6%). However, an age and gender wise stratification of prevalence of DED showed that the difference in prevalence of DED became insignificant after the age of 70 years, thus illustrating the complexity of interplay of these intrinsic factors.(Table 3) It is interesting that these findings are also reflected in a hospital based study from India where an age and gender stratification showed that males were more frequently affected during the 2^{nd} and 3^{rd} decade of life, while females were more affected during 4^{th} and 5^{th} decade of life, and the sex differences were insignificant beyond the age of 60 years. [22] Ahn et al. reported this similarly as noteworthy in their analysis of the above 40 years subset of population of the Korea National Health and Nutrition Examination Survey (2010–2012) wherein the females had a higher prevalence than males (13.6% vs. 4.9%), but females did not demonstrate an increasing prevalence with age as was seen in males in linear regression models and multivariate logistic regression analysis showed that ageing in females was protectively associated.[27] Tian et al. reported a prevalence of 33.8% in women and 24.1% in men in a Chinese population aged 20-95 years. While most of the studies report a higher prevalence of DED in females, Tong et al. reported a higher prevalence in males (8.2% vs. 4.9%) in a Malayan population.[28] However, as the study was based only on dry eye questionnaire in the absence of clinical grading, it is difficult to compare the results of this study with the present study.

Exposure to sunlight particularly ultraviolet radiation are hypothesized to be associated with the occurrence of DED with limited data available in literature. In the current study, the effect of sun exposure was evaluated and a positive association was observed with DED. A stronger association was observed between higher cumulative effective sun exposure and

394 the occurrence of DED (fifth quantile - OR 21.8; CI 1.5-2.2 vs second quantile- OR 1.2; CI
395 1.07-1.4). Um et al. in a population based study from South Korea similarly reported a
396 positive association between DED and longer exposure to sunshine (OR 1.015; CI 1.006-
397 1.023).[6] However, in this study average sunshine duration for the study location was used
398 for analysis overlooking the inter-individual differences in the exposure to sunlight based on
399 variation in the lifestyle and occupation of the individual. In the present study, an
400 individualized approach was used for calculating the approximate cumulative lifetime
401 effective sunlight exposure taking into account the effect of protective head gear and eye
402 gear with the help of Melbourne formula.[18] This observed association between DED and
403 ocular exposure to sunlight can have a strong clinical implication. Avoiding sunlight
404 exposure to the eyes can be added to the list of factors included in the lifestyle modification
405 which is core to the management of cases presenting with symptomatic DED.
406 In the present study history of smoking was found to have a positive association with DED.
407 Previous studies have shown variable results for smoking as a risk factor for DED and a
408 meta-analysis of available literature indicated that smoking may be associated with the risk
409 of DED in the normal population.[29] Similarly, Moss et al. in a population based study from
410 USA reported a positive association between smoking and DED (OR -1.44; CI 1.13-1.83) in
411 the participants aged 43-84 years after adjusting for age and gender.[30]Hence, avoidance
412 and cessation of smoking are worthwhile preventative and ameliorative measures to
413 suggest in this regard.
414 Oxidative stress is known to result in ocular surface changes and DED.[31,32] Both smoking
415 and ultraviolet radiation are risk factors for increased oxidative stress and as a corollary can
416 be considered as contributory risk factors for DED; as observed in our study. The role of
417 smoking in oxidative damage to ocular structures resulting in dry eye, lenticular changes and

418 retinal pigment epithelial cell changes has been reported in few studies.[31–34] Ocular
419 exposure with ultraviolet radiation resulting in oxidative stress has been extensively
420 explored in relation to corneal collagen crosslinking.[35] However, its direct impact on the
421 ocular surface is relatively unexplored. The rise of inflammatory mediators as a
422 consequence of oxidative stress can result in goblet cell damage and DED. Future studies
423 evaluating changes in tear film inflammatory markers with levels of UV radiation exposure
424 and conjunctival impression cytology can be performed to quantitatively test this hypothesis
425 and also explore any effects on the meibomian or lacrimal glands.
426 As far as exposure to indoor smoke is concerned, as wood, biomass fuel and coal is still used
427 by large proportion of the rural population in the world for the purpose of cooking and
428 heating, it still remains a tangible problem.[36–39] Respiratory disorders and increased risk
429 of cardiovascular events are the known complications of increased exposure to indoor
430 smoke.[36–41] In the present study, a positive association was observed between exposure
431 to indoor smoke and presence of DED. Hence, the proven associated health hazards
432 highlight a real need to sensitize the population and step-up supportive policies to switch to
433 smokeless fuel alternatives.
434
435 Regarding the effect of systemic diseases of hypertension and DM, both were found to be
436 risk factors for DED in our study. Some population based studies have shown similar results
437 while other have not. [2,42–44] Several factors can account for such variations such as
438 inherent differences in populations studied, other linked complex factors, limitations of
439 accuracy of determining the proper diagnosis, particularly exact duration of the illness along
440 with full details of nature and duration of treatment in epidemiological surveys in rural

areas. However, the results do confirm that underlying presence of both hypertension and diabetes can affect the occurrence of DED and should be accounted for if needed.

