

BMJ Open

The discrepancy between subjective symptoms and clinical findings in dry eye syndrome: a population based analysis

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-005296
Article Type:	Research
Date Submitted by the Author:	19-Mar-2014
Complete List of Authors:	Hua, Rui Yao, Kai; Yale University School of Medicine, Ophthalmology and Visual Science Hu, Yuedong; First Hospital of China Medical University, Ophthalmology Chen, Lei; First Hospital of China Medical University, Ophthalmology
Primary Subject Heading:	Ophthalmology
Secondary Subject Heading:	Ophthalmology, Epidemiology, Patient-centred medicine
Keywords:	MEDICAL EDUCATION & TRAINING, EPIDEMIOLOGY, OPHTHALMOLOGY, Corneal and external diseases < OPHTHALMOLOGY

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1 **The discrepancy between subjective symptoms and clinical findings in dry eye syndrome: a**
2 **population based analysis**

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25 **Abstract**

26 **Objectives:** To investigate the discrepancy between symptoms and clinical findings and influencing
27 factors in dry eye syndrome (DES).

28 **Setting:** The study was a population-based and cross-sectional study in northeast China performed,
29 during Jul to Aug, 2007. It was carried out in two rural districts of Zhuanghe and Dawa, which were
30 located about 377km and 177km from our hospital respectively.

31 **PARTICIPANTS:** A total of 2600 eligible residents from 1300 households were identified, and
32 valid responses were obtained from 2262 residents with the mean age of 48 (12-88) years (926
33 men and 1336 women; response rate, 87%).

34 **PRIMARY OUTCOME MEASURES:** All subjects received examinations of the amount of lacrimal
35 secretion and tear film break up time (BUT) and completed a questionnaire survey about
36 subjective symptoms.

37 **Results:** Of 2262 subjects, the discrepancy contained 960 subjects (42.44%) and there was a
38 significant difference between the occurrence of symptoms and clinical findings ($\chi^2=4.027$, $p =$
39 $0.045 < 0.05$). In addition, influencing factors included gender, smoking, environment and age.
40 Moreover, the Schirmer I test and tear film BUT demonstrated remarkable difference among the
41 group with neither symptoms nor clinical findings, the one with discrepancy, and the one with
42 both DE symptoms and positive clinical findings.

43 **Conclusion:** DES is a multi-stage disease related to multi-factors. It is of great importance to put
44 forward the pre-clinical phase concept and to screen in those outpatients with inducing factors,
45 and future interventions should focus on the discrepancy patients.

46 **Keywords:** discrepancy; dry eye syndrome; subjective symptoms; Schirmer I test; breaking up
47 time;

48 **Strengths and limitations of this study**

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2 49 This is the first report on the discrepancy between subjective symptoms and clinical findings in dry
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4 50 eye syndrome on large Chinese sample.

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6 51 Large-scale and population-based dry eye epidemiologic studies on the discrepancy are limited in
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9 52 China.

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11 53 Our study supported the results of the Diagnostic Methodology Subcommittee that the
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13 54 administration of a structured questionnaire to patients presenting to a clinic provides an
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15 55 excellent opportunity for screening patients with potential dry eye disease.

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17 56 We did not test tears osmotic pressure in the diagnostic protocol, and did not analyze the BMI and
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20 57 myocardial infarction or angina risk factors.

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22 58 This study also lacked of the other objective tests evaluating ocular surface.

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74 INTRODUCTION

75 Dry eye (DE) is a common disorder of tear film, including tear deficiency or excessive tear
76 evaporation, which is harmful to the inter-palpebral ocular surface and always associated with
77 symptoms of ocular discomforts^[1]. Posa A et al^[2] reported that the majority of those questioned
78 DE outpatients were 40 years of age or older (88%), female (59%) and described a variety of
79 subjective symptoms (65%) in Germany. Dietary supplementation with a combination of omega-3
80 essential fatty acids and antioxidants was proved to be an effective treatment for dry eye
81 symptoms.^[3] At present, it is easy to be ignored in clinics and the concept has not been widely
82 accepted in China as well. In addition to the primary auxiliary examinations including visual acuity,
83 external examination, as well as slit-lamp biomicroscopy (Su Zhou SIX-SIX Technological
84 Development Co. ,Ltd, China),^[4] further diagnostic tests should be performed to assess ocular
85 surface damage (staining with rose bengal, lissamine green, or fluorescein dye), tear film instability
86 (tear breakup time (BUT) test), as well as aqueous tear flow (schirmer test).^[5] It has been reported
87 that DE symptoms as evaluated subjectively in a questionnaire occurred in about 21% of
88 the adult population in China, and the authors also found that the depression was associated with
89 DE, in particular when the symptoms occurred in an older population from Beijing recently^[6,7].
90 Although there are so many population-based survey of such lesion,^[8,9] large-scale and
91 population-based dry eye epidemiologic studies on the discrepancy are limited in China. So we
92 conducted an extensive survey to study the discrepancy between subjective symptoms and clinical
93 findings and the influencing factors in dry eye syndrome (DES).

94 METHODS

95 The study was a population-based and cross-sectional study in northeast China performed, during
96 Jul to Aug, 2007. It was carried out in two rural districts of Zhuanghe and Dawa, which were
97 located about 377km and 177km from our hospital respectively. Especially, Zhuanghe (seaside)
98 was near the Bohai Sea, but Dawa (backland) was not. The inhabitants mainly lived from farming.

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2 99 All people living in the communities were officially registered by name, gender, and age at the
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4 100 local government's office, which ensured the boundaries of the communities and the size of the
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6 101 population of each of the communities were known before the start of the study. Home visits
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8 102 were performed according to the registration list, and all subjects were selected randomly,
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10 103 confirmed by door-to-door visitation. A total of 2600 eligible residents from 1300 households were
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12 104 identified, and valid responses were obtained from 2262 residents with the mean age of 48 (12-88)
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14 105 years (926 men and 1336 women; response rate, 87%).The subjects who had clear ocular surface
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16 106 disease history such as keratitis or conjunctivitis were excluded.

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20 107 All subjects were required to do a questionnaire survey and their amount of tear secretion and tear
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22 108 film BUT were recorded. As we know, the measurement of tear hyperosmolarity could be regarded
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24 109 as a "gold standard" for DES diagnosis^[4] because it gives rise to the apoptosis of cells of the
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26 110 conjunctiva and cornea, and triggers inflammatory cascades that contribute to further cell death,
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28 111 including loss of mucin-producing goblet cells, which exacerbating tear film instability.^[10] However
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30 112 it is hard to carry on such an approach under the epidemiological investigation condition.
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32 113 Alternatively, BUT is also considered as the best clinical test because it also measures this
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34 114 mechanism mentioned above, which has good overall accuracy,^[11] and appears to be more
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36 115 repeatable (varies less from visit to visit) than many other diagnostic tests.^[12] As a result, BUT is
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38 116 more suitable for epidemiological investigation.

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44 117 We evaluated DES using the following 7 questions developed and validated by Gulati A et al.^[6,13,14]
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46 118 The survey emphasized on the related ocular discomforts, including awareness, tearing, burning,
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48 119 blurring and fluctuating vision, irritation, foreign body sensation as well as tired eyes (Table 1). If
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50 120 three of seven questions were positive for one person simultaneously, we referred this person as
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52 121 symptoms positive. Additionally, smoking status was also recorded. These data were recorded by
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54 122 two investigators (RH, YDH) together.

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58 123 BUT: To avoid any interference, the BUT was performed before other DES tests. Fluorescein filter
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2 124 paper (Tianjin Jingming New Technological Development Co., Ltd, China) was wetted and smeared
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4 125 in low temporal side of bulbar conjunctiva. The subjects were advised to blink several times in
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6 126 order to smear the 2% fluorescein on the surface of cornea evenly. Then, tear film stability was
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8 127 measured by recording the interval between the last complete blink and the appearance of the
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10 128 first random dry spot through cobalt blue filter of slit lamp. It is necessary to ensure the
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12 129 standardization of the equipments and environmental condition.

13 130 Schirmer I test: To avoid ocular irritation to other examinations by the test strip, the Schirmer's test
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15 131 was performed at the end. Tear secretion test filter paper (Tianjin Jingming New Technological
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17 132 Development Co. ,Ltd, China) measuring 35mm in length with a bend at 5mm was used. One
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19 133 minute after topical anesthesia (20ml:80mg, oxybuprocaine hydrochloride eye drops, santan,
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21 134 Japan), the filter paper was placed at the junction of medial $\frac{2}{3}$ and lateral $\frac{1}{3}$ of the lower lid in
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23 135 the fornix. In addition, the test was carried out in dim illumination and under standard conditions
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25 136 of temperature and humidity. Then the length of wetting was recorded after 5min. After that, the
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27 137 subjects were requested to keep their eyes open.

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29 138 The definition of positive clinical findings in our study were: schirmer I test was less than 10mm
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31 139 per 5min and tear film BUT was less than 10s^[15].All the research and measurements adhered to
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33 140 the tenets of the Declaration of Helsinki and the study was approved by the Medical Research
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35 141 Ethics Committee of First Hospital of China Medical University. Written informed consent was
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37 142 obtained from all participants.

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39 143 All analyses were performed by SPSS version 19.0. The data were expressed as the median
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41 144 (min-max). Regression analysis was performed to adjust gender, age, smoking and geographical
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43 145 region. The Pearson Chi-square test was used to assess the proportions for the two cohorts as well
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45 146 as the influencing factors (gender and environment) in the subjects with positive clinical findings
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47 147 statistically. The influencing factors (age) in those subjects and the difference in Schirmer I test and
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49 148 BUT were analyzed by Kruskal - Wallis H test. A probability (p) value of less than 0.05 was
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2 149 considered statistically significant.

3
4 150 **RESULTS**

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6 151 Logistic showed that gender (OR = 2.059, $p < 0.0001$), smoking (OR = 2.263, $p < 0.0001$) and
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8 152 geographical region (seaside and backland) (OR = 0.272, $p < 0.0001$) were risk factors for DE
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10 153 symptoms, other than age (OR = 1.400, $p = 0.100 > 0.05$). Moreover, there was no relationship
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12 154 between symptoms and clinical findings in this study (OR = 1.112, $p = 0.495 > 0.05$).

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16 155 Not only that a total of 960 out of 2262 (42%) subjects had a discrepancy between symptoms and
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18 156 exams, but that 302 of 552 subjects reporting no symptoms had clinical DES findings (55%) and 658
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20 157 of 1770 reporting symptoms had no clinical findings (38%). There was a significant difference in the
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22 158 proportions for the two cohorts ($\chi^2=4.027$, $p = 0.045 < 0.05$) (Table 2). Of the 1302 subjects with
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24 159 both symptoms and clinical findings being positive, 1052 are positive and others are negative. The
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26 160 sensitivity and specificity of subjects to symptoms were 77.70% and 27.53% respectively, while the
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28 161 accuracy of subjects' perception to disease was 57.56%. In addition, positive predictive value and
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30 162 likelihood ratio were 61.52%, 1.072, and negative ones were 45.29%, 0.810, correspondingly.

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33 163 For the 1354 subjects with clinical findings being positive, 622 of 780 (87.12%) females had related
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35 164 symptoms; while, 390 of 574 (89.51%) males had related symptoms. Compared with males,
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37 165 females were more likely to show DE symptoms ($\chi^2=12.193$, $p < 0.0001$). At the same time, there
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39 166 were 574 out of 820 (70.00%) subjects with symptoms living in the seaside. On the contrary, the
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41 167 number of that in backland was 478 out of 534 (89.51%) subjects. Thus, subjects of backland took
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43 168 a higher proportion than that of seaside ($\chi^2=35.528$, $p < 0.0001$). Moreover, age showed significant
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45 169 difference on whether there was DE symptoms or not ($Z=1.983$, $P= 0.047 < 0.05$).

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48 170 While the Schirmer I test and tear film BUT demonstrated remarkable difference between no
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50 171 symptoms without clinical findings, the discrepancy, and DE symptoms with clinical findings
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52 172 positive subjects (Schirmer I test: $\chi^2=422.93$, $p < 0.0001$; BUT: $\chi^2=264.85$, $p < 0.0001$) (Table 3).

