PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The discrepancy between the subjectively reported symptoms and objectively measured clinical findings in dry eye: a population based analysis
AUTHORS	Hua, Rui; Yao, Kai; Hu, Yuedong; Chen, Lei

VERSION 1 - REVIEW

REVIEWER	Michael A. Lemp Georgetown University United States of America Serve as a consultant to the TearLab Corp, manufacturer of the TearLab osmometer in use for the diagnosis of dry eye and disease management.
REVIEW RETURNED	23-Apr-2014

GENERAL COMMENTS	This paper deals with an issue of high clinical importance i.e. the lack of concordance between objective signs and symptoms in dry eye disease. While the authors have cited number of papers in the literature, there are several recent papers which deal with this issue in detail and attempt to place the findings in a broader clinical perspective. See below. As the authors note, there are tests not performed e.g. tear osmolarity, which has been extensively investigated over the last several years. The studies cited here have not only found similar findings in clinical-based populations in the U.S. and Europe but also that none of the commonly used tests strongly correlate with each other or with symptoms. It is thought that each of these tests provides information independent of each other particularly in mild-moderate cases. In investigating the relationship of each signs and symptoms to a composite index of severity, it was found that of the objective 6 tests, only tear osmolarity results corresponded to increasing severity in a linear fashion. I think this article could be improved by reporting these findings and incorporating them into the discussion. This study provide additional information in a Chinese population which mirrors that seen in Amercan and European studies. Benjamin D. Sullivan, Leslie A. Crews,,Elisabeth M. Messmer, ,Gary N. Foulks, Kelly K. Nichols , Philipp Baenninger , Gerd Geerling ,Francisco C. Figueiredo , Michael A. Lemp. Correlations between commonly used objective signs and symptoms for the diagnosis of dry eye disease: Clinical implications. Acta Ophthalmogica, 2012 Dec 28. doi: 10.1111/aos.12012.

	Sullivan, Benjamin D. PhD; Crews, Leslie A. PhD; Sönmez, Bars MD; de la Paz, Maria F. MD; Comert, Ebru MD; Charoenrook, Victor MD; de Araujo, Aline L. MD; Pepose, Jay S. MD, PhD; Berg, Michael S. BA; Kosheleff, Valerie P. MS; Lemp, Michael A. MD Clinical Utility of Objective Tests for Dry Eye Disease: Variability Over Time and Implications for Clinical Trials and Disease Management Cornea 2012;31(9): 1000-1008. Sullivan BD, Whitmer D, Nichols KK, Tomlinson A, Foulks GN, Geerling G, Pepose JS, Kosheleff V, Porreco A, Lemp MA. An objective approach to dry eye severity. Invest Ophthalmol Vis Sci, 2010;51:6125-6130 This manuscript provides valuable new information on dry eye disease in a Chinese population. The authors are to be congratulated on a fine clinic-based study. Enlarging the discussion to include other recent findings should place their findings in a greater perspective.

REVIEWER	Barbara Caffery OD, PhD, FAAO. Toronto Eye Care Canada
REVIEW RETURNED	06-Jun-2014

GENERAL COMMENTS	I cannot understand the results. Both the written and Table reporting are confusing. This research paper is a cross sectional study of dry eye in a large group of Chinese subjects. They were chosen from a humid and an arid climate. The variables that were studied were symptoms of dry eye, fluorescein BUT and tear flow using Schirmer II. This is an important study because little is known of the prevalence of dry eye in China and its characteristics. There are many problems with the paper including some that are language related. I trust that this is easily rectified. My biggest problem comes from the lack of clear direction of the study and its process. How were subjects chosen, how were they examined and what were the results. The paper remains confusing to a clinician like me. I believe that you have a main goal of determining the correlation between signs and symptoms of dry eye. The secondary goals may be the correlation between the 2 signs that were measured, and the importance of the variables of age, sex, location and smoking in dry eye disease. This is important information that should be made clear in the paper. The following are specific areas that need correction or clarification. Abstract: Line 34: PRIMARY OUTCOME MEASURES: please add (Schirmer II) after “amount of tear secretion”. Line 37: RESULTS: The language here is difficult. The “discrepancy” is not defined. The authors should simply say that in this population