As for the effect of geographic location, the prevalence of DED showed a distinct variation in our study with the highest observed prevalence in Delhi NCR (Northern plains) (41.3%) compared to Guwahati (North-eastern hilly) (24%) and Prakasam (Southern coastal) (9.9%). Various climatic and environmental factors like sun-exposure, humidity and air pollution may be responsible for the observed difference in the three study locations. Literature review suggests that studies performed in controlled environment chambers report a more stable tear film in high humidity and low ambient temperatures.[45–47] In the current study, it was observed that Prakasam (Southern coastal), the center with highest humidity, had the lowest prevalence of DED while Delhi NCR (Northern plains), the center with the lowest humidity, had the highest prevalence of DED. This highlights the inverse relation of humidity as a risk factor for DED.

Delhi NCR (Northern plains), the location with highest air pollution level had the highest prevalence of DED in the population residing in this location. Similarly, Prakasam (Southern coastal), the location with lowest air pollution level had the lowest prevalence of DED. This observation supports the notion that air pollution is a risk factor for DED. Also, the average wind speed was highest in Prakasam (Southern coastal). This may explain a reduced exposure of the ocular surface to some air pollutants and resultant low prevalence of DED. Literature review also suggests a positive association between air pollution and prevalence of DED.[6,38,48–51] Exploring the interaction of pollution variables with DED in multi-logistic regression analysis could have added valuable information. However, the pollution

variables were not individual specific as the data was collected at the city level and hence could not be assessed in multi-logistic regression analysis. For the sake of scientific rigor, further validation of this aspect may be considered in future studies with long term monitoring of indoor air quality parameters of the participants using portable devices.

As for effect of altitude, in the current study, comparatively low prevalence of DED was observed in the population from the hilly region of Guwahati. Generally, literature suggests a high prevalence of DED in natives residing in very high altitudes.[2,12–14] This difference can be because the hills of Guwahati do not have a very high altitude. Moreover, the people residing there are also exposed to riverine and char environments. Therefore, the effect of altitude could not be conclusively determined in our study and needs to be further explored by assessing populations residing in extremely high altitude.

The study has strengths of providing a large population-based dataset with evaluation of both intrinsic and extrinsic risk factors following the guidelines of TFOS DEWS II in definitions and analysis, but may be considered to have some lacunae . Lack of individualized data for the air quality parameters and absence of detailed drug history for participants with history of hypertension on medication make it difficult to ascertain the exact impact of different air quality parameters or specific environmental pollutants and if the higher observed prevalence of DED in hypertensives was due to the hypertension *per se* or an adverse effect of particular anti-hypertensive agents such as beta blockers and diuretics as is currently believed.[52,53] Recently, an association between sleep disorder, physical activity, stress factors and depression with DED has come to fore. Additional data on sleep parameters could have been added to the study; however a proper assessment of

sleep disorder requires use of validated sleep questionnaire like Pittsburgh Sleep Quality Index (27 questions) or the Epworth Sleepiness Scale (8 questions).[54,55] As this was a large population based survey with 4 independent forms to be filled requiring over one hour per participant for complete evaluation, sleep assessment was not considered feasible. In the current study, only one case suffered from depression. Detailed data for physical activity *per se* was not collected, hence it is not possible to comment on the relationship from our study. In addition, data on usage of contact lens, eye cosmetics and visual display units would have been of additional interest; however as these are not commonly used in the rural Indian population aged ≥40 years studied, hence they could not be separately assessed. Similarly, the nature, pattern and extent of Meibomian gland dysfunction (MGD) which could be a contributing factor for symptoms of DED, though evaluated clinically on slit lamp examination, was not analysed. Also, hyperlipidaemia which has been reported to be associated with MGD and DED was not assessed as part of this study. These aspects have been included in the ongoing phase 2 of the study.