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58 173 **DISCUSSION**

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2 174 DE or dysfunctional tear syndrome is one of the most frequent diagnoses in ophthalmology. Its risk
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4 175 factors include age, sex (female gender), race, contact lens wear, environment with low humidity,
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6 176 systemic medications, and autoimmune disorders^[16].
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9 177 Tear film components are composed of meibomian lipids, ocular mucins and proteins, and its
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11 178 stability can be assessed via a number of tools designed for clinical as well as research purposes,
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13 179 including evaluation of tear break-up time and non-invasive break-time; topographic and
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15 180 interferometric techniques; confocal microscopic methods; aberrometry; and visual function
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17 181 tests^[17]. In the present study, Schirmer I test and BUT were performed. It has been reported that
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19 182 there was no close correlation between the eye symptoms and the accessory examinations of
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21 183 Sjögren's syndrome patients, as found in this research that numbers of patients are insensitive to
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23 184 the dry-eye symptoms with the discrepancy being 42.44%. With the positive and negative
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25 185 likelihood ratio being 1.072 and 0.810 respectively (both close to 1), it is suggested that the
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27 186 possibilities of evaluating the state from symptoms both correctly and wrongly are basically the
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29 187 same with each other. It is indicated that the possibilities of evaluating the disease from symptoms
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31 188 both correctly and wrongly are basically the same with each other.
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37 189 Similarly, as proved by Schein OD^[18], it was concluded that there existed distinguished difference
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39 190 between the chief complaint of patients and the lab studies results. So it seemed difficult to
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41 191 distinguish such lesions apparently. To our knowledge, there are several reasons for the
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43 192 discrepancy between subjective symptoms and clinical findings, which seems so important to our
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45 193 routine clinical work.
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49 194 First, there is gender difference. Chia EM et al insisted that women tend to show the dry-eye
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51 195 symptoms, which may be related to the hormone level,^[19] as the androgen pool of
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53 196 non-autoimmune dry eye patients with Meibomian glands malfunctions(MGD) is significantly
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55 197 depleted compared with that of non-MGD and control cases^[20]. This supported our study.
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2 198 Second, the environment plays an important role. Nichols JJ^[21] reported that the dry-eye symptoms
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4 199 were more likely to develop in patients with contact lens, compared to those with glasses, while
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6 200 the normal visual counterparts seldom had any complaints. It is the decrease of the cornea
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8 201 sensitivity that leads to the high morbidity of ocular surface disease in Sjögren's syndrome and the
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10 202 decrease of the DE symptoms^[22]. Uchino M et al^[14] also found that using contact len was a
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12 203 common DE risk factor in both genders. It was reported that corneal sensory afferents respond to
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14 204 irritating and potentially damaging stimuli, as well as drying that occurs with evaporation of the
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16 205 tear film. Furthermore, DE also can modify the properties of corneal afferents and affect their
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18 206 capability to regulate secretion^[23].
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20 207 In addition, DE in the workplace is associated with increasing use of screens and electronic devices
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22 208 and environmental conditions in modern office designs and other environments. Also it is affected
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24 209 by the occupational exposure to ionizing radiation, chemicals or atmospheric dust with increased
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26 210 ocular dryness^[24]. In addition, it is suggested that high precorneal relative humidity protects the
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28 211 precorneal tear film against desiccation and airborne chemicals and reduces the development of
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30 212 eye irritation by airborne sensory irritants^[25]. Da Wa as a backland, has lower humidity in the
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32 213 atmosphere, which leads to distinctive dry-eye symptoms.
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34 214 Similar to Uchino M's study that ophthalmic findings revealed short BUT and corneal staining
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36 215 accompanied by normal Schirmer test values, we also found the discrepancy between subjective
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38 216 symptoms and clinical findings in DES^[26]. In the subjects with clinical findings being positive, the
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40 217 subjects with complaints of DE symptoms had less tear secretion volume and lower tear film
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42 218 stability, which suggested the existence of a "latent stage". According to the severity of the
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44 219 amount of tear secretion and tear film BUT, we tried to rank all subjects: 1. No symptoms without
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46 220 clinical findings; 2. The discrepancy between DE symptoms and clinical findings; 3. DE symptoms
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48 221 with clinical findings being positive. The rank may represent the lesions progression. Moreover, we
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50 222 should pay more attention to the discrepancy stage (2), which are tended to be ignored.
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2 223 It was widely considered that the increase in age is closely related to the severity of the DE
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4 224 symptoms. Recently, it has been reported that DE is prevalent among young to middle-aged
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6 225 Japanese visual display terminal users. Increased risk for DED was noted in women aged over 30
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8 226 years.^[26] In this survey, we found that the age was not a risk factor for DE symptoms in all samples,
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10 227 which may be due to the discrepancy, but there was a significant difference in the subjects with
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12 228 clinical findings being positive.

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16 229 As therapy strategies, we need to treat both signs and symptoms of the discrepancy subjects.
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18 230 Currently, artificial tear emulsion may be an effective way to treat the signs and symptoms of DE in
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20 231 meibomian gland dysfunction (MGD) cases^[27]. On the other hand, Barabino S et al^[28] reported that
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22 232 the combination of hyaluronic acid and tamarind seed polysaccharide also could improve the
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24 233 symptoms of DE effectively.

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28 234 Even so, the study had some limitations. For example, we did not test tears osmotic pressure in
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30 235 the diagnostic protocol, and did not analyze the BMI and myocardial infarction or angina risk
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32 236 factors, as reported by Uchino M^[26]. This study also lacked of the other objective tests evaluating
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34 237 ocular surface. These will be improved in our future study.

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37 238 Our study suggested that there were so many potential DES without any symptoms. The
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39 239 occupations of the population in this study are mainly farmers, so we should pay more attention
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41 240 to the special group. In addition, it is necessary to screen in those outpatients with inducing
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43 241 factors, and future interventions should focus on the discrepancy patients. Similarly, the
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45 242 Diagnostic Methodology Subcommittee also concluded that the administration of a structured
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47 243 questionnaire to patients presenting to a clinic provides an excellent opportunity for screening
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49 244 patients with potential dry eye disease.^[11]

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53 245 In conclusion, DES is a multi-stage disease related to multi-factors, and influencing factors of DE
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55 246 symptoms included gender, smoking, environment as well as age. It is of great importance to make
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1
2 247 the progression of the disease clear, put forward the pre-clinical phase concept and recognize the
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4 248 discrepancy, which may contribute to the prevention, diagnosis and treatment.

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7 249 There is no financial Support and any conflict of interest for this study.

8
9 250 **Acknowledgments**

10
11 251 This work was supported in part by Dr Lei Liu, Dr Yizhou Sun and Dr Jun Chen in the follow-up in
12
13 252 Department of Ophthalmology, First Hospital of China Medical University.

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16 253 **Authors' contributions**

17
18 254 Study concept and design: LC and RH. Acquisition of data: RH and YDH. Analysis and interpretation
19
20 255 of data: RH YDH and LC. Drafting of the manuscript: RH and KY. Critical revision of the manuscript
21
22 256 for important intellectual content: LC. All authors read and approved the final manuscript.

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25 257 **Competing Interests**

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30 259 **Data Sharing Statement**

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32 260 No additional data

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Table 1 Dry eye questionnaire for this survey

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1. Do your eyes ever feel dry?

 2. Do your eyes ever have tearing?

 3. Do your eyes ever feel burning?

 4. Do your eyes ever have blurring and fluctuating vision?

 5. Do your eyes ever feel irritation?

 6. Do your eyes ever feel foreign body sensation?

 7. Do your eyes ever feel tired?

Possible answers to the questions were 'none or rarely', 'sometimes', and 'often or all the time'. The positive symptoms was defined as having 'sometimes' or 'often or all the time'.

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4 370 **Table 2 Discrepancy between symptoms and clinical findings**

		Clinical findings		
		DE	normal	total
Symptoms	DE	1052	658	1710
	normal	302	250	552
	Total	1354	908	2262

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Table 3 Comparison of Schirmer I test and tear film break up time

Symptoms	Clinical findings	Schirmer I test (mm)	BUT (s)
Normal	Normal	22.0 (2.0-30.0)	12.5 (0.0-30.0)
Discrepancy		15.0 (0.0-30.0)	9.0 (0.0-30.0)
DE	DE	5.0 (0.0-30.0)	4.0 (0.0-20.0)

For peer review only

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	√ 1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	√ 2	Explain the scientific background and rationale for the investigation being reported
Objectives	√ 3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	√ 4	Present key elements of study design early in the paper
Setting	√ 5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	√ 6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case
Variables	√ 7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	√ 8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	√ 9	Describe any efforts to address potential sources of bias
Study size	√ 10	Explain how the study size was arrived at
Quantitative variables	√ 11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	√ 12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses

Continued on next page

Results		
Participants	√ 13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
Descriptive data	√ 14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)
Outcome data	√ 15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures
Main results	√ 16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	√ 17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	√ 18	Summarise key results with reference to study objectives
Limitations	√ 19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	√ 20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	√ 21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	√ 22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The discrepancy between subjective symptoms and clinical findings in dry eye syndrome: a population based analysis

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-005296.R1
Article Type:	Research
Date Submitted by the Author:	18-Jun-2014
Complete List of Authors:	Hua, Rui Yao, Kai; Yale University School of Medicine, Ophthalmology and Visual Science Hu, Yuedong; First Hospital of China Medical University, Ophthalmology Chen, Lei; First Hospital of China Medical University, Ophthalmology
Primary Subject Heading:	Ophthalmology
Secondary Subject Heading:	Ophthalmology, Epidemiology, Patient-centred medicine
Keywords:	MEDICAL EDUCATION & TRAINING, EPIDEMIOLOGY, OPHTHALMOLOGY, Corneal and external diseases < OPHTHALMOLOGY

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1 **The discrepancy between subjective symptoms and clinical findings in dry eye syndrome: a**
2 **population based analysis**

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25 **Abstract**

26 **Objectives:** To investigate the discrepancy between symptoms and clinical findings and influencing
27 factors in dry eye syndrome (DES).

28 **Setting:** The study was a population-based and cross-sectional study in northeast China performed,
29 during Jul to Aug, 2007. It was carried out in two rural districts of Zhuanghe and Dawa, which were
30 located about 377km and 177km from our hospital respectively.

31 **PARTICIPANTS:** A total of 2600 eligible residents from 1300 households were identified, and
32 valid responses were obtained from 2262 residents with the mean age of 48 (12-88) years (926
33 men and 1336 women; response rate, 87%).

34 **PRIMARY OUTCOME MEASURES:** All subjects received examinations of the amount of lacrimal
35 secretion and tear film break up time (BUT) and completed a questionnaire survey about
36 subjective symptoms.

37 **Results:** Of 2262 subjects, the discrepancy contained 960 subjects (42.44%) and there was a
38 significant difference between the occurrence of symptoms and clinical findings ($\chi^2=4.027$, $p =$
39 $0.045 < 0.05$). In addition, influencing factors included gender, smoking, environment and age.
40 Moreover, the Schirmer I test and tear film BUT demonstrated remarkable difference among the
41 group with neither symptoms nor clinical findings, the one with discrepancy, and the one with
42 both DE symptoms and positive clinical findings.

43 **Conclusion:** DES is a multi-stage disease related to multi-factors. It is of great importance to put
44 forward the pre-clinical phase concept and to screen in those outpatients with inducing factors,
45 and future interventions should focus on the discrepancy patients.