	"there was a significant….. line 38. In line 39 what do you mean by influencing factors. Were these factors associated with increased signs or symptoms of dry eye? Line 40-42: This sentence makes little sense to me. Do you mean that Schirmer and BUT did not correlate? If so state this. Do you mean they did not correlate with the group who had no symptoms and with the group who had symptoms? Line 44- Conclusions: I am not clear about the "pre-clinical phase concept". Do you mean patients who have symptoms of dry eye and yet show no aqueous deficiency or evaporative signs? Line 45: You must define the "discrepancy patients" clearly. Line 46-47: use the term break up time. Line 49: Should read "to our knowledge" this is the first……. syndrome in a large Chinese sample. Line 51: Please make sure discrepancy is defined for the reader. Line 53: How did your study show that the questionnaire actually helped. I think that your results show that there are many patients with dry eye symptoms but few with dry eye signs???? Line 56: Do you mean tear osmolarity? Also where do BMI and myocardial infarction fit into this study? I did not read about them in the screening. Introduction: Line 76: The world "always" does not apply to dry eye definitions today. Your reference (1) is old and you should use the DEWS 2007 definition here. Line 77: You are talking about risk factors here and that is the terminology that should be used. Line 79: If you wish to discuss treatments for dry eye you must include the normal techniques of drops and lid care etc. as well as omrga-3s. Line 81: Perhaps you can make this sentence clearer by saying "At present, dry eye is often ignored….." Line 90: The word" lesion" is not appropriate here. Perhaps you can call this a condition or disease or syndrome. Line 92: The purpose of your study was to determine the lack of correlation between symptoms of dry eye and two tests of dry eye. Methods: Line 95: The study was "conducted" between July and August of 2007. Line 97-98: The Zhuanghe district is located near the Bohai Sea while the Dawa district in inland. The majority of the inhabitants in

	both districts were farmers. Line 99: Is it true that the subjects were selected from the official registry by name etc? What were the inclusion and exclusion criteria used for this selection? Was age a factor? Line 102: What does it mean to select randomly? What did the door to door visit confirm? Line 103: What is an “eligible” resident? Please define this. Line 104: Who did not give valid responses? What does an invalid response look like? Line 105: How did you screen for ocular surface disease, keratitis or conjunctivitis? Line 107: Did these subjects go to the hospital for the testing? Lines 108-116: These comments are not part of Methods. They belong in Discussion. Line 117: You evaluated dry eye symptoms with the questionnaire not DES or dry eye syndrome. Refer to Table 1 here. Line 118: Leave out the words “on the”. Line 120: “Those subjects who identified 3 of 7 questions as positive were labelled as symptom positive”. Line 121-122: You mention that 2 people recorded the questionnaire results. Do you mean that 2 people conducted an in house interview of these people? If so please tell us this early in the Methods. Lines 123-129: Where is this taking place? Did they bring a slit lamp to the subject’s home? Line 128: Please state what you did to standardize the equipment etc. Line 130: This is the Schirmer II test and should be identified as such. Normally the Schirmer 1 test is used in dry eye clinics and is done first to avoid the addition of any fluid added to the eye. Line 135: Again I do not know how you kept the conditions constant. Line 139-142: The matter of Ethics should be stated at the beginning of the Methods. Line 144: geographical- spelling Results: Line 151: Your results should begin with those that pertain to your primary purpose of showing how symptoms and signs of dry eye do not correlate. Then add the risk factors for dry eye symptoms. What risk factors did you find for dry eye signs? Line 155: I think this sentence means that 42% of subjects had symptoms and no signs or signs and no symptoms. You might want to say that of the 960 subjects whose signs and symptoms did not correlate, 302 had no symptoms but objective signs and 658 had

	symptoms and no objective signs. However, I am very unclear about who reported what. Please tell me how many had symptoms, how many had low BUT and how many had low Schrimers and then tell me the correlation of these variables. Line 157: I do not understand the significant difference in the two cohorts. Which cohorts are we talking about? I do not understand Table 2. In summary, lines 155-172 are very difficult for me to understand. Discussion: Line 174: Please choose DE or DES and use it throughout the paper. Line 181-188: This section needs to be rewritten. Why are you mentioning Sjogren's syndrome when this is not the scope of this study? Line 189: You wish to discuss the problem of symptoms versus signs in dry eye disease. You suggest that one of the reasons for this discrepancy is gender. This does not make sense to me. I would like you to tell me how the population that you studied differed by gender in its presentation of symptoms and signs. Line 198: You wish to discuss the environment and dry eye disease. I think that your choice of populations in very different humidity areas is important here and should be discussed. I would not add the corneal sensitivity information as it does not relate to your study. Line 207: Why are you discussing workplace use of screens and devices when your population was mainly farmers? Line 214: You mention a study that showed a lack of correlation between 3 objective dry eye tests: Schirmer versus BUT and staining. You then say that you ALSO found differences between subjective and objective findings. This is not a true comparison. Line 219: I like the idea of describing a possible progression of dry eye. Line 226: I do not understand what you mean by saying that age was not a risk factor for DE symptoms in all samples. What samples are you taking about? Line 227: what is the discrepancy? Line 229: I am assuming that discrepancy subjects are those with signs and no symptoms or symptoms with no signs. What in your study suggests that you must treat these patients? Philosophy is fine but does this relate in any way to your study. Line 237: The study limitations must be mentioned. The biggest problem is not evaluating the ocular surface or the meibomian glands. I am not sure why you want to add the specific systemic examples of BMI and MI. Line 246: Are these risk factors obtained from your study? You did have all of these variables in your study but never reported on the location and smoking differences.

	This is an important paper but it requires a good deal of revision to make it readable.