Conclusion

To conclude, this study has provided reliable new information on the prevalence of dry eye in India in populations residing in geographically diverse regions and evaluated the various known risk factors for DED and sun exposure. The study has confirmed the association of DED with intrinsic factors like increasing age, female gender, BMI, hypertension and diabetes mellitus, and extrinsic factors like exposure to sunlight, smoking and indoor smoke. The place of residence and livelihood influenced the prevalence of DED which had the highest prevalence in plains when compared to hills and coastal region for which air pollution and humidity could have had important influences as the prevalence of DED was

highest in the location with highest air pollution and lowest humidity. The study highlights the importance of various extrinsic risk factors for DED which are often missed out while counselling patients presenting with DED. This information can help in advocacy, guide policy making and allocation of resources for preventive and therapeutic measures and these factors can be added to the list of lifestyle modification which is an essential component in the management of all patients of DED. It makes a strong case for counselling to minimize direct sun-exposure of eye, cease smoking, reduce indoor air pollution by using smokeless fuels and if necessary for patients severely affected, greater measures to improve living environments with avoidance of high pollution and low humidity levels. Lastly, the study has highlighted the complex interplay of a multitude of factors involved in the genesis and manifestations of DED and indicates the care needed to interpret and apply information generated by various studies.

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Conflict of Interest

The authors have no conflict of interest.

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Figure Legends

Figure 1: Flowchart showing the study methodology

Figure 2: Bar-graph showing age-wise stratified prevalence of dry eye disease in males and females

Figure 3: Stratification of the overall participants and participants with dry eye disease based on gender, site of residence and occupation

Figure 4: Stratification of the overall participants and participants with dry eye disease based on risk factors of smoking, sun-exposure and exposure to indoor smoke.

Table legends

Table 1: Demographic characteristics of participants examined for the SEED (Sun Exposure, Environment and Dry eye disease) study

Table 2: Climatic parameters at the three locations during mid-point of the study (2013)

Table 3: Prevalence (95% Confidence Intervals, CI) of Dry Eye Disease (DED) in three geographical locations of India, among population aged ≥40 years

Table 4: Site-specific prevalence of dry eye disease (DED) and its association with various risk factors

Table 5: Multiple logistic regression showing association of dry eye disease with various risk factors

Table 6: Review of literature of studies evaluating environmental risk factors for Dry Eye Disease (DED)

Supplementary Table 1: Demographic profile of the participant and non-participant population of the study

Supplementary Table 2: A gender wise multi-logistic regression analysis showing association of DED with various risk factors

Supplementary Table 3: Multivariate regression analysis showing correlation of Dry eye disease with various risk factors including systolic and diastolic hypertension

Table 1: Demographic characteristics of participants examined for the SEED (Sun Exposure, Environment and Dry eye disease) study

	Delhi-NCR (Northern Plains) n (%)	**Guwahati (North-eastern Hilly)** n (%)	**Prakasam (Southern Coastal)** n (%)	**All Centers** n (%)
Age (Years)				
Mean age (±SE)	55.3 (0.20)	53.4 (0.20)	54.6 (0.21)	54.5 (0.12)
Gender				
Male	1,614 (44.9)	1,491 (46.2)	1,321 (45.4)	4,426 (45.5)
Female	1,981 (55.1)	1,740 (53.9)	1,588 (54.6)	5,309 (54.5)
Education n (%)				
Illiterate	1,769 (49.2)	1,306 (40.4)	1,924 (66.2)	5,000 (51.4)
Studied up to primary	532 (14.8)	779 (24.1)	487 (16.7)	1,798 (18.5)
Middle School (class 6-8)	471 (13.1)	294 (9.1)	169 (5.8)	934 (9.6)
High School (class 9-12)	721 (20.1)	742 (23.0)	262 (9.0)	1,725 (17.7)
Graduation	102 (2.8)	101 (3.1)	65 (2.2)	268 (2.8)
Occupation (%)				
Primarily Indoor	569 (15.9)	102 (3.2)	1,062 (36.5)	1,733 (17.8)
Primarily Outdoor	3,021 (84.2)	3,121 (96.8)	1,847 (63.5)	7,989 (82.2)
Diabetes Mellitus (%)	206 (5.8)	166 (5.3)	460 (16.2)	832 (8.7)
Hypertension (%)	1,309 (36.7)	1,140 (35.6)	1,247 (43.8)	3,696 (38.5)
Body Mass Index (%)				
<25 kg/m^2	2554 (71.8)	2686 (85.5)	1743 (64.3)	6983 (74.2)
≥25 kg/m^2	1002 (28.1)	456 (14.5)	967 (35.7)	2425 (25.8)
Lifetime cumulative effective sun exposure (Thousand hours)				
Median	114.14	72.76	109.89	96.067
Range (min.-max.)	7.30-314.10	7.30-223.76	7.30-252.18	7.305-314.10