46 **Keywords:** discrepancy; dry eye syndrome; subjective symptoms; Schirmer I test; breaking up
47 time;

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2 50 **Strengths and limitations of this study**
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4 51 This is the first report on the discrepancy between subjective symptoms and clinical findings in dry
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6 52 eye syndrome on large Chinese sample.
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9 53 Large-scale and population-based dry eye epidemiologic studies on the discrepancy are limited in
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11 54 China.
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14 55 Our study supported the results of the Diagnostic Methodology Subcommittee that the
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16 56 administration of a structured questionnaire to patients presenting to a clinic provides an
17
18 57 excellent opportunity for screening patients with potential dry eye disease.
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21 58 We did not test tears osmotic pressure in the diagnostic protocol, and did not analyze the BMI and
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23 59 myocardial infarction or angina risk factors.
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25 60 This study also lacked of the other objective tests evaluating ocular surface.
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4 **76 INTRODUCTION**

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7 77 Dry eye (DE) is a common disorder of tear film, including tear deficiency or excessive tear
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9 78 evaporation, which is harmful to the inter-palpebral ocular surface and always associated with
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11 79 symptoms of ocular discomforts^[1]. Posa A et al^[2] reported that the majority of those questioned
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13 80 DE outpatients were 40 years of age or older (88%), female (59%) and described a variety of
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15 81 subjective symptoms (65%) in Germany. Dietary supplementation with a combination of omega-3
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17 82 essential fatty acids and antioxidants was proved to be an effective treatment for dry eye
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19 83 symptoms.^[3] At present, it is easy to be ignored in clinics and the concept has not been widely
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21 84 accepted in China as well. In addition to the primary auxiliary examinations including visual acuity,
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23 85 external examination, as well as slit-lamp biomicroscopy (Su Zhou SIX-SIX Technological
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25 86 Development Co. ,Ltd, China),^[4] further diagnostic tests should be performed to assess ocular
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27 87 surface damage (staining with rose bengal, lissamine green, or fluorescein dye), tear film instability
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29 88 (tear breakup time (BUT) test), as well as aqueous tear flow (schirmer test).^[5] It has been reported
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31 89 that DE symptoms as evaluated subjectively in a questionnaire occurred in about 21% of
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33 90 the adult population in China, and the authors also found that the depression was associated with
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35 91 DE, in particular when the symptoms occurred in an older population from Beijing recently^[6,7].
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37 92 Although there are so many population-based survey of such lesion,^[8,9] large-scale and
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39 93 population-based dry eye epidemiologic studies on the discrepancy are limited in China. So we
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41 94 conducted an extensive survey to study the discrepancy between subjective symptoms and clinical
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43 95 findings and the influencing factors in dry eye syndrome (DES).
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51 **METHODS**

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54 97 The study was a population-based and cross-sectional study in northeast China performed, during
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56 98 Jul to Aug, 2007. It was carried out in two rural districts of Zhuanghe and Dawa, which were
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58 99 located about 377km and 177km from our hospital respectively. Especially, Zhuanghe (seaside)
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2 100 was near the Bohai Sea, but Dawa (backland) was not. The inhabitants mainly lived from farming.
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4 101 All people living in the communities were officially registered by name, gender, and age at the
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6 102 local government's office, which ensured the boundaries of the communities and the size of the
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8 103 population of each of the communities were known before the start of the study. Home visits
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10 104 were performed according to the registration list, and all subjects were selected randomly,
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12 105 confirmed by door-to-door visitation. A total of 2600 eligible residents from 1300 households were
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14 106 identified, and valid responses were obtained from 2262 residents with the mean age of 48 (12-88)
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16 107 years (926 men and 1336 women; response rate, 87%).The subjects who had clear ocular surface
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18 108 disease history such as keratitis or conjunctivitis were excluded.
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23 109 All subjects were required to do a questionnaire survey and their amount of tear secretion and tear
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25 110 film BUT were recorded. As we know, the measurement of tear hyperosmolarity could be regarded
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27 111 as a "gold standard" for DES diagnosis^[4] because it gives rise to the apoptosis of cells of the
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29 112 conjunctiva and cornea, and triggers inflammatory cascades that contribute to further cell death,
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31 113 including loss of mucin-producing goblet cells, which exacerbating tear film instability.^[10] However
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33 114 it is hard to carry on such an approach under the epidemiological investigation condition.
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35 115 Alternatively, BUT is also considered as the best clinical test because it also measures this
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37 116 mechanism mentioned above, which has good overall accuracy,^[11] and appears to be more
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39 117 repeatable (varies less from visit to visit) than many other diagnostic tests.^[12] As a result, BUT is
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41 118 more suitable for epidemiological investigation.
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46 119 We evaluated DES using the following 7 questions developed and validated by Gulati A et al.^[6,13,14]
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48 120 The survey emphasized on the related ocular discomforts, including awareness, tearing, burning,
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50 121 blurring and fluctuating vision, irritation, foreign body sensation as well as tired eyes (Table 1). If
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52 122 three of seven questions were positive for one person simultaneously, we referred this person as
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54 123 symptoms positive. Additionally, smoking status was also recorded. These data were recorded by
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56 124 two investigators (RH, YDH) together.
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2 125 BUT: To avoid any interference, the BUT was performed before other DES tests. Fluorescein filter
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4 126 paper (Tianjin Jingming New Technological Development Co., Ltd, China) was wetted and smeared
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6 127 in low temporal side of bulbar conjunctiva. The subjects were advised to blink several times in
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8 128 order to smear the 2% fluorescein on the surface of cornea evenly. Then, tear film stability was
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10 129 measured by recording the interval between the last complete blink and the appearance of the
11
12 130 first random dry spot through cobalt blue filter of slit lamp. It is necessary to ensure the
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14 131 standardization of the equipments and environmental condition.
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18 132 Schirmer I test: To avoid ocular irritation to other examinations by the test strip, the Schirmer's test
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20 133 was performed at the end. Tear secretion test filter paper (Tianjin Jingming New Technological
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22 134 Development Co. ,Ltd, China) measuring 35mm in length with a bend at 5mm was used. One
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24 135 minute after topical anesthesia (20ml:80mg, oxybuprocaine hydrochloride eye drops, santan,
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26 136 Japan), the filter paper was placed at the junction of medial $\frac{2}{3}$ and lateral $\frac{1}{3}$ of the lower lid in
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28 137 the fornix. In addition, the test was carried out in dim illumination and under standard conditions
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30 138 of temperature and humidity. Then the length of wetting was recorded after 5min. After that, the
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32 139 subjects were requested to keep their eyes open.
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36 140 The definition of positive clinical findings in our study were: schirmer I test was less than 10mm
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38 141 per 5min and tear film BUT was less than 10s^[15].All the research and measurements adhered to
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40 142 the tenets of the Declaration of Helsinki and the study was approved by the Medical Research
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42 143 Ethics Committee of First Hospital of China Medical University. Written informed consent was
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44 144 obtained from all participants.
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48 145 All analyses were performed by SPSS version 19.0. The data were expressed as the median
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50 146 (min-max). Regression analysis was performed to adjust gender, age, smoking and geographical
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52 147 region. The Pearson Chi-square test was used to assess the proportions for the two cohorts as well
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54 148 as the influencing factors (gender and environment) in the subjects with positive clinical findings
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56 149 statistically. The influencing factors (age) in those subjects and the difference in Schirmer I test and
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2 150 BUT were analyzed by Kruskal - Wallis H test. A probability (p) value of less than 0.05 was
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4 151 considered statistically significant.

6 152 **RESULTS**

8
9 153 Logistic showed that gender (OR = 2.059, p < 0.0001), smoking (OR = 2.263, p < 0.0001) and
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11 154 geographical region (seaside and backland) (OR = 0.272, p < 0.0001) were risk factors for DE
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13 155 symptoms, other than age (OR = 1.400, p = 0.100 > 0.05). Moreover, there was no relationship
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15 156 between symptoms and clinical findings in this study (OR = 1.112, p = 0.495 > 0.05).

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17
18 157 Not only that a total of 960 out of 2262 (42%) subjects had a discrepancy between symptoms and
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20 158 exams, but that 302 of 552 subjects reporting no symptoms had clinical DES findings (55%) and 658
21
22 159 of 1770 reporting symptoms had no clinical findings (38%). There was a significant difference in the
23
24 160 proportions for the two cohorts ($\chi^2=4.027$, p = 0.045 < 0.05) (Table 2). Of the 1302 subjects with
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26 161 both symptoms and clinical findings being positive, 1052 are positive and others are negative. The
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28 162 sensitivity and specificity of subjects to symptoms were 77.70% and 27.53% respectively, while the
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30 163 accuracy of subjects' perception to disease was 57.56%. In addition, positive predictive value and
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32 164 likelihood ratio were 61.52%, 1.072, and negative ones were 45.29%, 0.810, correspondingly.

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35 165 For the 1354 subjects with clinical findings being positive, 622 of 780 (87.12%) females had related
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37 166 symptoms; while, 390 of 574 (89.51%) males had related symptoms. Compared with males,
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39 167 females were more likely to show DE symptoms ($\chi^2=12.193$, p < 0.0001). At the same time, there
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41 168 were 574 out of 820(70.00%) subjects with symptoms living in the seaside. On the contrary, the
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43 169 number of that in backland was 478 out of 534 (89.51%) subjects. Thus, subjects of backland took
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45 170 a higher proportion than that of seaside($\chi^2=35.528$, p < 0.0001). Moreover, age showed significant
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47 171 difference on whether there was DE symptoms or not (Z=1.983, P= 0.047 < 0.05).

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49 172 While the Schirmer I test and tear film BUT demonstrated remarkable difference between no
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51 173 symptoms without clinical findings, the discrepancy, and DE symptoms with clinical findings
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53 174 positive subjects (Schirmer I test: $\chi^2=422.93$, p < 0.0001; BUT: $\chi^2=264.85$, p < 0.0001) (Table 3).

1
2 175 **DISCUSSION**
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4 176 DE or dysfunctional tear syndrome is one of the most frequent diagnoses in ophthalmology. Its risk
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6 177 factors include age, sex (female gender), race, contact lens wear, environment with low humidity,
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8 178 systemic medications, and autoimmune disorders^[16].

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11 179 Tear film components are composed of meibomian lipids, ocular mucins and proteins, and its
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13 180 stability can be assessed via a number of tools designed for clinical as well as research purposes,
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15 181 including evaluation of tear break-up time and non-invasive break-time; topographic and
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17 182 interferometric techniques; confocal microscopic methods; aberrometry; and visual function
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19 183 tests^[17]. In the present study, Schirmer I test and BUT were performed. It has been reported that
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21 184 there was no close correlation between the eye symptoms and the accessory examinations of
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23 185 Sjögren's syndrome patients, as found in this research that numbers of patients are insensitive to
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25 186 the dry-eye symptoms with the discrepancy being 42.44%. With the positive and negative
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27 187 likelihood ratio being 1.072 and 0.810 respectively (both close to 1), it is suggested that the
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29 188 possibilities of evaluating the state from symptoms both correctly and wrongly are basically the
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31 189 same with each other. It is indicated that the possibilities of evaluating the disease from symptoms
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33 190 both correctly and wrongly are basically the same with each other.
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39 191 Similarly, as proved by Schein OD^[18], it was concluded that there existed distinguished difference
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41 192 between the chief complaint of patients and the lab studies results. So it seemed difficult to
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43 193 distinguish such lesions apparently. To our knowledge, there are several reasons for the
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45 194 discrepancy between subjective symptoms and clinical findings, which seems so important to our
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47 195 routine clinical work.
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51 196 First, there is gender difference. Chia EM et al insisted that women tend to show the dry-eye
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53 197 symptoms, which may be related to the hormone level,^[19] as the androgen pool of
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55 198 non-autoimmune dry eye patients with Meibomian glands malfunctions(MGD) is significantly
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57 199 depleted compared with that of non-MGD and control cases^[20]. This supported our study.
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2 200 Second, the environment plays an important role. Nichols JJ^[21] reported that the dry-eye symptoms
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4 201 were more likely to develop in patients with contact lens, compared to those with glasses, while
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6 202 the normal visual counterparts seldom had any complaints. It is the decrease of the cornea
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9 203 sensitivity that leads to the high morbidity of ocular surface disease in Sjögren's syndrome and the
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11 204 decrease of the DE symptoms^[22]. Uchino M et al^[14] also found that using contact len was a
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13 205 common DE risk factor in both genders. It was reported that corneal sensory afferents respond to
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15 206 irritating and potentially damaging stimuli, as well as drying that occurs with evaporation of the
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17 207 tear film. Furthermore, DE also can modify the properties of corneal afferents and affect their
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19 208 capability to regulate secretion^[23].
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21 209 In addition, DE in the workplace is associated with increasing use of screens and electronic devices
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23 210 and environmental conditions in modern office designs and other environments. Also it is affected
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25 211 by the occupational exposure to ionizing radiation, chemicals or atmospheric dust with increased
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27 212 ocular dryness^[24]. In addition, it is suggested that high precorneal relative humidity protects the
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29 213 precorneal tear film against desiccation and airborne chemicals and reduces the development of
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31 214 eye irritation by airborne sensory irritants^[25]. Da Wa as a backland, has lower humidity in the
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33 215 atmosphere, which leads to distinctive dry-eye symptoms.
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35 216 Similar to Uchino M's study that ophthalmic findings revealed short BUT and corneal staining
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37 217 accompanied by normal Schirmer test values, we also found the discrepancy between subjective
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39 218 symptoms and clinical findings in DES^[26]. In the subjects with clinical findings being positive, the
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41 219 subjects with complaints of DE symptoms had less tear secretion volume and lower tear film
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43 220 stability, which suggested the existence of a "latent stage". According to the severity of the
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45 221 amount of tear secretion and tear film BUT, we tried to rank all subjects: 1. No symptoms without
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47 222 clinical findings; 2. The discrepancy between DE symptoms and clinical findings; 3. DE symptoms
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49 223 with clinical findings being positive. The rank may represent the lesions progression. Moreover, we
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51 224 should pay more attention to the discrepancy stage (2), which are tended to be ignored.
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2 225 It was widely considered that the increase in age is closely related to the severity of the DE
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4 226 symptoms. Recently, it has been reported that DE is prevalent among young to middle-aged
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6 227 Japanese visual display terminal users. Increased risk for DED was noted in women aged over 30
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8 228 years.^[26] In this survey, we found that the age was not a risk factor for DE symptoms in all samples,
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10 229 which may be due to the discrepancy, but there was a significant difference in the subjects with
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12 230 clinical findings being positive.