VERSION 1 – AUTHOR RESPONSE

The question by Reviewer #1
1. I think this article could be improved by reporting these findings and incorporating them into the discussion. This study provide additional information in a Chinese population which mirrors that seen in Amercan and European studies. Benjamin D. Sullivan, Leslie A. Crews,,Elisabeth M. Messmer, ,Gary N. Foulks, Kelly K. Nichols , Philipp Baenninger , Gerd Geerling ,Francisco C. Figueiredo , Michael A. Lemp. Correlations between commonly used objective signs and symptoms for the diagnosis of dry eye disease: Clinical implications. Acta Ophthalmogica, 2012 Dec 28. doi: 10.1111/aos.12012. Sullivan, Benjamin D. PhD; Crews, Leslie A. PhD; Sönmez, Bars MD; de la Paz, Maria F. MD; Comert, Ebru MD; Charoenrook, Victor MD; de Araujo, Aline L. MD; Pepose, Jay S. MD, PhD; Berg, Michael S. BA; Kosheleff, Valerie P. MS; Lemp, Michael A. MD Clinical Utility of Objective Tests for Dry Eye Disease: Variability Over Time and Implications for Clinical Trials and Disease Management Cornea 2012;31(9): 1000-1008. Sullivan BD, Whitmer D, Nichols KK, Tomlinson A, Foulks GN, Geerling G, Pepose JS, Kosheleff V, Porreco A, Lemp MA. An objective approach to dry eye severity. Invest Ophthalmol Vis Sci, 2010;51:6125-6130
Answer: We thank the reviewer for these comments. Yes, we have added these information in the discussion part.edited these parts as your suggestions.
The question by Reviewer #2
1. Line 34: PRIMARY OUTCOME MEASURES: please add (Schirmer II) after “amount of tear secretion”.
Answer: We thank the reviewer for these comments. Yes, we have edited these parts as your suggestions.
2. Line 37: RESULTS: The language here is difficult. The “discrepancy” is not defined. The authors should simply say that in this population “there was a significant….. line 38.
Answer: We thank the reviewer for these comments. Yes, we have edited these parts as your suggestions, and added the definition of discrepancy in the article.
3. In line 39 what do you mean by influencing factors. Were these factors associated with increased signs or symptoms of dry eye?
Answer: We thank the reviewer for these comments. DE or dysfunctional tear syndrome is one of the most frequent diagnoses in ophthalmology. Its risk factors include age, sex (female gender), race, contact lens wear, environment with low humidity, systemic medications, and autoimmune disorders (Kaštelan S, Tomić M, Salopek-Rabatić J, Novak B. Diagnostic Procedures and Management of Dry Eye. Biomed Res Int 2013:309723.) The influencing factors were associated with increased subjective symptoms of DE, and we have added this information as your suggestions.
4. Line 40-42: This sentence makes little sense to me. Do you mean that Schirmer and BUT did not correlate? If so state this. Do you mean they did not correlate with the group who had no symptoms and with the group who had symptoms?
Answer: We thank the reviewer for these comments. I mean this subjective symptoms did not correlated with the results of Schirmer and BUT. So we changed this expression into “Moreover, the Schirmer II test and tear film BUT demonstrated remarkable difference among the normal group, the discrepancy, and the subjects with both DE symptoms and positive clinical findings.”
5. Line 44- Conclusions: I am not clear about the “pre-clinical phase concept”. Do you mean patients who have symptoms of dry eye and yet show no aqueous deficiency or evaporative signs?
Answer: We thank the reviewer for these comments. Yes, we have added this sentence “the patients who have symptoms of dry eye and yet show no aqueous deficiency or evaporative signs” as your suggestions.
6. Line 45: You must define the “discrepancy patients” clearly.
Answer: We thank the reviewer for these comments. Yes, we have added the definition of