Table 2: Climatic parameters at the three locations in India during the mid-point of the study (2013)

Region **Parameters**	**Delhi-NCR** **(Northern Plains)**	**Guwahati** **(North-eastern Hilly)**	**Prakasam** **(Southern Coastal)**
UVA (mean ± SD) (Wm^{-2})	10.92 ± 3.87	11.23± 3.33	13.05 ± 3.48
UVB (mean ± SD) (Wm^{-2})	0.25 ± 0.11	0.28 ± 0.11	0.35 ± 0.10
AOD (mean ± SD)	0.64 ± 0.38	0.49 ± 0.36	0.46 + 0.19
AQI	179	127	68
Humidity (mean ± SD) (%)	65.24 ± 21.70	80.57 ± 9.09	73.94 ± 4.86
Precipitation (mm)	1085.4	1650.5	1219.2
Temperature (°C)			
Mean ± SD	24.51 ± 7.41	24.91 ± 4.77	28.03 ±2.10
Minimum	19.0	19.4	24.2
Maximum	31.8	31.1	31.8
Average Wind Speed (km/hr)	6.5	3.4	8.4
Air pollutants ($\mu g/m^3$)			
Sulfur dioxide			
Mean	4.1	7	13.4
Maximum	10.5	12	56.1
Minimum	3.4	3.2	4
Nitrogen dioxide			
Mean	63.7	15.7	18
Maximum	108.2	22.7	81.3
Minimum	31.7	9.8	8.9
PM10			
Mean	218.8	141.2	67.8
Maximum	473.5	325.7	198.4
Minimum	60.2	38	19

Footnote

NCR- National capital region; UVA- Ultraviolet-A; UVB- Ultraviolet-B; AOD- Aerosol optical depth; AQI- Air quality index; PM10- Particulate matter ≤10µm.

Table 3: Age-wise Prevalence (95% Confidence Intervals, CI) of Dry Eye Disease (DED) in three geographical locations of India, among population aged ≥40 years

	Overall		Gender				
			Male		Female		
	n	DED % (CI)	n	DED % (CI)	n	DED % (CI)	*p†*
All participants	9733	26.2 (25.3-27.1)	4,426	24.0 (22.7-25.2)	5,307	28.0 (26.8-29.2)	***<0.001***
Age Group							
40-49 years	3,998	20.7 (19.5-22.0)	1727	18.9 (17.0-20.7)	2271	22.1 (20.4-23.9)	0.011
50-59 years	2,438	26.8 (25.1-28.6)	1138	22.8 (20.4-25.3)	1300	30.3 (27.8-32.8)	0.000
60-69 years	1,981	29.1 (27.1-31.1)	900	26.8 (23.9-29.7)	1081	31.0 (28.2-33.8)	0.040
>70 years	1,316	37.2 (34.5-39.8)	661	35.6 (31.9-39.2)	655	38.8 (35-42.5)	0.226
p value*		***<0.001***		**<0.001**		**<0.001**	

Footnote

* represents p-value of comparison of prevalence across age-groups, calculated using Chi-square tests

† represents p-value of comparison of prevalence across males and females, calculated using Chi-square tests

Table 4: Site-specific prevalence of dry eye disease (DED) and its association with various risk factors