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15 231 As therapy strategies, we need to treat both signs and symptoms of the discrepancy subjects.
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17 232 Currently, artificial tear emulsion may be an effective way to treat the signs and symptoms of DE in
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19 233 meibomian gland dysfunction (MGD) cases^[27]. On the other hand, Barabino S et al^[28] reported that
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21 234 the combination of hyaluronic acid and tamarind seed polysaccharide also could improve the
22
23 235 symptoms of DE effectively.

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26 236 Even so, the study had some limitations. For example, we did not test tears osmotic pressure in
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28 237 the diagnostic protocol, and did not analyze the BMI and myocardial infarction or angina risk
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30 238 factors, as reported by Uchino M^[26]. This study also lacked of the other objective tests evaluating
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32 239 ocular surface. These will be improved in our future study.

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35 240 Our study suggested that there were so many potential DES without any symptoms. The
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37 241 occupations of the population in this study are mainly farmers, so we should pay more attention
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39 242 to the special group. In addition, it is necessary to screen in those outpatients with inducing
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41 243 factors, and future interventions should focus on the discrepancy patients. Similarly, the
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43 244 Diagnostic Methodology Subcommittee also concluded that the administration of a structured
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45 245 questionnaire to patients presenting to a clinic provides an excellent opportunity for screening
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47 246 patients with potential dry eye disease.^[11]

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50 247 In conclusion, DES is a multi-stage disease related to multi-factors, and influencing factors of DE
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52 248 symptoms included gender, smoking, environment as well as age. It is of great importance to make
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1
2 249 the progression of the disease clear, put forward the pre-clinical phase concept and recognize the
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4 250 discrepancy, which may contribute to the prevention, diagnosis and treatment.

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6
7 251 There is no financial Support and any conflict of interest for this study.

8
9 252 **Acknowledgments**

10
11 253 This work was supported in part by Dr Lei Liu, Dr Yizhou Sun and Dr Jun Chen in the follow-up in
12
13 254 Department of Ophthalmology, First Hospital of China Medical University.

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15
16 255 **Authors' contributions**

17
18 256 Study concept and design: LC and RH. Acquisition of data: RH and YDH. Analysis and interpretation
19
20 257 of data: RH YDH and LC. Drafting of the manuscript: RH and KY. Critical revision of the manuscript
21
22 258 for important intellectual content: LC. All authors read and approved the final manuscript.

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25 259 **Competing Interests**

26
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28 260 There is no financial Support and any conflict of interest for this study.

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30 261 **Data Sharing Statement**

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32 262 No additional data available

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2 347 **Table 1 Dry eye questionnaire for this survey**

- 3
4 1. Do your eyes ever feel dry?
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6 2. Do your eyes ever have tearing?
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8 3. Do your eyes ever feel burning?
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10 4. Do your eyes ever have blurring and fluctuating vision?
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12 5. Do your eyes ever feel irritation?
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14 6. Do your eyes ever feel foreign body sensation?
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16 7. Do your eyes ever feel tired?
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18 348 Possible answers to the questions were 'none or rarely', 'sometimes', and 'often or all the time'. The positive
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20 349 symptoms was defined as having 'sometimes' or 'often or all the time'.
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368 **Table 2 Discrepancy between symptoms and clinical findings**

		Clinical findings		
		DE	normal	total
	DE	1052	658	1710
Symptoms	normal	302	250	552
	Total	1354	908	2262

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391 **Table 3 Comparison of Schirmer I test and tear film break up time**

Symptoms	Clinical findings	Schirmer I test (mm)	BUT (s)
Normal	Normal	22.0 (2.0-30.0)	12.5 (0.0-30.0)
Discrepancy		15.0 (0.0-30.0)	9.0 (0.0-30.0)
DE	DE	5.0 (0.0-30.0)	4.0 (0.0-20.0)

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For peer review only

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1 **The discrepancy between subjective symptoms and clinical findings in dry eye syndrome: a**
2 **population based analysis**

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25 **Abstract**

26 **Objectives:** To investigate the discrepancy between symptoms and clinical findings and influencing
27 factors in dry eye ~~syndrome~~ (DES).

28 **Setting:** The study was a population-based and cross-sectional study in northeast China performed,
29 during Jul to Aug, 2007. It was carried out in two rural districts of Zhuanghe and Dawa, which were
30 located about 377km and 177km from our hospital respectively.

31 **PARTICIPANTS:** A total of 2600 eligible residents from 1300 households were identified, and
32 valid responses were obtained from 2262 residents with the mean age of 48 (12-88) years (926
33 men and 1336 women; response rate, 87%). The subjects with the disagreement between the
34 occurrence of symptoms and clinical findings, was regarded to the discrepancy.

35 **PRIMARY OUTCOME MEASURES:** All subjects received examinations of the amount of lacrimal
36 secretion (Schirmer II) and tear film break up time (BUT) and completed a questionnaire survey
37 about subjective symptoms.

38 **Results:** ~~In~~Of 2262 subjects, the discrepancy contained 960 subjects (42.44%) with and there was
39 a significant difference between the occurrence of symptoms and clinical findings ($\chi^2=4.027$, $p =$
40 $0.045 < 0.05$). In addition, influencing factors for subjective symptoms included gender, smoking,
41 environment and age. Moreover, the Schirmer I| test and tear film BUT demonstrated remarkable
42 difference among the normal group, _with neither symptoms nor clinical findings, the one with
43 discrepancy, and the subjectone with both DE symptoms and positive clinical findings.

44 **Conclusion:** DES is a multi-stage disease related to multi-factors. It is of great importance to put
45 forward the pre-clinical phase concept (the patients who have symptoms of dry eye and yet show
46 no aqueous deficiency or evaporative signs) and to screen in those outpatients with inducing
47 factors, and future interventions should focus on the discrepancy patients.

48 **Keywords:** discrepancy; dry eye syndrome; subjective symptoms; Schirmer I| test; breaking up
49 time;

Strengths and limitations of this study

To our knowledge, ~~t~~his is the first report on the discrepancy between subjective symptoms and clinical findings in dry eye syndrome on large Chinese sample.

Large-scale and population-based dry eye epidemiologic studies on the discrepancy are limited in China.

Our study supported the results of the Diagnostic Methodology Subcommittee 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.

We did not test tears osmotic pressure (tear osmolarity) in the diagnostic protocol, ~~and did not analyze the BMI and myocardial infarction or angina risk factors.~~

This study also lacked of the other objective tests evaluating ocular surface.

INTRODUCTION

Dry eye (DE) is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface

~~Dry eye (DE) is a common disorder of tear film, including tear deficiency or excessive tear evaporation, which is harmful to the inter palpebral ocular surface and always associated with symptoms of ocular discomforts~~^[1]. Posa A et al^[2] reported that the risk factorsmajority of those questioned DE outpatients were 40 years of age or older (88%), female (59%) and described a variety of subjective symptoms (65%) in Germany. Compared with isotonic 0.1% Sodium Hyaluronate eye drops, hypotonic 0.18% Sodium Hyaluronate eye drops were reported to be effective in improving tear film stability and ocular surface integrity in patients with mild DE.^[3] In addition, dietary supplementation with a combination of omega-3 essential fatty acids and antioxidants was proved to be an effective treatment for dry eye symptoms.^[4,5] At present, dry eye is often ignored ~~At present, it is easy to be ignored~~ in clinics and the concept has not been widely accepted in China as well. In addition to the primary auxiliary examinations including visual acuity, external examination, as well as slit-lamp biomicroscopy (Su Zhou SIX-SIX Technological Development Co. ,Ltd, China),^[54] further diagnostic tests should be performed to assess ocular surface damage (staining with rose bengal, lissamine green, or fluorescein dye), tear film instability (tear breakup time (BUT) test), as well as aqueous tear flow (schirmer test).^[65] It has been reported that DE symptoms as evaluated subjectively in a questionnaire occurred in about 21% of the adult population in China, and the authors also found that the depression was associated with DE, in particular when the symptoms occurred in an older population from Beijing recently^[76,87]. Although there are so many population-based survey of such conditionlesion,^[98,109] large-scale and population-based dry eye epidemiologic studies on the discrepancy are limited in China. So we conducted an extensive survey to ~~study the discrepancy between subjective symptoms and clinical~~

~~findings and the influencing factors in dry eye syndrome (DES) determine the lack of correlation between symptoms and two tests of DE.~~

METHODS

The study was a population-based and cross-sectional study in northeast China ~~conducted~~performed, during Jul to Aug, 2007. It was carried out in two rural districts of Zhuanghe and Dawa, which were located about 377km and 177km from our hospital respectively. Especially, ~~the Zhuanghe district is located near the Bohai Sea, while the Dawa district is inland. The majority of the inhabitants in both districts were farmers. Zhuanghe (seaside) was near the Bohai Sea, but Dawa (backland) was not. The inhabitants mainly lived from farming.~~ All people living in the communities were officially registered by name, gender, and age at the local government's office, which ensured the boundaries of the communities and the size of the population of each of the communities were known before the start of the study. Home visits were performed according to the registration list, ~~and a self-administered questionnaire was distributed~~and. All enrolled subjects aged 12 or older were selected by cluster sampling randomly, and confirmed by door-to-door visitation. Excluding ineligible population owing to death, moving out of the town, nursing, or hospitalization. A total of 2600 eligible residents from 1300 households were identified, and valid responses were obtained from 2262 residents with the mean age of 48 (12-88) years (926 men and 1336 women; response rate, 87%). If the subject was unwilling to join this study, or did not receive all the tests, one invalid response was recorded. 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. The eligible subjects were requested to come to a certain room in each community for investigation. All the research and measurements adhered to the tenets of the Declaration of Helsinki and the study was approved by the Medical Research Ethics Committee of First Hospital of China Medical University. Written informed consent was obtained from all participants.

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2 125 All subjects were required to do a questionnaire survey and their amount of tear secretion and tear
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4 126 film BUT were recorded at the scene of the epidemiological investigation. ~~As we know, the~~
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6 127 ~~measurement of tear hyperosmolarity could be regarded as a “gold standard” for DES diagnosis^[4]~~
7
8 128 ~~because it gives rise to the apoptosis of cells of the conjunctiva and cornea, and triggers~~
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10 129 ~~inflammatory cascades that contribute to further cell death, including loss of mucin-producing~~
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12 130 ~~goblet cells, which exacerbating tear film instability.^[10] However it is hard to carry on such an~~
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14 131 ~~approach under the epidemiological investigation condition. Alternatively, BUT is also considered~~
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16 132 ~~as the best clinical test because it also measures this mechanism mentioned above, which has~~
17
18 133 ~~good overall accuracy,^[11] and appears to be more repeatable (varies less from visit to visit) than~~
19
20 134 ~~many other diagnostic tests.^[12] As a result, BUT is more suitable for epidemiological investigation.~~
21
22 135 We evaluated dry eye symptomsDES using the following 7 questions developed and validated by
23
24 136 Gulati A et al.^[7,113,124] The survey emphasized ~~on the~~ related ocular discomforts, including
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26 137 awareness, tearing, burning, blurring and fluctuating vision, irritation, foreign body sensation as
27
28 138 well as tired eyes (Table 1). Those subjects who identified 3 of 7 questions as positive were
29
30 139 labelled as symptom positive ~~three of seven questions were positive for one person~~
31
32 140 ~~simultaneously, we referred this person as symptoms positive~~. Additionally, smoking status was
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34 141 also recorded. These data were recorded by two investigators (RH, YDH) together, who conducted
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36 142 an in house interview of these people.
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38 143 BUT: To avoid any interference, the BUT was performed before other DES tests. Fluorescein filter
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40 144 paper (Tianjin Jingming New Technological Development Co., Ltd, China) was wetted and smeared
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42 145 in low temporal side of bulbar conjunctiva. The subjects were advised to blink several times in
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44 146 order to smear the 2% fluorescein on the surface of cornea evenly. Then, tear film stability was
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46 147 measured by recording the interval between the last complete blink and the appearance of the
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48 148 first random dry spot through cobalt blue filter of slit lamp. It is necessary to ensure the
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50 149 standardization of the equipments ~~and environmental condition~~. For example, the same type slit
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2 150 lamps should be used.