discrepancy in the article as your suggestions.
7. Line 46-47: use the term break up time.
Answer: We thank the reviewer for these comments. Yes, we have edited these parts as your suggestions.
8. Line 49: Should read "to our knowledge" this is the first……. syndrome in a large Chinese sample.
Answer: We thank the reviewer for these comments. Yes, we have edited these parts as your suggestions.
9. Line 51: Please make sure discrepancy is defined for the reader.
Answer: We thank the reviewer for these comments. Yes, we have added the definition of discrepancy in the article as your suggestions.
10. Line 53: How did your study show that the questionnaire actually helped. I think that your results show that there are many patients with dry eye symptoms but few with dry eye signs?
Answer: We thank the reviewer for these comments. I mean a structural questionnaire is help. This is not linked to this specific questionnaire in the present study. Of the 2262 subjects, 1710 subjects had symptoms and 1354 subjects had low BUT and Schrimers. The Diagnostic Methodology Subcommittee concluded that the administration of a structured questionnaire to patients presenting to a clinic provides an excellent opportunity for screening patients with potential dry eye disease (Bron, AJ. Methodologies to diagnose and monitor dry eye disease: report of the Diagnostic Methodology Subcommittee of the International Dry Eye WorkShop (2007). 2007; Ocul Surf 5(2):108-152.)
11. Line 56: Do you mean tear osmolarity? Also where do BMI and myocardial infarction fit into this study? I did not read about them in the screening.
Answer: We thank the reviewer for these comments. Yes, we have added "tear osmolarity" in this part, and deleted "BMI" and "myocardial infarction".
12. Line 76: The world "always" does not apply to dry eye definitions today. Your reference (1) is old and you should use the DEWS 2007 definition here.
Answer: We thank the reviewer for these comments. Yes, we have edited these parts as your suggestions.
13. Line 77: You are talking about risk factors here and that is the terminology that should be used.
Answer: We thank the reviewer for these comments. Yes, we have edited these parts as your suggestions.
14. Line 79: If you wish to discuss treatments for dry eye you must include the normal techniques of drops and lid care etc. as well as omrga-3s.
Answer: We thank the reviewer for these comments. Yes, we have added this information as your suggestions.
15. Line 81: Perhaps you can make this sentence clearer by saying "At present, dry eye is often ignored….."
Answer: We thank the reviewer for these comments. Yes, we have edited these parts as your suggestions.
16. Line 90: The word" lesion" is not appropriate here. Perhaps you can call this a condition or disease or syndrome.
Answer: We thank the reviewer for these comments. Yes, we have edited these parts as your suggestions.
17. Line 92: The purpose of your study was to determine the lack of correlation between symptoms of dry eye and two tests of dry eye.
Answer: We thank the reviewer for these comments. Yes, we have edited these parts as your suggestions.
18. Line 95: The study was "conducted" between July and August of 2007.
Answer: We thank the reviewer for these comments. Yes, we have edited these parts as your suggestions.
19. Line 97-98: The Zhuanghe district is located near the Bohai Sea while the Dawa district in inland. The majority of the inhabitants in both districts were farmers.

Answer: We thank the reviewer for these comments. Yes, we have edited these parts as your suggestions.
20. Line 99: Is it true that the subjects were selected from the official registry by name etc? What were the inclusion and exclusion criteria used for this selection? Was age a factor?
Answer: We thank the reviewer for these comments. Yes, the subjects were selected from the official registry by name etc. Age was a factor, and all enrolled subjects aged 12 or older were selected by cluster sampling, and confirmed by door-to-door visitation. Excluding ineligible population owing to death, moving out of the town, nursing, or hospitalization. The subjects who had clear ocular surface disease history such as keratitis or conjunctivitis were excluded. Besides, if these lesions were detected by the slit lamp at the scene, the corresponding subjects were excluded too. We have added this information as your suggestion.
21. Line 102: What does it mean to select randomly? What did the door to door visit confirm?
Answer: We thank the reviewer for these comments. There was a misunderstanding for the word “randomly”, and actually, all enrolled subjects aged 12 or older were selected by cluster sampling, and inclusion and exclusion were confirmed by door-to-door visitation partially.
22. Line 103: What is an “eligible” resident? Please define this.
Answer: We thank the reviewer for these comments. The inclusion and exclusion criteria of enrolled subjects have been added. Excluding ineligible population owing to death, moving out of the town, nursing, or hospitalization.
23. Line 104: Who did not give valid responses? What does an invalid response look like?
Answer: We thank the reviewer for these comments. If the subject was unwilling to join this study, or did not receive all the tests, one invalid response was recorded. We have added this information as your suggestion.
24. Line 105: How did you screen for ocular surface disease, keratitis or conjunctivitis?
Answer: We thank the reviewer for these comments. We asked the ocular surface disease history such as keratitis or conjunctivitis. Besides, we also used the slit lamp to detect these lesions at the scene.
25. Line 107: Did these subjects go to the hospital for the testing?
Answer: We thank the reviewer for these comments. The eligible subjects were requested to come to a certain room in each the community for investigation. We have added this information as your suggestion.
26. Lines 108-116: These comments are not part of Methods. They belong in Discussion.
Answer: We thank the reviewer for these comments. Yes, we have edited these parts as your suggestions.
27. Line 117: You evaluated dry eye symptoms with the questionnaire not DES or dry eye syndrome. Refer to Table 1 here.
Answer: We thank the reviewer for these comments. Yes, we have edited these parts as your suggestions.
28. Line 118: Leave out the words “on the”.
Answer: We thank the reviewer for these comments. Yes, we have edited these parts as your suggestions.
29. Line 120: “Those subjects who identified 3 of 7 questions as positive were labelled as symptom positive”.
Answer: We thank the reviewer for these comments. Yes, we have edited these parts as your suggestions.
30. Line 121-122: You mention that 2 people recorded the questionnaire results. Do you mean that 2 people conducted an in house interview of these people? If so please tell us this early in the Methods.
Answer: We thank the reviewer for these comments. Yes, these data were recorded by two investigators (RH, YDH) together, who conducted an in house interview of these people, and we have added this information as your suggestions.
31. Lines 123-129: Where is this taking place? Did they bring a slit lamp to the subject’s home? Line 128: Please state what you did to standardize the equipment etc.