Risk Factor	Delhi NCR (Northern Plains)		Guwahati (North-eastern Hilly)		Prakasam (Southern Coastal)		Overall	
	n	DED *	N	DED *	n	DED	n	DED*
SOCIO-DEMOGRAPHIC FACTORS								
Age Group								
40-49 years	1427	461 (32.3)	1454	279 (19.2)	1117	89 (8.0)	3,998	829 (20.7)
50-59 years	881	374 (42.5)	802	200 (24.9)	755	80 (10.6)	2,438	654 (26.8)
60-69 years	746	345 (46.3)	603	162 (26.9)	632	69 (10.9)	1,981	576 (29.1)
70+ years	540	304 (56.3)	371	135 (36.4)	405	50 (12.4)	1,316	489 (37.2)
p value†		***<0.001***		***<0.001***		***0.036***		***<0.001***
Gender								
Male	1614	645 (40.0)	1491	298 (20.0)	1321	119 (9.0)	4,426	1062 (24.0)
Female	1980	839 (42.4)	1739	478 (27.5)	1588	169 (10.6)	5,307	1486 (28.0)
p value†		*0.144*		***<0.001***		*0.142*		***<0.001***
Site								
Delhi NCR/Plain	-	-	-	-	-	-	3,594	1484 (41.3)
Guwahati/Hilly	-	-	-	-	-	-	3,230	776 (24.0)
Prakasam/Coastal	-	-	-	-	-	-	2,909	288 (9.9)
p value†	-	-	-	-	-	-		***<0.001***
Occupation								
Primarily Indoor	569	259 (45.5)	101	37 (36.6)	1062	116 (10.9)	1732	412 (23.8)
Primarily Outdoor	3020	1223 (40.5)	3121	737 (23.6)	1847	172 (9.3)	7988	2132 (26.7)
p value†		***0.026***		***0.003***		*0.160*		***0.013***
HEALTH BEHAVIOR RISK FACTORS								
Smoking								
Yes	1993	874 (43.9)	723	153 (21.2)	868	71 (8.2)	3584	1098 (30.6)
No	1601	610 (38.1)	2501	622 (24.9)	2041	217 (10.6)	6143	1449 (23.6)
p value†		***<0.001***		***0.040***		***0.043***		***<0.001***
Indoor smoke exposure								
Yes	2323	997 (42.9)	2958	748 (25.3)	1651	175 (10.6)	6932	1920 (27.7)
No	1271	487 (38.3)	272	28 (10.3)	1258	113 (9.0)	2801	628 (22.4)
p value†		***0.007***		***<0.001***		*0.148*		***<0.001***
Lifetime cumulative effective sun exposure								
1st quintile	468	166 (35.5)	912	180 (19.7)	567	38 (6.7)	1947	384 (19.7)
2nd quintile	506	188 (37.2)	1186	277 (23.4)	253	15 (5.9)	1945	480 (24.7)
3rd quintile	649	248 (38.2)	682	179 (26.3)	616	50 (8.1)	1947	477 (24.5)
4th quintile	840	334 (39.8)	347	102 (29.4)	760	79 (10.4)	1947	515 (26.5)
5th quintile	1131	548 (48.5)	100	37 (37.0)	711	106 (14.9)	1942	691 (35.6)
p value†		***<0.001***		***<0.001***		***<0.001***		***<0.001***
Protective eye gear/ head gear use								
Yes	3533	1461 (41.4)	3015	728 (24.2)	2900	288 (9.9)	9448	2477 (26.2)
No	61	23 (37.7)	214	48 (22.4)	8	0 (0.0)	283	71 (25.1)
p value†		*0.566*		*0.570*		*0.348*		*0.670*

SYSTEMIC RISK FACTORS								
Diabetes Mellitus								
Yes	206	96 (46.6)	166	42 (25.3)	460	53 (11.5)	832	191 (23.0)
No	3365	1379 (41.0)	2995	714 (23.8)	2381	231 (9.7)	8741	2324 (26.6)
p value†		*0.112*		*0.667*		*0.234*		***0.023***
Hypertension								
Yes	1309	625 (47.4)	1139	311 (28.5)	1247	102 (8.2)	3695	1038 (28.1)
No	2254	849 (38.0)	2061	459 (21.7)	1599	183 (11.4)	5914	1484 (25.1)
p value†		***<0.001***		***<0.001***		***0.004***		**0.001**
Body Mass Index								
<25 kg / m^2	2553	1087 (42.6)	2686	635 (23.6)	1743	220 (12.6)	6974	1942 (27.8)
≥25 kg / m^2	1002	378 (37.7)	456	113 (24.8)	*967*	51 (5.2)	2423	542 (22.4)
p value †		***0.008***		*0.597*		**<0.001**		**<0.001**

*Note: * values represent number of participants with DED and row %; † p-value calculated using chi-square test*

Table 5: Centre-wise and overall multiple logistic regression analyses showing association of dry eye disease with various risk factors