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4 151 Schirmer III test: To avoid ocular irritation to other examinations by the test strip, the Schirmer's
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6 152 test was performed at the end. Tear secretion test filter paper (Tianjin Jingming New Technological
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8 153 Development Co. ,Ltd, China) measuring 35mm in length with a bend at 5mm was used. One
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10 154 minute after topical anesthesia (20ml:80mg, oxybuprocaine hydrochloride eye drops, santan,
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12 155 Japan), the filter paper was placed at the junction of medial 2/3 and lateral 1/3 of the lower lid in
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14 156 the fornix. In addition, the test was carried out in dim illumination and under standard conditions
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16 157 of temperature and humidity. For example, the indoor temperature and humidity should be kept at
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18 158 20-25°C, and 45%-65% by air condition respectively. Then the length of wetting was recorded after
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20 159 5min. After that, the subjects were requested to keep their eyes open.

21
22 160 The definition of positive clinical findings in our study were: schirmer I test was less than 10mm
23
24 161 per 5min and tear film BUT was less than 10s^[1,35]. The subjects with the disagreement between the
25
26 162 occurrence of symptoms and clinical findings, was regarded to the discrepancy.~~All the research and~~
27
28 163 ~~measurements adhered to the tenets of the Declaration of Helsinki and the study was approved by~~
29
30 164 ~~the Medical Research Ethics Committee of First Hospital of China Medical University. Written~~
31
32 165 ~~informed consent was obtained from all participants.~~

33
34 166 All analyses were performed by SPSS version 19.0. The data were expressed as the median
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36 167 (min-max). Regression analysis was performed to adjust gender, age, smoking and geographical
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38 168 region. The Pearson Chi-square test was used to assess the proportions for the two cohorts as well
39
40 169 as the influencing factors (gender and environment) in the subjects with positive clinical findings
41
42 170 statistically. The influencing factors (age) in those subjects and the difference in Schirmer I test
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44 171 and BUT were analyzed by Kruskal - Wallis H test. A probability (p) value of less than 0.05 was
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46 172 considered statistically significant.

173 RESULTS

174 ~~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 symptoms, other than age (OR = 1.400, p = 0.100 > 0.05). Moreover, there was no relationship between symptoms and clinical findings in this study (OR = 1.112, p = 0.495 > 0.05).~~

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 Not only that a total of 960 out of 2262 (42%) subjects had a discrepancy between symptoms and exams, but that 302 of 552 subjects reporting no symptoms had clinical DES findings (55%) and 658 of 1770 reporting symptoms had no clinical findings (38%). There was a significant difference in the proportions for the two cohorts ($\chi^2=4.027$, p = 0.045 < 0.05) (Table 2). Of the 1302 subjects with both symptoms and clinical findings being positive, 1052 are positive and others are negative. The sensitivity and specificity of subjects to symptoms were 77.70% and 27.53% respectively, while the accuracy of subjects` perception to disease was 57.56%. In addition, positive predictive value and likelihood ratio were 61.52%, 1.072, and negative ones were 45.29%, 0.810, correspondingly.

Logistic showed that there was no relationship between symptoms and clinical findings in this study (OR = 1.112, p = 0.495 > 0.05). Moreover, 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, other than age (OR = 1.400, p = 0.100 > 0.05).

For the 1354 subjects with clinical findings being positive, 622 of 780 (87.12%) females had related symptoms; while, 390 of 574 (89.51%) males had related symptoms. Compared with males, females were more likely to show DE symptoms ($\chi^2=12.193$, p < 0.0001). At the same time, there were 574 out of 820(70.00%) subjects with symptoms living in the seaside. On the contrary, the number of that in backland was 478 out of 534 (89.51%) subjects. Thus, subjects of backland took a higher proportion than that of seaside($\chi^2=35.528$, p< 0.0001). Moreover, age showed significant difference on whether there was DE symptoms or not (Z=1.983, P= 0.047<0.05).

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2 199 While the Schirmer I test and tear film BUT demonstrated remarkable difference between the
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4 200 normal group, no symptoms without clinical findings, the discrepancy, and the subjects with both
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6 201 DE symptoms and positive clinical findings~~DE symptoms with clinical findings~~ positive subjects
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9 202 (Schirmer I test: $\chi^2=422.93$, $p<0.0001$; BUT: $\chi^2=264.85$, $p<0.0001$) (Table 3).

11 203 DISCUSSION

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14 204 DE or dysfunctional tear syndrome is one of the most frequent diagnoses in ophthalmology. Its risk
15
16 205 factors include age, sex (female gender), race, contact lens wear, environment with low humidity,
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18 206 systemic medications, and autoimmune disorders^[146].

19
20
21 207 Tear film components are composed of meibomian lipids, ocular mucins and proteins, and its
22
23 208 stability can be assessed via a number of tools designed for clinical as well as research purposes,
24
25 209 including evaluation of tear break-up time and non-invasive break-time; topographic and
26
27
28 210 interferometric techniques; confocal microscopic methods; aberrometry; and visual function
29
30 211 tests^[157]. In the present study, Schirmer I test and BUT were performed. As we know, the
31
32 212 measurement of tear hyperosmolarity could be regarded as a “gold standard” for DE diagnosis^[5]
33
34 213 because it gives rise to the apoptosis of cells of the conjunctiva and cornea, and triggers
35
36 214 inflammatory cascades that contribute to further cell death, including loss of mucin-producing
37
38 215 goblet cells, which exacerbating tear film instability.^[16] Sullivan BD, et al reported that tear film
39
40 216 osmolarity had the lowest variability among commonly used signs of DE, and reductions in
41
42 217 osmolarity preceded changes in symptoms during a 3-month therapy.^[17] In addition, tear film
43
44 218 osmolarity was proved to be the single best marker of disease severity across normal,
45
46 219 mild/moderate, and severe DE.^[18] However it is hard to carry on such an approach under the
47
48 220 epidemiological investigation condition. Alternatively, BUT is also considered as the best clinical
49
50 221 test because it also measures this mechanism mentioned above, which has good overall
51
52 222 accuracy,^[19] and appears to be more repeatable (varies less from visit to visit) than many other
53
54 223 diagnostic tests.^[20] As a result, BUT is more suitable for epidemiological investigation.
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1
2 224 ~~The .It has been reported that there was no close correlation between the eye symptoms and the~~
3
4 225 ~~accessory examinations of Sjögren's syndrome patients, as found in this research that~~ numbers of
5
6 226 patients are insensitive to the dry-eye symptoms with the discrepancy being 42.44%. With the
7
8
9 227 positive and negative likelihood ratio being 1.072 and 0.810 respectively (both close to 1), ~~it is~~
10
11 228 ~~suggested that the possibilities of evaluating the state from symptoms both correctly and wrongly~~
12
13 229 ~~are basically the same with each other.~~ It is indicated that the possibilities of evaluating the disease
14
15
16 230 from symptoms both correctly and wrongly are basically the same with each other.
17
18 231 Similarly, as proved by Schein OD^[2148], it was concluded that there existed distinguished difference
19
20 232 between the chief complaint of patients and the lab studies results. So it seemed difficult to
21
22 233 distinguish such lesions apparently. To our knowledge, there are several reasons for the
23
24 234 discrepancy between subjective symptoms and clinical findings, which seems so important to our
25
26
27 235 routine clinical work.
28
29
30 236 First, there is gender difference. Chia EM et al insisted that women tend to show the dry-eye
31
32 237 symptoms, which may be related to the hormone level,^[2249] as the androgen pool of
33
34 238 non-autoimmune dry eye patients with Meibomian glands malfunctions(MGD) is significantly
35
36 239 depleted compared with that of non-MGD and control cases^[2320]. This supported our study. In the
37
38
39 240 present study, females were more likely to show DE symptoms.
40
41
42 241 Second, the environment plays an important role. Nichols JJ^[221] ~~reported that the dry eye symptoms~~
43
44 242 ~~were more likely to develop in patients with contact lens, compared to those with glasses, while~~
45
46 243 ~~the normal visual counterparts seldom had any complaints. It is the decrease of the cornea~~
47
48 244 ~~sensitivity that leads to the high morbidity of ocular surface disease in Sjögren's syndrome and the~~
49
50 245 ~~decrease of the DE symptoms^[22]. Uchino M et al^[44] also found that using contact lens was a~~
51
52 246 ~~common DE risk factor in both genders. It was reported that corneal sensory afferents respond to~~
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54 247 ~~irritating and potentially damaging stimuli, as well as drying that occurs with evaporation of the~~
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1
2
3 248 tear film. Furthermore, DE also can modify the properties of corneal afferents and affect their
4
5 249 capability to regulate secretion^[23]. Predicted roles of environmental conditions, such as wind speed
6
7 250 and relative humidity, on tear-film stability agree with clinical observations. More importantly,
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9
10 251 locally elevated evaporation leads to hyperosmolar spots in the tear film and, hence, vulnerability
11
12 252 to epithelial irritation. In addition to evaporation rate, tear-film instability depends on the strength
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14
15 253 of healing flow from the neighboring region outside the breakup region,^[24]
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17
18 254 Many DE patients are sensitive to adverse environments where tear evaporation rate (TER)
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20 255 increases, due to a reverse correlation with environmental humidity in the range of 5% to
21
22 256 70%, with TER reduced to zero at 70% relative humidity.^[25] In addition, adult patients with
23
24
25 257 mild-to-moderate dry eye and asymptomatic subjects of similar ages can experience acute
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28 258 exacerbation, after exposing to controlled low humidity (5% relative humidity, desiccating
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30 259 environment) for 2 hours.^[26] Moreover, Tesón M, et al reported that compared with a simulated
31
32
33 260 standard condition of 23°C, 45% relative humidity, and 930 millibars of barometric pressure, a
34
35 261 simulated in-flight condition of 23°C, 5% relative humidity, localized air flow, and 750 millibars will
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38 262 aggravate the symptom, the reduction in tear stability and volume.^[27] These
39
40 263 environmental conditions causes tear hyperosmolarity, because, although the water evaporates
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43 264 from the ocular surface at normal rates, it is from a reduced aqueous tear pool. Tear film
44
45 265 hyperosmolarity causes hyperosmolarity of the ocular surface epithelial cells and stimulates a
46
47
48 266 cascade of inflammatory events involving MAP kinases and NFkB signaling pathways.^[1] Therefore,
49
50 267 to avoid tear film disruption and possible ocular surface damage,
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52
53 268 the environmental conditions of dry locations need to be improved or the tear film should be
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55 269 protected against adverse environmental conditions.^[28] Da Wa as a backland, has lower
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57
58 270 humidity in the atmosphere, which leads to distinctive dry-eye symptoms, for increasing the
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2
3 271 periocular humidity has a significant positive impact on ocular comfort in patients with dry eye.^[29]
4
5 272 On the other hand, Sayin N, et al. reported that cigarette smoking seems to affect the Schirmer
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7 273 score, TBUT value, and hexagonal cells of the corneal endothelium,^[30] which supported our
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10 274 results.
11
12 275 ~~In addition, DE in the workplace is associated with increasing use of screens and electronic devices~~
13
14 276 ~~and environmental conditions in modern office designs and other environments. Also it is affected~~
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16 277 ~~by the occupational exposure to ionizing radiation, chemicals or atmospheric dust with increased~~
17
18 278 ~~ocular dryness^[24]. In addition, it is suggested that high preocular relative humidity protects the~~
19
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21 279 ~~precorneal tear film against desiccation and airborne chemicals and reduces the development of~~
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23 280 ~~eye irritation by airborne sensory irritants^[25]. Da Wa as a backland, has lower humidity in the~~
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25
26 281 ~~atmosphere, which leads to distinctive dry eye symptoms.~~
27
28 282 ~~Similar to~~ Uchino M's study that ophthalmic findings revealed short BUT and corneal staining
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30 283 accompanied by normal Schirmer test values,^[31,26] while, ~~we also~~ found the discrepancy between
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32
33 284 subjective symptoms and clinical findings with the accordance of BUT and Schirmer test in DES^[26].
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35 285 Similarly, no consistent relationship was found between common signs and symptoms of DE in the
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37
38 286 EU and United States. Moreover, symptoms alone are insufficient for the diagnosis and
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40 287 management of DE and argue for a consensus of clinical signs that better reflect all aspects of
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42 288 the disease.^[32] In the subjects with clinical findings being positive, the subjects with complaints of
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44
45 289 DE symptoms had less tear secretion volume and lower tear film stability, which suggested the
46
47 290 existence of a "latent stage". Sullivan BD, et al. also reported that the initiation and progression
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49
50 291 of DE is multifactorial and supports the rationale for redefining severity on the basis of a
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52 292 continuum of clinical signs.^[18] ~~In this study, a~~ According to the severity of the amount of tear
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54 293 secretion and tear film BUT, we tried to rank all subjects: 1. No symptoms without clinical findings;
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57 294 2. The discrepancy between DE symptoms and clinical findings; 3. DE symptoms with clinical
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2 295 findings being positive. The rank may represent the lesions progression. Moreover, we should pay
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4 296 more attention to the discrepancy stage (2), which are tended to be ignored.