Answer: We thank the reviewer for these comments. The eligible subjects were requested to come to a certain room in each community to receive these tests. It is necessary to ensure the standardization of the equipments. For example, the same type slit lamps should be used. We have added this information as your suggestion.
32. Line 130: This is the Schirmer II test and should be identified as such. Normally the Schirmer 1 test is used in dry eye clinics and is done first to avoid the addition of any fluid added to the eye.
Answer: We thank the reviewer for these comments. Yes, we have edited these parts as your suggestions.
33. Line 135: Again I do not know how you kept the conditions constant.
Answer: We thank the reviewer for these comments. The indoor temperature and humidity should be kept at 20-25℃, and 45%-65% by air condition respectively. We have added this information as your suggestion.
34. Line 139-142: The matter of Ethics should be stated at the beginning of the Methods.
Answer: We thank the reviewer for these comments. Yes, we have edited these parts as your suggestions.
35. Line 144: geographical- spelling
Answer: We thank the reviewer for these comments. Yes, we have edited these parts as your suggestions.
36. Line 151: Your results should begin with those that pertain to your primary purpose of showing how symptoms and signs of dry eye do not correlate. Then add the risk factors for dry eye symptoms. What risk factors did you find for dry eye signs?
Answer: We thank the reviewer for these comments. Yes, we have edited these parts as your suggestions. In addition, logistic showed that gender ($OR = 2.059$, $p < 0.0001$), smoking ($OR = 2.263$, $p < 0.0001$) and geographical region (seaside and backland) ($OR = 0.272$, $p < 0.0001$) were risk factors for DE subjective symptoms.
37. Line 155: I think this sentence means that 42% of subjects had symptoms and no signs or signs and no symptoms. You might want to say that of the 960 subjects whose signs and symptoms did not correlate, 302 had no symptoms but objective signs and 658 had symptoms and no objective signs. However, I am very unclear about who reported what. Please tell me how many had symptoms, how many had low BUT and how many had low Schrimers and then tell me the correlation of these variables.
Answer: We thank the reviewer for these comments. Yes, we have edited these parts as your suggestions." Of the 2262 subjects, 1710 subjects had symptoms and 1354 subjects had low BUT and Schrimers. Additionally, the discrepancy contained 960 subjects (42.44%) with significant difference ($\chi2=4.027$, $p = 0.045 < 0.05$) (Table 2)."
38. Line 157: I do not understand the significant difference in the two cohorts. Which cohorts are we talking about? I do not understand Table 2.
Answer: We thank the reviewer for these comments. The two cohorts were referred to the discrepancy group and others. There was a misunderstanding of "cohorts". We have edited these parts as your suggestions.
39. In summary, lines 155-172 are very difficult for me to understand.
Answer: We thank the reviewer for these comments. Yes, we have edited these parts to be more clear as your suggestions.
40. Line 174: Please choose DE or DES and use it throughout the paper.
Answer: We thank the reviewer for these comments. Yes, we have chose "DE", and used it throughout the paper as your suggestions.
41. Line 181-188: This section needs to be rewritten. Why are you mentioning Sjogren's syndrome when this is not the scope of this study?
Answer: We thank the reviewer for these comments. We have deleted Sjogren's syndrome, and added new references, and rewritten this section as your suggestions.
42. Line 189: You wish to discuss the problem of symptoms versus signs in dry eye disease. You suggest that one of the reasons for this discrepancy is gender. This does not make sense to me. I

would like you to tell me how the population that you studied differed by gender in its presentation of symptoms and signs.
Answer: We thank the reviewer for these comments. Yes, in the present study, females were more likely to show DE subjective symptoms. We have added this as your suggestion.
43. Line 198: You wish to discuss the environment and dry eye disease. I think that your choice of populations in very different humidity areas is important here and should be discussed. I would not add the corneal sensitivity information as it does not relate to your study.
Answer: We thank the reviewer for these comments. Yes, we have edited these parts and added new references as your suggestions.
44. Line 207: Why are you discussing workplace use of screens and devices when your population was mainly farmers?
Answer: We thank the reviewer for these comments. Yes, we have deleted these parts as your suggestions.
45. Line 214: You mention a study that showed a lack of correlation between 3 objective dry eye tests: Schirmer versus BUT and staining. You then say that you ALSO found differences between subjective and objective findings. This is not a true comparison.
Answer: We thank the reviewer for these comments. Yes, we have edited these parts as your suggestions. And then, we added new references, for example, “no consistent relationship was found between common signs and symptoms of DE in the EU and United States. Moreover, symptoms alone are insufficient for the diagnosis and management of DE and argue for a consensus of clinical signs that better reflect all aspects of the disease(31. Sullivan BD, Crews LA, Messmer EM, Foulks GN, Nichols KK, Baenninger P, Geerling G, Figueiredo F, Lemp MA.Correlations between commonly used objective signs and symptoms for the diagnosis of dry eye disease: clinical implications.Acta Ophthalmol. 2014;92(2):161-166.)”
46. Line 226: I do not understand what you mean by saying that age was not a risk factor for DE symptoms in all samples. What samples are you taking about? Line 227: what is the discrepancy?
Answer: We thank the reviewer for these comments. Age was not a risk factor for DE symptoms in all enrolled subjects, and the subjects with the disagreement between the occurrence of symptoms and clinical findings, was regarded to the discrepancy. We have added this information in the paper.
47. Line 229: I am assuming that discrepancy subjects are those with signs and no symptoms or symptoms with no signs. What in your study suggests that you must treat these patients? Philosophy is fine but does this relate in any way to your study.
Answer: We thank the reviewer for these comments. As therapy strategies, we need to treat both signs and symptoms of the discrepancy subjects, because in this stage, Schirmer II test and BUT have already decreased, compared with the normal subjects in the present study. But we often ignore these conditions in clinics, due to the lack of symptoms or clinical findings. We have added this information as your suggestion.
48. Line 237: The study limitations must be mentioned. The biggest problem is not evaluating the ocular surface or the meibomian glands. I am not sure why you want to add the specific systemic examples of BMI and MI.
Answer: We thank the reviewer for these comments. Yes, we have added this problem and deleted BMI and MI as your suggestion.
49. Line 246: Are these risk factors obtained from your study? You did have all of these variables in your study but never reported on the location and smoking differences.
Answer: We thank the reviewer for these comments. Yes, these risk factors are obtained from this study, and we found that smoking (OR = 2.263, $p < 0.0001$) and geographical region (seaside and backland) (OR = 0.272, $p < 0.0001$) were risk factors for DE subjective symptoms. In addition, the environmental conditions of dry locations need to be improved or the tear film should be protected against adverse environmental conditions (Abusharha AA, Pearce EI.The effect of low humidity on the human tear film.Cornea. 2013;32(4):429-434). In addition, we have added the reference “Sayin N, et al. reported that cigarette smoking seems to affect the Schirmer score, TBUT value, and hexagonal cells of the corneal endothelium (30. Sayin N, Kara N, Pekel G, Altinkaynak H.Effects of chronic