	Delhi-NCR (Northern Plains) n= 3595		Guwahati (North-eastern Hilly) n= 3231		Prakasam (Southern Coastal) n= 2909		All Centers n= 9735	
	OR (95% CI)	**p value**	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**
Gender								
Male	1	-	1	-	1	-	1	-
Female	1.0 (0.8, 1.3)	0.889	1.4 (1.1, 1.7)	0.001	0.8 (0.4, 1.5)	0.462	1.2 (1.0, 1.4)	**0.017**
Smoking								
No	1	-	1	-	1	-	1	-
Yes	1.3 (1.1, 1.6)	**<0.001**	1.0 (0.8, 1.3)	0.739	0.7 (0.5, 1.1)	0.107	1.2 (1.0, 1.3)	**0.019**
Indoor Smoke								
No	1	-	1	-	1	-	1	-
Yes	1.4 (1.1, 1.7)	**0.014**	2.7 (1.8, 4.2)	**<0.001**	1.6 (0.8, 3.1)	0.144	1.3 (1.1, 1.5)	**0.006**
Lifetime Cumulative Effective Sun Exposure								
1st quintile	1	-	1	**-**	1	-	1	-
2nd quintile	1.1 (0.8, 1.4)	0.640	1.3 (1.0, 1.6)	**0.043**	0.8 (0.4, 1.6)	0.603	1.2 (1.0, 1.4)	0.056
3rd quintile	1.1 (0.9, 1.4)	0.459	1.5 (1.1, 1.9)	**0.002**	1.0 (0.7, 1.7)	0.861	1.3 (1.1, 1.5)	**0.005**
4th quintile	1.1 (0.9, 1.4)	0.382	1.8 (1.3, 2.4)	**<0.001**	1.5 (1.0, 2.3)	0.072	1.4 (1.2, 1.6)	**<0.001**
5th quintile	1.5 (1.2, 1.9)	**0.001**	2.8 (1.7, 4.5)	**<0.001**	2.1 (1.3, 3.2)	**0.001**	1.8 (1.5, 2.2)	**<0.001**
Diabetes Mellitus								
No	1	-	1	-	1	-	1	-
Yes	1.2 (0.9, 1.6)	0.205	1.0 (0.7, 1.5)	0.980	1.8 (1.3, 2.6)	**0.001**	1.2 (1.0, 1.5)	**0.031**
Hypertension								
No	1	-	1	-	1	-	1	**-**
Yes	1.5 (1.3, 1.7)	**<0.001**	1.3 (1.1, 1.5)	**0.009**	0.7 (0.5, 0.9)	**0.003**	1.3 (1.2, 1.4)	**<0.001**
BMI								
<25 kg/ m^2	1		1		1		1	
≥25 kg/ m^2	0.8 (0.7, 0.9)	**0.009**	1.0 (0.8, 1.3)	0.923	0.4 (0.3, 0.6)	**<0.001**	0.8 (0.7, 0.9)	**<0.001**
Site								
Delhi NCR/Plain	-		-		-		1	-
Guwahati/Hilly	-		-		-		0.5 (0.4, 0.6)	**<0.001**
Prakasam/Coastal	-		-		-		0.2 (0.1, 0.2)	**<0.001**

Footnotes

Note: Only participants with dry eye disease on clinical evaluation were assessed and participants with no dry eye disease were included as controls. OR=Odd Ratio; CI=Confidence Interval; NCR-National capital region.

The values of OR and CI have been rounded off to first decimal place.

Independent variables include: Gender, Smoking, Indoor Smoke, Lifetime cumulative effective sun exposure, diabetes mellitus, hypertension and site of study

778 **Table 6: Review of literature of studies evaluating environmental risk factors for Dry Eye Disease (DED)**

Author	Type of Study	Sample Size	Site of Study	Study population	Age (mean)	Gender (M/F)	Diagnostic criteria	Prevalence	Risk Factors Assessed	Results
Um et al.[6], 2014	Population based Cross-sectional study	16,431	South Korea	>30 years age of the 5th KNHANES	NA	43:57	Previously diagnosed by ophthalmologist with presence of symptoms	10.4% (Diagnosed cases) 17.7% (Symptoms only)	Age, gender, sunshine exposure, region (urban/rural), city size, temperature, wind speed, humidity, sunshine duration, precipitation, air pollutants (SO_2, NO_2, CO, Ozone, PM10)	**Positive association** Age Female gender Urban area Higher temperature Longer sunshine Air pollutant- SO_2 **Negative association** Humidity
Galor et al.[48], 2014	Retrospective study	3,410,000	USA	Patients with ICD-9 code for DED in Veterans Administration eye between 2006-2011	NA	NA	NA	19.6%	AOD, Atmospheric pressure, Humidity, temperature	**Positive association** Air pollution Air pressure Longitude Latitude **Negative association** Wind speed Humidity
Zhong et al.[49], 2018	Retrospective study	25,818	Taiwan	Patients with ICD-9 code for DED at National Health Insurance of Taiwan from 2004 to 2013	51.1±17.7 years	31:69	NA	-	Air pollutants - CO, NO_2, Ozone, PM2.5, PM10, and SO_2, and meteorological data, Relative humidity and temperature	**Positive association** Age Female gender Air pollution – CO, NO_2 Temperature **Negative association** Relative humidity
Yu et al.[50]A, 2019	Hospital based cross sectional study	23,922	China	Cases presenting to ophthalmology clinics in China between July to December 2013	NA	49:51	Chinese dry-eye diagnostic criteria*	61.6%	Age, gender, history of kerato-refractive surgery, history of diseases (DM, arthritis and thyroid diseases), medication history, air	**Positive association** Age Female gender History of kerato-refractive surgery Arthritis, thyroid disease