5
6 297 It was widely considered that the increase in age is closely related to the severity of the DE
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8 298 symptoms. Recently, it has been reported that DE is prevalent among young to middle-aged
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10 299 Japanese visual display terminal users. Increased risk for DED was noted in women aged over 30
11
12 300 years. ^[3126] In this survey, we found that the age was not a risk factor for DE symptoms in all
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14 301 subjectssamples, which may be due to the discrepancy, but there was a significant difference in the
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16 302 subjects with clinical findings being positive.

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18 303 As therapy strategies, we need to treat both signs and symptoms of the discrepancy subjects,
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20 304 because in this stage, Schirmer II test and BUT have already decreased, compared with the normal
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22 305 subjects in the present study. But we often ignore these conditions in clinics, due to the lack of
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24 306 symptoms or clinical findings. Currently, artificial tear emulsion may be an effective way to treat
25
26 307 the signs and symptoms of DE in meibomian gland dysfunction (MGD) cases^[3327]. On the other
27
28 308 hand, Barabino S et al^[3428] reported that the combination of hyaluronic acid and tamarind seed
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30 309 polysaccharide also could improve the symptoms of DE effectively.

31
32 310 Even so, the study had some limitations. For example, we did not test tears osmotic pressure in
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34 311 the diagnostic protocol, and did not evaluate the ocular surface or the meibomian glands.~~analyze~~
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36 312 ~~the BMI and myocardial infarction or angina risk factors, as reported by Uchino M^[26]~~. This study
37
38 313 also lacked of the other objective tests evaluating ocular surface. These will be improved in our
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40 314 future study.

41
42 315 Our study suggested that there were so many potential DES without any symptoms. The
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44 316 occupations of the population in this study are mainly farmers, so we should pay more attention
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46 317 to the special group. In addition, it is necessary to screen in those outpatients with inducing
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48 318 factors, and future interventions should focus on the discrepancy patients. Similarly, the
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50 319 Diagnostic Methodology Subcommittee also concluded that the administration of a structured
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2 320 questionnaire to patients presenting to a clinic provides an excellent opportunity for screening
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4 321 patients with potential dry eye disease.^[194]
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6 322 In conclusion, DES is a multi-stage disease related to multi-factors, and influencing factors of DE
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8 323 symptoms included gender, smoking, environment as well as age. It is of great importance to make
9
10 324 the progression of the disease clear, put forward the pre-clinical phase concept and recognize the
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12 325 discrepancy, which may contribute to the prevention, diagnosis and treatment.
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16 326 There is no financial Support and any conflict of interest for this study.
17

18 327 **Authors' contributions**

19
20 328 Study concept and design: LC and RH. Acquisition of data: RH and YDH. Analysis and interpretation
21
22 329 of data: RH YDH and LC. Drafting of the manuscript: RH and KY. Critical revision of the manuscript
23
24 330 for important intellectual content: LC. All authors read and approved the final manuscript.
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26

27 331 **Acknowledgments**

28
29 332 This work was supported in part by Dr Lei Liu, Dr Yizhou Sun and Dr Jun Chen in the follow-up in
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31 333 Department of Ophthalmology, First Hospital of China Medical University.
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Table 1 Dry eye questionnaire for this survey

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1. Do your eyes ever feel dry?
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2. Do your eyes ever have tearing?
 3. Do your eyes ever feel burning?
 4. Do your eyes ever have blurring and fluctuating vision?
 5. Do your eyes ever feel irritation?
 6. Do your eyes ever feel foreign body sensation?
 7. Do your eyes ever feel tired?
-

Possible answers to the questions were 'none or rarely', 'sometimes', and 'often or all the time'.

The positive symptoms was defined as having 'sometimes' or 'often or all the time'.

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Table 2 Discrepancy between symptoms and clinical findings

		Clinical findings		
		DE	normal	total
Symptoms	DE	1052	658	1710
	normal	302	250	552
	Total	1354	908	2262

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Table 3 Comparison of Schirmer II test and tear film break up time

Symptoms	Clinical findings	Schirmer II test (mm)	BUT (s)
Normal	Normal	22.0 (2.0-30.0)	12.5 (0.0-30.0)
Discrepancy		15.0 (0.0-30.0)	9.0 (0.0-30.0)
DE	DE	5.0 (0.0-30.0)	4.0 (0.0-20.0)

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	√ 1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	√ 2	Explain the scientific background and rationale for the investigation being reported
Objectives	√ 3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	√ 4	Present key elements of study design early in the paper
Setting	√ 5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	√ 6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case
Variables	√ 7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	√ 8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	√ 9	Describe any efforts to address potential sources of bias
Study size	√ 10	Explain how the study size was arrived at
Quantitative variables	√ 11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	√ 12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses

Continued on next page

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Results

Participants	√ 13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
Descriptive data	√ 14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)
Outcome data	√ 15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures
Main results	√ 16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	√ 17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

Discussion

Key results	√ 18	Summarise key results with reference to study objectives
Limitations	√ 19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	√ 20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	√ 21	Discuss the generalisability (external validity) of the study results

Other information

Funding	√ 22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based
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*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The discrepancy between the subjectively reported symptoms and objectively measured clinical findings in dry eye: a population based analysis

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-005296.R2
Article Type:	Research
Date Submitted by the Author:	29-Jul-2014
Complete List of Authors:	Hua, Rui; First Hospital of China Medical University, Ophthalmology Yao, Kai; Yale University School of Medicine, Ophthalmology and Visual Science Hu, Yuedong; First Hospital of China Medical University, Ophthalmology Chen, Lei; First Hospital of China Medical University, Ophthalmology
Primary Subject Heading:	Ophthalmology
Secondary Subject Heading:	Ophthalmology, Epidemiology, Patient-centred medicine
Keywords:	MEDICAL EDUCATION & TRAINING, EPIDEMIOLOGY, OPHTHALMOLOGY, Corneal and external diseases < OPHTHALMOLOGY

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1 **The discrepancy between the subjectively reported symptoms and objectively measured clinical**
2 **findings in dry eye: a population based analysis**

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25 **Abstract**

26 **Objective:** To investigate the discrepancy between patient-reported symptoms and measured
27 clinical findings and influencing factors in dry eye (DE).

28 **Setting:** A population-based, cross-sectional study was performed from July-August 2007 in
29 northeast China. The study was performed on populations originating from two rural districts that
30 are respectively located approximately 377 km and 177 km from our hospital.

31 **Participants:** A total of 2600 eligible residents from 1300 households were identified, and valid
32 responses were obtained from 2262 residents, with a mean subject age of 48 (range: 12-88) years
33 (926 men and 1336 women; response rate, 87%).

34 **Primary Outcome Measures:** The primary outcome variables measured in this study were
35 patient-reported symptoms of DE, tear film break up time (BUT) and Schirmer scores (Schirmer II).

36 **Results:** Subjects with normal BUT and Schirmer scores without any DE symptoms were defined as
37 the control group. Subjects presenting with abnormal BUT and Schirmers scores and symptoms of
38 DE were defined as the DE group. Finally, subjects presenting with disparities between the
39 occurrence of DE symptoms and measured clinical findings, were regarded as the discrepancy. Out
40 of 2262 subjects, the discrepant group contained 960 subjects (42.44%) with significant difference
41 ($\chi^2=4.027$, $p = 0.045 < 0.05$). We found that the factors that influenced the subjective reporting of
42 DE symptoms included gender, smoking status, environment and age. Finally, Schirmer II test and
43 tear film BUT values were found to be remarkably different amongst control, DE, and discrepant
44 groups.

45 **Conclusion:** The development of DE can be related to many factors. It is of great importance to put
46 forward the pre-clinical phase concept (patients who are symptomatic for DE and yet show no
47 aqueous deficiency or evaporative signs) and to screen outpatients with DE-inducing features.
48 Future interventions should focus on patients demonstrating a discrepancy between self-reported
49 symptomology and measured clinical findings.

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Keywords: discrepancy; dry eye syndrome; subjective symptoms; Schirmer I test; break up time

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2 75 **Strengths and limitations of this study**
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4 76 To our knowledge, this is the first report describing the discrepancy between subjective symptoms
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6 77 and objectively measured clinical findings in dry eye in a large Chinese patient sample.
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9 78 Large-scale, population-based dry eye epidemiologic studies on this discrepancy have been limited
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11 79 in China.
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13 80 Our study supports results produced by the Diagnostic Methodology Subcommittee, which
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15 81 demonstrated that the administration of a structured questionnaire to patients at the time of
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17 82 presentation to the clinic provides an excellent opportunity to screen for patients suffering from
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19 83 potential dry eye disease.
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23 84 Tear osmotic pressure (tear osmolarity) was not measured in our diagnostic protocol.
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25 85 Our protocol also excluded some of the other known clinical tests for evaluating the ocular
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27 86 surface.
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INTRODUCTION

Dry eye (DE) is a disorder affecting the tear ducts and ocular surface, which can be caused by many factors, and which produces symptoms including ocular discomfort, visual disturbances, and tear film instability. DE can also lead to potential damage of the ocular surface and is accompanied by both increased tear film osmolarity and inflammation of the ocular surface^[1]. Despite these considerations, the diagnosis of DE is frequently overlooked in the clinic and has not yet been widely accepted in China. When clinically identifying DE, in addition to primary auxiliary examinations, including measurement of visual acuity, external examination, and slit-lamp biomicroscopy,^[2] further diagnostic tests should be performed to evaluate the extent of ocular surface damage (e.g., staining with rose bengal, lissamine green, or fluorescein dye), tear film instability (e.g., tear breakup time (BUT) test), and the aqueous tear flow (e.g., schirmer test)^[3] of a given patient. It has recently been reported that DE symptoms, as evaluated subjectively in patient questionnaires, occurs in approximately 21% of the adult population within China. Furthermore, it was found that psychological depression is associated with DE, particularly in aging patient populations from Beijing^[4,5]. Although population-based survey studies of DE have been performed globally,^[6,7] the nature of this disorder has not been well documented within Chinese populations. Therefore, we performed the present survey to examine the lack of correlation between the subjective presentation of DE symptoms, and two objective clinical tests of DE, within selected Chinese patient groups. Additionally, we analysed the correlation of smoking and environmental humidity to the incidence of DE.