smoking on central corneal thickness, endothelial cell, and dry eye parameters.Cutan Ocul Toxicol. 2013 Oct 22. [Epub ahead of print])" which supported our results.

Again, we thank both reviewers and the editor for taking time to help us improve our manuscript. Please don't hesitate to let us know if you have any further questions and comments.

VERSION 2 – REVIEW

REVIEWER	Barbara Caffery Toronto Eye Care Canada
REVIEW RETURNED	25-Jun-2014

GENERAL COMMENTS	Abstract: Line33-34: The labelling of the population as "discrepancy" belongs in Results Line 35 the primary outcome variables are symptoms of DE, BUT and Schirmer scores Line 38: start with the definition of who has DE and who does not. Do you need to have both low BUT and Schirmers? What does normal mean? Then describe what the discrepancy group is. Then results. Line 44: Why are you discussing a multi stage disease here? You do not show us that the symptomatic patients go on to have dry eye signs. Line 50- these comments belong in the Discussion. Introduction Line82-87- I would leave out the information of subjective symptoms and the treatment sentences. Line 97- Although there are many population based survey studies of dry eye in the world, there are few in China. Therefore we conducted…. Line 101. add "Secondarily we and analyzed the association of smoking and humidity in dry eye." Methods: Line 112- How were the questionnaires distributed? Line 125- does this mean that they came to the clinic to do the questionnaire or was it done at home? Line 148- We used standardized slit lamps at all visits. Line159- I think that you mean that the subjects were asked to blink normally. Line161- Do you need both test scores to be positive or just one?

	Line 167- geographical sp Line 178- Schirmers sp Line 179- I think you are saying that 960 of the total population who had a positive symptoms score but negative BUT and/or Schirmer or the opposite. What is the statistical analysis here? I think you want to erase the Chi squared data and Table 2. Line 183- I do not understand this sentence. What do you mean by positive or negative? Line 185- What do you mean by the ratio of subjects to symptoms? What is the accuracy of subject to disease? Do you mean that those who had no symptoms but had signs? Please make this section clear to the reader. Line 196- Please use the word percentage and not number. Line 199- You have not yet defined the "normal" group. Please do so somewhere. Line200- I think your groups add up to all your subects so you might just say that. Discussion: Line 207 ..components include meibomian…. Line 211- I think you should limit your discussion of tear osmolarity as it is not a part of this paper. Just talk briefly about it as impractical for your study. Line 224- Here you are discussing BUT and its clinical usage and the difference compared to symptoms. You state the findings in your study and you should then recognize that symptoms do not correlate well with BUT and therefore clinically you have learned to do both. That is important in your study. Line 236- I do not see how sex differences in symptoms tells us why there are differences between signs and symptoms. I would include this information only to say that your findings agree with the Cia study and that female sex is a risk factor for DE. Line249- This is an important part of the discussion but seems long. I would summarize the points relating to regional humidity and simply mention the indoor environmental studies briefly. Line 282- The issue of signs and symptoms not correlating is not uncommon in many disease including g headache and autoimmune disease. Having a combination of tests and set criteria for diagnosis and differentiation is an important part of the ongoing research in dry eye. So I would make this point strongly. Line 292- Then comes the idea that you have determined a progress of the disease. In fact you have not. You have done a cross-sectional study and recorded your findings. That is as far as you can go. You might suggest a future longitudinal study in which you follow the symptomless and see what happens. Line 300- here you state that age is not a risk factor for DE but later

	you say that it is. Please clarify. Line303- I would not g into treatment here as it does not apply to this study. Table 2: please use a legend that I can understand. Table 3: Please add a legend that allows me to read this chart easily. This paper needs an editor for grammar and language.