									pollutant data (CO, NO_2, Ozone, PM10, PM2.5, SO_2), relative humidity, mean air pressure, and air temperature	Antihistaminic, diuretic, duodenal ulcer drug, diazepam Air Pollutants-Ozone, PM2.5, SO_2
Current study	Population based Cross-sectional study (part of ICMR-EYE SEE Study)	9,735	India-Plain/ Delhi NCR, Hilly/Guwahati, Coastal/Prakasam	Population with age ≥40 years	54.5±0.1 years	46:54	TFOS-DEWS II diagnostic criteria (OSDI≥13 and TBUT<10 or ocular surface staining> 5 corneal spots/>9 conjunctival spots)	26.2% (TBUT <10-34.5%; Schirmer I <5 -27.5%; Ocular surface staining - 1.7%; OSDI ≥ 13 - 65.4%)	Age, Gender, Occupation, DM, HTN, life-time cumulative effective sun-exposure, smoking, indoor smoke, ultra-violet radiation, humidity, temperature, air pollution (AOD, AQI, PM10, SO_2, NO_2),	**Positive association** Age Female gender HTN Lifetime cumulative effective sun-exposure Smoking Indoor smoke **Negative association** Site of residence (hills & coastal region) **Possible positive association** Air pollution – NO_2, PM10, AQI, AOD **Possible negative association** Humidity Temperature Wind speed

* (1) presence of at least one of the six symptoms: dry sensation, foreign body sensation, burning sensation, eyesight fatigue, discomfort and vision fluctuation; (2) TBUT≤5 s or Schirmer I test ≤5 mm/5 min; (3) a positive diagnosis of fluorescein staining accompanied by one of the results: 5 s<TBUT≤10 s or 5 mm/5 min < Schirmer I test ≤10 mm/5 min. The presence of (1) was essential for disease diagnosis. Subjects showing the presence of a combination of (1) and (2), or (1) and (3) were diagnosed with DED.

Footnotes: KNHANES - Korea National Health and Nutrition Examination Survey; SO_2 - Sulphur dioxide; NO_2 - Nitrogen dioxide; CO - Carbon mono-oxide; PM10 - Particulate matter 10 µm; ICD - International classification of disease; DED - Dry eye disease; AOD- aerosol optical depth; PM2.5 - Particulate matter 2.5 µm; NCR- National capital region; DM - Diabetes mellitus; OSDI- Ocular Surface Disease Index; TBUT- Tear break up time; HTN –Hypertension; AQI-Air quality index.

Supplementary Table 1: Demographic profile of the participant and non-participant population of the study

	Non-Participant n (%)	Participant n (%)	Overall n (%)
Age group			
40-49	1,169 (22.6)	3,998 (77.4)	5,167 (100)
50-59	610 (20)	2,437 (80)	3,047 (100)
60-69	320 (13.9)	1,981 (86.1)	2,301 (100)
≥70	189 (12.5)	1,317 (87.5)	1,506 (100)
Gender			
Male	1614 (26.7)	4426 (73.3)	6040 (100)
Female	674 (11.3)	5307 (88.7)	5981 (100)
Study Site			
Delhi	758 (17.4)	3595 (84.6)	4353 (100)
Guwahati	911 (22)	3229 (78)	4140 (100)
Prakasam	619 (17.5)	2909 (82.5)	3528 (100)

Supplementary Table 2: A gender wise multi-logistic regression analysis showing association of DED with various risk factors