METHODS

A population-based, cross-sectional study was performed on patients living in northeast China from July to August, 2007. The study was carried out in two rural districts, Zhuanghe and Dawa, which are located approximately 377 km and 177 km from our hospital, respectively. The Zhuanghe district is located near the Bohai Sea, while the Dawa district is inland. The majority of

1
2 125 inhabitants from either district work as farmers. All of the people living in these communities were
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4 126 officially registered by name, gender, and age through the local government, ensuring that the
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6 127 boundaries and population density of each community were known at the beginning of the study.
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9 128 Home visits were performed according to these registration lists. All of the enrolled subjects were
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11 129 aged 12 and over and were selected via cluster sampling. Subject choices were confirmed by
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13 130 door-to-door visitation. Residents were deemed ineligible and excluded from study for reasons
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16 131 including death, moving out of town, nursing, or hospitalisation. A total of 2600 eligible residents
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18 132 from 1300 households were identified, and valid responses were obtained from 2262 residents,
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21 133 with a mean age of 48 (range: 12-88) years (926 men and 1336 women; response rate, 87%). If a
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23 134 subject was unwilling to join the study, or did not receive all the tests outlined in our diagnostic
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25 135 protocol, an invalid response was recorded. Subjects with a documented history of ocular surface
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28 136 disease, such as keratitis or conjunctivitis, were excluded. Additionally, subjects were excluded if
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30 137 such lesions were detected via slit lamp (Su Zhou SIX-SIX Technological Development Co., Ltd,
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32 138 China) during initial visitation. After answering a self-administered questionnaire distributed by
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35 139 the investigators, all of the eligible subjects from the same community were then brought to a
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37 140 central location for clinical investigation. All the experiments and measurements adhered to the
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39 141 ethical principles of the Declaration of Helsinki and were approved by the Medical Research Ethics
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42 142 Committee of the First Hospital of China Medical University. Written informed consent was
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44 143 obtained from all participants.

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46 144 All subjects were first required to complete a questionnaire survey about epidemiological
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48 145 investigation (the clinic); following this, their tear secretion volumes and tear film BUT values were
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51 146 recorded.

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53 147 We evaluated DE symptoms using the 7 questions developed and validated by Gulati A et al.^[4,8,9],
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55 148 which focus on ocular discomforts including awareness, tearing, burning, blurring and fluctuating
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58 149 vision, irritation, foreign body sensation, and tired eyes (Table 1). Those subjects who identified a
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2 150 minimum of 3 out of 7 questions as positive were considered “symptom positive.” Smoking status
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4 151 was also recorded. The above data were jointly recorded by two investigators (RH, YDH) during in
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6 152 home interviews of prospective subjects.
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9 153 BUT: To avoid any interference, the BUT was performed prior to other DE tests. Fluorescein filter
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11 154 paper (Tianjin Jingming New Technological Development Co., Ltd, China) was moisturised and
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13 155 placed on the eye to coat the lower temporal side of the bulbar conjunctiva. The subjects were
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16 156 advised to blink several times to ensure that the corneal surface became evenly coated with 2%
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18 157 fluorescein. Then, tear film stability was measured using a slit lamp equipped with a cobalt blue
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21 158 filter to record the time elapsed from the last complete blink to the appearance of the first
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23 159 random dry spot. The slit lamp and filter were standardised across the studies.
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26 160 Schirmer test: To avoid ocular irritation caused by the test strip from interfering with other
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28 161 examinations, the Schirmer’s test was the final test performed during patient evaluation. Tear
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30 162 secretion test filter paper (Tianjin Jingming New Technological Development Co., Ltd, China)
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32 163 measuring 35 mm in length, with a bend at 5 mm, was used. At one minute following the
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34 164 application of topical anaesthesia (20 ml:80 mg, oxybuprocaine hydrochloride eye drops, Santan,
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36 165 Japan), the filter paper was placed at the junction of the medial $\frac{2}{3}$ and lateral $\frac{1}{3}$ of the lower lid
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39 166 in the fornix. In addition, the test was carried out under dim illumination and standardised
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42 167 conditions of temperature and humidity (temperature and humidity were maintained at 20-25°C
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44 168 and 45-65%, respectively). Then, the amount of moisture present on the filter paper was recorded
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46 169 at 5 min after paper application. Afterwards, the subjects were asked to blink normally. Positive
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49 170 clinical findings were defined as a patient having both a Schirmer II test result of less than 10 mm
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51 171 per 5 min and a tear film BUT value of less than 10 s^[10]. Subjects with normal BUT and Schirmers
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53 172 scores, and without any reported symptoms of DE, were defined as the control group. Subjects
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56 173 with abnormal BUT and Schirmers scores, as well as reported symptoms of DE, were defined as the
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58 174 DE group. Finally, subjects producing inconsistencies between symptom occurrence and clinical
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2 175 findings were regarded as the discrepancy.

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4 176 All data were analysed using SPSS (version 19.0) and expressed as median values (min-max).

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6 177 Regression analysis was performed to adjust for gender, age, smoking status and geographical

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8 178 location. The Pearson Chi-square test was used to assess the proportional values between the two

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10 179 cohorts, as well as the influencing factors (gender and environment) in subjects with positive

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12 180 clinical findings. The influencing factors (age) in those subjects, and the differences in Schirmer I

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14 181 test and BUT values were analysed using the Kruskal-Wallis H test. P-values of less than 0.05 were

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16 182 considered statistically significant.

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21 183 **RESULTS**

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23 184 Of the 2262 subjects studied, 1710 subjects presented with symptoms of DE and 1354 subjects had

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25 185 low BUT and Schirmers values. Additionally, the discrepant group contained 960 (302+658, 42.44%)

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27 186 subjects ,which is significant in statistics (Pearson Chi-square test: $\chi^2=4.027$, $p = 0.045 < 0.05$; Table

28
29 187 2). Of the 1302 subjects demonstrating consistency between reported symptoms and measured

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31 188 clinical findings, 1052 were within the DE group, and the remainder accounted for the control

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33 189 group. The sensitivity and specificity of DE identification based on subject symptoms were 77.70%

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35 190 (1052/1354) and 27.53% (250/908), respectively, while the accuracy of using the subjects' perceived

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37 191 symptoms for DE identification was 57.56% ((1052+250)/2262). Additionally, the positive predictive

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39 192 value and likelihood ratios were 61.52% (1052/1710) and 1.072 (77.70%/(1-27.53%)), respectively,

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41 193 while the negative predictive value and likelihood ratios were 45.29% (250/552) and 0.810

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43 194 ((1-77.70%)/27.53%), respectively.

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45 195 Logistic analysis showed that there was no relationship between symptom presentation and

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47 196 clinical findings in this study (OR = 1.112, $p = 0.495 > 0.05$). Moreover, gender (OR = 2.059, $p <$

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49 197 0.0001), smoking status (OR = 2.263, $p < 0.0001$), and geographical region (coastal region or inland

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51 198 region; OR = 0.272, $p < 0.0001$) were risk factors for subjectively reported DE symptoms, rather

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53 199 than age (OR = 1.400, $p = 0.100 > 0.05$).

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2 200 Of the 1354 subjects with positive clinical findings, 622 out of 780 (87.12%) female subjects
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4 201 presented with related symptoms, while 390 of 574 (89.51%) males presented with related
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6 202 symptoms. Compared with males, females were more likely to experience symptoms of DE
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9 203 ($\chi^2=12.193$, $p < 0.0001$). Of patients living coastal region, 574 out of 820 (70.00%) subjects
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11 204 presented with DE symptomology, while the percentage of symptomatic patients living inland was
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13 205 89.51% (478 out of 534 subjects). Thus, subjects living inland made up a higher proportion than
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16 206 those living seaside ($\chi^2=35.528$, $p < 0.0001$). Furthermore, significant differences in whether
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18 207 subjects presented with DE symptomology were found to correlate with patient age ($Z=1.983$, $p=$
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21 208 $0.047 < 0.05$).

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23 209 There were remarkable differences in the values obtained for Schirmer II testing and tear film BUT
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25 210 among our three study groups (Schirmer II test: $\chi^2=422.93$, $p < 0.0001$; BUT: $\chi^2=264.85$, $p < 0.0001$;
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27
28 211 Table 3).

29 30 212 **DISCUSSION**

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32 213 DE or dysfunctional tear syndrome is one of the most frequent diagnoses in the practice of
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34 214 ophthalmology. Risk factors for the syndrome include age, sex (female gender), race, use of contact
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36 215 lenses, environmental conditions of low humidity, systemic medications, and autoimmune
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38 216 disorders^[11].

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41 217 Tear film components contain meibomian lipids, ocular mucins and proteins. Tear film stability can
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43 218 be assessed via a number of approaches developed for clinical as well as research purposes,
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45 219 including evaluation of tear break-up time and non-invasive break-time, topographic and
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47 220 interferometric techniques, confocal microscopic methods, aberrometry, and visual function
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49 221 tests^[12]. In the present study, Schirmer II testing and BUT were performed. It is widely accepted
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51 222 that measurements of tear hyperosmolarity are the “gold standard” for diagnosing DE, ^[2] as DE
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53 223 leads to cell apoptosis in the conjunctiva and cornea and triggers inflammatory cascades that
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55 224 contribute to further cell death, including the loss of mucin-producing goblet cells, which
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2 225 exacerbates tear film instability.^[13] However, such approaches are difficult to perform under the
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4 226 conditions of epidemiological investigation. Alternatively, BUT is also considered a top choice in
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6 227 clinical testing, as it also measures the mechanisms discussed above with good overall accuracy,^[14]
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8 228 and appears to be more repeatable across patient visits than many other diagnostic tests.^[15] As a
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10 229 result, BUT is a more suitable choice for epidemiological investigation.

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13 230 The number of patients comprising the discrepant group, those who did not report DE
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15 231 symptomology, was 42.44%. With the positive and negative likelihood ratio values both being close
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17 232 to 1 (1.072 and 0.810, respectively), it was found that the possibility of correctly identifying DE
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19 233 based on symptomology alone is equivalent to the possibility of incorrectly identifying it.

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22 234 Similarly, Schein OD^[16] concluded that there exists distinct differences between the chief
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24 235 symptomatic complaints of patients and lab results, making it difficult to distinguish such lesions.

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26 236 To our knowledge, there are several reasons behind the disparities found between subjective
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28 237 self-reporting and the measured clinical findings that are vital to performing routine clinical work.

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30 238 First, there are gender differences. Chia EM et al. reported that women have a higher tendency to
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32 239 develop symptomatic DE. This finding may be associated with gender-related hormone levels,^[17] as
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34 240 the androgen pool of non-autoimmune DE patients with Meibomian glands malfunctions (MGD) is
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36 241 significantly depleted compared with that of non-MGD and control cases^[18]. Our findings agree
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38 242 with the Chia study that female gender is a risk factor for DE.