VERSION 2 – AUTHOR RESPONSE

The questions by the reviewer, Prof. Barbara Caffery
1.Title: The discrepancy between symptoms and clinical signs in dry eye syndrome: a population based analysis. Please decide if you are using dry eye syndrome or dry eye and make it the same throughout the paper.
Answer: We thank the reviewer for these great comments. We have edited these parts per your suggestions.
2. Line33-34: The labelling of the population as "discrepancy" belongs in Results
Answer: We thank the reviewer for these great comments. We have edited this part per your suggestions.
3. Line 35 the primary outcome variables are symptoms of DE, BUT and Schirmer scores
Answer: We thank the reviewer for these great comments. We have edited these parts per your suggestions.
4. Line 38: start with the definition of who has DE and who does not. Do you need to have both low BUT and Schirmers? What does normal mean? Then describe what the discrepancy group is. Then results.
Answer: We thank the reviewer for these great comments. We have edited these parts per your suggestions, as "Subjects with normal BUT and Schirmer scores without any DE symptoms were defined as the control group. Subjects presenting with abnormal BUT and Schirmers scores and symptoms of DE were defined as the DE group. Finally, subjects presenting with disparities between the occurrence of DE symptoms and measured clinical findings, were regarded as the discrepancy."
5. Line 44: Why are you discussing a multi stage disease here? You do not show us that the symptomatic patients go on to have dry eye signs.
Answer: We thank the reviewer for these great comments. We have edited these parts per your suggestions. We changed these into "The development of DE can be related to many factors."
6. Line 50- these comments belong in the Discussion.
Answer: We thank the reviewer for these great comments. The "Strengths and limitations of this study" part is required by BMJ OPEN, and we also added these comments into the Discussion.
7. Line82-87- I would leave out the information of subjective symptoms and the treatment sentences.
Answer: We thank the reviewer for these great comments. We have edited this part per your suggestions.
8. Line 97- Although there are many population based survey studies of dry eye in the world, there are few in China. Therefore we conducted….
Answer: We thank the reviewer for these great comments. We have edited this part per your suggestions.
9. Line 101. add "Secondarily we and analyzed the association of smoking and humidity in dry eye."
Answer: We thank the reviewer for these great comments. We have edited this part per your suggestions.

10. Line 112- How were the questionnaires distributed?
Answer: We thank the reviewer for these great comments. The questionnaires were distributed by the investigators, during the initial home visit and previously, the investigators should identify the enrolled subjects according the standard in the present study. We have edited this part per your suggestions.
11. Line 125- does this mean that they came to the clinic to do the questionnaire or was it done at home?
Answer: We thank the reviewer for these great comments. The subjects do the questionnaire at home. And “After answering a self-administered questionnaire distributed by the investigators, all of the eligible subjects from the same community were then brought to a central location for clinical investigation.” We have edited this part per your suggestions.
12. Line 148- We used standardized slit lamps at all visits.
Answer: We thank the reviewer for these great comments. We have edited this part per your suggestions.
13. Line159- I think that you mean that the subjects were asked to blink normally.
Answer: We thank the reviewer for these great comments. Yes and we have edited this part according to your suggestions.
14. Line161- Do you need both test scores to be positive or just one?
Answer: We thank the reviewer for these great comments. We need both test scores to be positive.
15. Line 167- geographical sp
Answer: We thank the reviewer for these great comments, and we have edited this part according to your suggestions.
16. Line 178- Schirmers sp
Answer: We thank the reviewer for these great comments, and we have edited this part according to your suggestions.
17. Line 179- I think you are saying that 960 of the total population who had a positive symptoms score but negative BUT and/or Schirmer or the opposite. What is the statistical analysis here? I think you want to erase the Chi squared data and Table 2.
Answer: We thank the reviewer for these great comments, and we have edited this part according to your suggestions. “Of the 2262 subjects studied, 1710 subjects presented with symptoms of DE and 1354 subjects had low BUT and Schirmers values. Additionally, the discrepant group contained 960 (302+658, 42.44%) subjects ,which is significant in statistics (Pearson Chi-square test: $\chi 2=4.027$, $p = 0.045 < 0.05$; table 2).”
18. Line 183- I do not understand this sentence. What do you mean by positive or negative?
Answer: We thank the reviewer for these great comments, and we have edited this part according to your suggestions. “Of the 1302 subjects demonstrating consistency between reported symptoms and measured clinical findings, 1052 were within the DE group, and the remainder accounted for the control group.”
19. Line 185- What do you mean by the ratio of subjects to symptoms? What is the accuracy of subject to disease? Do you mean that those who had no symptoms but had signs? Please make this section clear to the reader.
Answer: We thank the reviewer for these great comments, and we have edited this part according to your suggestions. “The sensitivity and specificity of DE identification based on subject symptoms were 77.70% (1052/1354) and 27.53% (250/908), respectively, while the accuracy of using the subjects’ perceived symptoms for DE identification was 57.56% ((1052+250)/2262). Additionally, the positive predictive value and likelihood ratios were 61.52% (1052/1710) and 1.072 (77.70%/(1-27.53%)), respectively, while the negative predictive value and likelihood ratios were 45.29% (250/552) and 0.810 ((1-77.70%)/27.53%), respectively.”
20. Line 196- Please use the word percentage and not number.
Answer: We thank the reviewer for these great comments, and we have edited this part according to your suggestions.
21. Line 199- You have not yet defined the “normal” group. Please do so somewhere.
Answer: We thank the reviewer for these great comments, and we have defined the normal subjects