	Male n= 4314		Female n= 5143	
	OR (95% CI)	**p value**	**OR (95% CI)**	**p value**
Smoking				
No	1	-	1	-
Yes	1.2 (1.0, 1.4)	0.112	1.1 (0.9, 1.4)	0.16
Indoor Smoke				
No	1		1	
Yes	1.7 (1.4, 2.0)	**<0.001**	1.1 (0.3, 1.4)	0.294
Lifetime Cumulative Effective Sun Exposure				
1st quintile	1	-	1	**-**
2nd quintile	1.2 (0.9, 1.5)	0.172	1.2 (0.9, 1.4)	0.168
3rd quintile	1.6 (1.3, 2.1)	**<0.001**	1.1 (0.9, 1.4)	0.420
4th quintile	1.6 (1.3, 2.0)	**<0.001**	1.3 (1.1, 1.7)	**0.013**
5th quintile	2.1 (1.3, 268)	**<0.001**	1.8 (1.4, 2.3)	**<0.001**
Diabetes Mellitus				
No	1	-	1	-
Yes	1.2 (0.9, 1.6)	0.226	1.3 (1.0, 1.6)	0.06
Hypertension				
No	1	-	1	-
Yes	1.3 (1.1, 1.6)	**0.001**	1.2 (1.1, 1.4)	**0.002**
BMI				
< 25	1	**-**	1	**-**
>= 25	.7 (0.5-0.8)	**<0.001**	0.8 (0.7-0.97)	**0.021**
Site				
Delhi NCR/Plain	1	-	1	-
Guwahati/Hilly	0.3 (0.3, 0.4)	**<0.001**	0.6 (0.5, 0.7)	**<0.001**
Prakasam/Coastal	0.2 (0.1, 0.2)	**<0.001**	0.2 (0.1, 0.2)	**<0.001**

Footnotes

OR- Odd's ratio; CI- Confidence interval; NCR- National capital region

Supplementary Table 3: Multivariate regression analysis showing association of dry eye disease with various risk factors including systolic and diastolic hypertension

	Delhi n= 3534		Guwahati n= 3065		Prakasam n= 2620		Overall Population n= 9219	
	OR (95% CI)	**p value**	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**
Gender								
Male	1		1		1		1	
Female	1.0 (0.8, 1.3)	0.860	1.4 (1.1, 1.7)	**0.001**	0.8 (0.4, 1.5)	0.446	1.2 (1.0,1.4)	**0.014**
Smoking								
No	1		1		1		1	
Yes	1.3 (1.1, 1.6)	**<0.001**	1.0 (0.8, 1.3)	0.811	0.7 (0.5, 1.1)	0.092	1.2 (1.0, 1.3)	**0.022**
Indoor Smoke								
No	1		1		1		1	
Yes	1.4 (1.1, 1.7)	**0.012**	2.7 (1.8, 4.2)	**<0.001**	1.6 (0.9, 3.1)	0.141	1.3 (1.1, 1.5)	**0.004**
Lifetime Cumulative Effective Sun Exposure								
1st quintile	1		1		1		1	
2nd quintile	1.1 (0.8, 1.4)	0.524	1.2 (1.0, 1.6)	**0.047**	0.8 (0.4, 1.6)	0.595	1.2 (1.0, 1.4)	**0.056**
3rd quintile	1.1 (0.9, 1.4)	0.368	1.5 (1.1, 1.9)	**0.003**	1.0 (0.7, 1.7)	0.861	1.3 (1.1, 1.5)	**0.005**
4th quintile	1.1 (0.9, 1.5)	0.280	1.8 (1.4, 2.5)	**<0.001**	1.5 (1.0, 2.3)	0.061	1.4 (1.2, 1.7)	**<0.001**
5th quintile	1.5 (1.2, 1.9)	**<0.001**	2.9 (1.8, 4.6)	**<0.001**	2.1 (1.4, 3.3)	0.001	1.9 (1.6, 2.2)	**<0.001**
Diabetes Mellitus								
No	1		1		1		1	
Yes	1.2 (0.9, 1.7)	0.161	1.0 (0.7, 1.5)	0.984	1.7 (1.2, 2.5)	**0.002**	1.3 (1.0, 1.5)	**0.017**
Systolic Hypertension								
No	1		1		1		1	
Yes	1.4 (1.2, 1.6)	**<0.001**	1.1 (0.9, 1.4)	0.243	0.6 (0.5, 0.9)	**0.009**	1.2 (1.0, 1.3)	**0.010**
Diastolic Hypertension								
No	1		1		1		1	
Yes	1.1 (0.9, 1.4)	0.305	1.2 (0.9, 1.6)	0.290	1.0 (0.6, 1.6)	0.990	1.1 (1.0, 1.3)	0.111
BMI								
<25 kg/ m^2	1		1		1		1	
≥25 kg/ m^2	0.8 (0.7, 0.9)	**0.007**	1.0 (0.8, 1.3)	0.789	0.4 (0.3, 0.5)	**<0.001**	0.8 (0.7, 0.9)	**<0.001**
Site								
Delhi NCR/Plain	-	-	-	-	-	-	-	
Guwahati/Hilly	-	-	-	-	-	-	0.5 (0.5,0.6)	**<0.001**
Prakasam/Coastal	-	-	-	-	-	-	0.2 (0.1, 0.2)	**<0.001**