as control group.
22. Line200- I think your groups add up to all your subects so you might just say that.
Answer: We thank the reviewer for these great comments. Yes we want to express that “There were remarkable differences in the values obtained for Schirmer II testing and tear film BUT among our three study groups”.
23. Line 207 ..components include meibomian….
Answer: We thank the reviewer for these great comments, and we have edited this part according to your suggestions.
24. Line 211- I think you should limit your discussion of tear osmolarity as it is not a part of this paper. Just talk briefly about it as impractical for your study.
Answer: We thank the reviewer for these great comments, and we have edited this part according to your suggestions.
25. Line 224- Here you are discussing BUT and its clinical usage and the difference compared to symptoms. You state the findings in your study and you should then recognize that symptoms do not correlate well with BUT and therefore clinically you have learned to do both. That is important in your study.
Answer: We thank the reviewer for these great comments, and we have edited this part according to your suggestions.
26. Line 236- I do not see how sex differences in symptoms tells us why there are differences between signs and symptoms. I would include this information only to say that your findings agree with the Cia study and that female sex is a risk factor for DE.
Answer: We thank the reviewer for these great comments, and we have edited this part according to your suggestions. In the present study, gender ($OR = 2.059$, $p < 0.0001$) was a risk factor for subjectively reported DE symptoms. Moreover, of the 1354 subjects with positive clinical findings, 622 out of 780 (87.12%) female subjects presented with related symptoms, while 390 of 574 (89.51%) males presented with related symptoms. Compared with males, females were more likely to experience symptoms of DE ($\chi2=12.193$, $p < 0.0001$).
27. Line249- This is an important part of the discussion but seems long. I would summarize the points relating to regional humidity and simply mention the indoor environmental studies briefly.
Answer: We thank the reviewer for these great comments, and we have edited this part according to your suggestions.
28. Line 282- The issue of signs and symptoms not correlating is not uncommon in many disease including g headache and autoimmune disease. Having a combination of tests and set criteria for diagnosis and differentiation is an important part of the ongoing research in dry eye. So I would make this point strongly.
Answer: We thank the reviewer for these great comments, and we have edited this part according to your suggestions. The lack of correlation between objective clinical findings and subjective symptomatic reporting is not an uncommon one. For example, early detection of glaucoma is often difficult as it is frequently asymptomatic during the initial stages of the disease. Thus, studies have shown that the majority of glaucoma cases are not diagnosed until later stage disease progression has occurred.
29. Line 292- Then comes the idea that you have determined a progress of the disease. In fact you have not. You have done a cross-sectional study and recorded your findings. That is as far as you can go. You might suggest a future longitudinal study in which you follow the symptomless and see what happens.
Answer: We thank the reviewer for these great comments, and we have mentioned that future longitudinal studies will be necessary to follow DE lesion progression in asymptomatic subjects, according to your suggestions. Actually, this was a cross sectional investigation. So we just ranked and classified the subjects according to the severity of the reduction in tear secretion and tear film BUT values. We did not determine a progress of the disease in this study.
30. Line 300- here you state that age is not a risk factor for DE but later you say that it is. Please clarify.

Answer: We thank the reviewer for these great comments. In this survey, age was not found to be a risk factor for symptomatic DE across all subjects; however, in subjects with positive clinical findings, we found that subject age did correlate significantly with whether there was a presence of DE symptomology. We suggest that this may be influenced by the inclusion of the discrepant group in our analyses. We have added this information in the discussion.
31. Line303- I would not g into treatment here as it does not apply to this study.
Answer: We thank the reviewer for these great comments, and we have edited this part according to your suggestions.
32. Table 2: please use a legend that I can understand.
Answer: We thank the reviewer for these great comments, and we have added a legend as “Reported DE symptoms and clinical findings.”
33. Table 3: Please add a legend that allows me to read this chart easily.
Answer: We thank the reviewer for these great comments, and we have added a legend as “Primary outcome variables of tear film BUT and Schirmer scores (Schirmer II) among the subject groups.”
34. This paper needs an editor for grammar and language.
Answer: We thank the reviewer for these great comments. We have edited these parts per your suggestions. The revised manuscript has been extensively revised by native English-speaking editors in American Journal Experts Company.