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40 243 Second, environmental conditions play an important role in the development of DE. For example,
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42 244 locally elevated evaporation rates lead to hyperosmolar spots within the tear film and subsequent
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44 245 vulnerability to epithelial irritation. In addition to evaporation rates, tear film instability depends
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46 246 on the strength of healing flow from the neighbouring regions of the eye that lie outside the
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48 247 breakup region.^[19] Many DE patients are sensitive to adverse environments, where tear
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50 248 evaporation rates (TER) increase due to a reverse correlation when environmental humidity is in
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2 249 the range of 5% to 70%. In fact, TER is reduced to zero at 70% relative humidity.^[20] Additionally,
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4 250 adult patients exhibiting mild-to-moderate DE and asymptomatic subjects of similar ages can both
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7 251 experience acute exacerbation of the disorder following exposure to a controlled desiccating
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10 252 environment (5% relative humidity) for 2 hours.^[21] Dawa, being an inland location, generally has
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12 253 lower atmospheric humidity which leads to distinctive DE symptomology, as increasing
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14 254 periocular humidity has been demonstrated to have a significant positive impact on ocular comfort
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17 255 in DE patients.^[22] Additionally, Sayin N, et al. reported that cigarette smoking appears to affect
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20 256 Schirmer score values, TBUT values, and the hexagonal cells of the corneal endothelium,^[23] which
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22 257 further supports our results.
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25 258 The lack of correlation between objective clinical findings and subjective symptomatic reporting is
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27 259 not an uncommon one. For example, early detection of glaucoma is often difficult as it is
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30 260 frequently asymptomatic during the initial stages of the disease. Thus, studies have shown that the
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32 261 majority of glaucoma cases are not diagnosed until later stage disease progression has occurred.^[24]
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35 262 In a study performed by Uchino M, ophthalmic findings revealed short BUT and corneal staining
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37 263 accompanied by normal Schirmer test values,^[25] while we found a discrepancy in DE between
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40 264 subjective symptom reporting and measured clinical findings with regard to BUT and Schirmer test
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42 265 values. Similarly, no consistent relationship was found between self-reported symptoms of DE and
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45 266 objectively measured clinical findings in the EU and United States. As symptomology alone is
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48 267 insufficient for the diagnosis and management of DE, it is arguable that a consensus
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50 268 of clinical signs is needed to better reflect all aspects of the disease.^[26] Thus, a combined test and
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53 269 set criteria for diagnosis and differentiation of DE is important towards improving future DE
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56 270 research. Additionally, in subjects producing positive clinical findings, symptomatic complaints of
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58 271 DE were found to be accompanied by reduced tear secretion volumes and lower tear film stability
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3 272 values, which suggests the existence of a “latent stage” in DE. Sullivan BD, et al. also reported that
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5 273 the initiation and progression of DE is multifactorial, which further supports the rationale for
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7 274 redefining DE severity on the basis of a continuum of clinical symptoms.^[27] In this study, we
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10 275 ranked all subjects according to the severity of the reduction in tear secretion and tear film BUT
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12 276 values. Subjects were classified as having: 1. No presentation of symptoms or measured clinical
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15 277 findings; 2. Disparity between DE symptom presentation and positive or negative measured clinical
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17 278 findings; and, 3. Symptomatic of DE with positive measured clinical findings.
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19 279 Future longitudinal studies will be necessary to follow DE lesion progression in asymptomatic
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21 280 subjects. Furthermore, more attention needs to be devoted towards following subjects that
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23 281 present with a discrepancy between symptomatic reporting and measured clinical findings – a
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25 282 group which has historically been disregarded in DE research.
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28 283 It was widely accepted that increasing subject age is closely related to the severity of the DE
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30 284 symptomology. It has recently been reported that DE is prevalent among young to middle-aged
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32 285 Japanese subjects who use visual display terminals. An increased DE risk was also noted in women
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34 286 aged over 30 years.^[25] In this survey, age was not found to be a risk factor for symptomatic DE
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36 287 across all subjects; however, in subjects with positive clinical findings, we found that subject age
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38 288 did correlate significantly with whether there was a presence of DE symptomology. We suggest
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40 289 that this may be influenced by the inclusion of the discrepant group in our analyses.
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42
43 290 Our study did include some inherent limitations. For example, we did not test tear osmotic
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45 291 pressure in our diagnostic protocol, and did not directly evaluate the ocular surface or the
46
47 292 meibomian glands. Our protocol also lacked some of the additional objective tests that can be
48
49 293 used to evaluate the ocular surface. These limitations will be addressed in future studies.
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52 294 Our findings suggest that there are many subjects that potentially suffer from DE despite a lack of
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54 295 reported symptomology. The population examined in this study was comprised mainly of farmers,
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2 296 which suggests that more attention should be paid to this special group. Additionally, it is
3
4 297 necessary to screen those outpatients possessing DE inducing factors, and future interventions
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6 298 should focus on patients demonstrating discrepancies between symptomology and measured
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9 299 clinical findings. Similarly, the Diagnostic Methodology Subcommittee also concluded that the
10
11 300 administration of a structured questionnaire to patients presenting to the clinic provides an
12
13 301 excellent opportunity for screening patients with potential DE disease.^[14]

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16 302 In conclusion, the causes of DE are multi-factorial, and factors that influence the severity of DE
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18 303 symptomology include gender, smoking, environment and age. Moving forward, it is of great
19
20 304 importance to make the progression of DE clear, to put forward the pre-clinical phase concept and
21
22 305 to recognise the discrepancies found in many subjects, all of which may contribute favourably to
23
24 306 the prevention, diagnosis and treatment of DE.

25 26 27 28 307 **Acknowledgments**

29
30 308 This work was supported in part by Dr. Lei Liu, Dr. Yizhou Sun, and Dr. Jun Chen of the Department
31
32 309 of Ophthalmology, First Hospital of China Medical University. We also thank the American Journal
33
34 310 Experts (AJE) for assisting in the preparation of this manuscript.

35 36 37 311 **Contributorship statement**

38
39 312 Study concept and design: LC and RH. Acquisition of data: RH and YDH. Analysis and interpretation
40
41 313 of data: RH YDH and LC. Drafting of the manuscript: RH and KY. Critical revision of the manuscript
42
43 314 for intellectual content: LC. All authors have read and approved of the final manuscript.

44 45 46 315 **Competing interests**

47
48
49 316 There were no conflicts of financial interest for this study.

50 51 317 **Funding**

52
53 318 This research received no specific grant from any funding agency in the public, commercial or
54
55 319 not-for-profit sectors.

56 57 58 59 320 **Data sharing statement**

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2 321 No additional data are available.
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45 **Table 1. Dry eye questionnaire used in this survey.**

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- 47 1. Do your eyes ever feel dry?
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- 49 2. Do your eyes ever have tearing?
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- 52 3. Do your eyes ever feel burning?
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- 54 4. Do your eyes ever have blurring and fluctuating vision?
- 55
- 56 5. Do your eyes ever feel irritation?
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6. Do your eyes ever feel foreign body sensation?

7. Do your eyes ever feel tired?

Possible answers to the questions were “none or rarely”, “sometimes”, and “often or all the time”.

Positive symptoms were defined by the answers “sometimes” or “often or all the time”.

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Table 2. Reported DE symptoms and clinical findings.

	Clinical findings			
		DE	Control	Total
Symptoms	DE	1052	658	1710
	Control	302	250	552

Total 1354 908 2262

432 *The discrepant group contained 960 (302+658, 42.44%) subjects ,which is significant in statistics
 433 (Pearson Chi-square test: $\chi^2=4.027$, $p = 0.045 < 0.05$). The sensitivity and specificity of DE
 434 identification based on subject symptoms were 77.70% (1052/1354) and 27.53% (250/908),
 435 respectively, while the accuracy of using the subjects' perceived symptoms for DE identification
 436 was 57.56% ((1052+250)/2262). The positive predictive value was 61.52% (1052/1710), while the
 437 negative predictive value was 45.29% (250/552).

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450 **Table 3. Primary outcome variables of tear film BUT and Schirmer scores (Schirmer II) among the**
 451 **subject groups.**

Symptoms	Clinical findings	Schirmer II test (mm)	BUT (s)
Normal	Normal	22.0 (2.0-30.0)	12.5 (0.0-30.0)
Discrepancy		15.0 (0.0-30.0)	9.0 (0.0-30.0)

1
2 DE DE 5.0 (0.0-30.0) 4.0 (0.0-20.0)
3

4 452 *There were remarkable differences in the values obtained for Schirmer II testing and tear film BUT
5
6 453 among our three study groups (Schirmer II test: $\chi^2=422.93$, $p<0.0001$; BUT: $\chi^2=264.85$, $p<0.0001$).
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2 1 | The discrepancy between **the** **subjectively reported** symptoms and **objectively measured** clinical
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4 2 | findings in dry eye **syndrome**: a population based analysis
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Abstract

Objectives: To investigate the discrepancy between patient-reported symptoms and measured clinical findings and influencing factors in dry eye (DE).

Setting: ~~The study was a~~ population-based ~~and~~, cross-sectional study was performed from July-August 2007 in northeast China ~~performed, during Jul to Aug, 2007. It was carried out~~The study was performed on populations originating from in two rural districts of Zhuanghe and Dawa, two rural districts which that were are respectively respectively located about 3 approximately 3777km km and 1777km km from our hospital respectively, respectively.

Participants/ARTICIPANTS: ~~—~~A total of 2600 eligible residents from 1300 households were identified, and valid responses were obtained from 2262 residents, with ~~the a~~ mean subject age of 48 (range: 12-88) years (926 men and 1336 women; response rate, 87%). ~~The subjects with the disagreement between the occurrence of symptoms and clinical findings, was regarded to the discrepancy.~~

Primary/RIMARY Outcome/UTCOME Measures/EASURES: ~~†~~The primary outcome variables measured in this study were patient-reported signs/symptoms of DE, tear film break up time (BUT) and Schirmer scores (Schirmer II). All subjects received examinations of the amount of lacrimal secretion (Schirmer II) and tear film break up time (BUT) and completed a questionnaire survey about subjective symptoms.

Results: ~~—~~We defined the sSubjects with normal BUT and Schirmers scores, but without any DE symptoms, were defined as the normal/control group. And if the sSubjects with presenting with both abnormal BUT and Schirmers scores, as well as and DE signs/symptoms of DE, they were considered defined as the DE group was labeled. And then/Finally, the subjects with the disagreement presenting with disparities between the occurrence of DE signs/symptoms and measured clinical findings, were regarded to as the discrepancy. In Out of 2262 subjects, ~~the the~~ discrepancy group contained 960 subjects (42.44%) with significant difference ($\chi^2=4.027$, $p =$

0.045 < 0.05). ~~In addition, We found that the influencing factors for that influenced the subjective~~
~~subjective reporting of DE~~ symptoms included gender, smoking status, environment and age.
~~Moreover Finally, the~~ Schirmer II test and tear film BUT values were found to be demonstrated
~~remarkably difference different amongst the normal control, DE, and discrepant group, the~~
~~discrepancy, and the DE group.s. subjects with both DE symptoms and positive clinical findings.~~

Conclusion: ~~DE The development of DE is can be a multi-stage disease~~ related to many
~~DE~~ factors. It is of great importance to put forward the pre-clinical phase concept (~~the~~ patients who
~~have sign~~ symptoms of are symptomatic for dry eye DE and yet show no aqueous deficiency or
evaporative signs), ~~and to~~ and to screen ~~in those~~ outpatients with inducing DE-inducing
factors/features, ~~and~~ future interventions should focus on the discrepancy patients
demonstrating a discrepancy between self-reported symptomology and measured clinical findings.

Keywords: discrepancy; dry eye syndrome; subjective symptoms; Schirmer I test; break up time;

Strengths and limitations of this study

To our knowledge, this is the first report ~~on describing~~ the discrepancy between subjective
symptoms and objectively measured clinical findings in dry eye ~~syndrome~~ in a large Chinese
patient sample.

Large-scale ~~and,~~ population-based dry eye epidemiologic studies on ~~the this~~ discrepancy are have
been limited in China.

Our study ~~supported~~ supports the results ~~of produced by~~ the Diagnostic Methodology
Subcommittee, ~~that~~ which demonstrated that the administration of a structured questionnaire to
patients ~~presenting at the time of presentation to a the~~ clinic provides an excellent opportunity ~~for~~
to screen for patients with suffering from potential dry eye disease.

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2 74 | ~~We did not test t~~ears osmotic pressure (tear osmolarity) was not measured in ~~the our~~ diagnostic
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4 75 | protocol.

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6 76 | ~~This study~~Our protocol also ~~lacked~~excluded some of the other ~~objective~~known clinical tests for
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8 77 | evaluating the ocular surface.
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93 INTRODUCTION

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49 94 | Dry eye (DE) is a ~~multifactorial disease~~order of affecting the tear ~~ducts~~ and ocular surface, which
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51 95 | can be caused by multi-many factors, and leading~~which produces to that results in~~
52
53 96 | ~~signs~~symptoms ~~symptoms~~ of including ocular discomfort, visual disturbances, and tear film
54
55 97 | instability. ~~DE with~~ can also lead to potential damage ~~to of~~ the ocular surface. ~~It, and is~~ and is
56
57 98 | accompanied by both the increased ~~osmolarity of the~~ tear film osmolarity and inflammation of the
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1
2 99 ocular surface^[1]. Posa A et al^[2] reported that the risk factors of those questioned DE outpatients
3
4 100 were 40 years of age or older (88%), female (59%) and described a variety of subjective symptoms
5
6 101 (65%) in Germany. Compared with isotonic 0.1% Sodium Hyaluronate eye drops, hypotonic 0.18%
7
8 102 Sodium Hyaluronate eye drops were reported to be effective in improving tear film stability and
9
10 103 ocular surface integrity in patients with mild DE.^[3] In addition, dietary supplementation with a
11
12 104 combination of omega 3 essential fatty acids and antioxidants was proved to be an
13
14 105 effective treatment for dry eye symptoms.^[4] ~~At present~~ Despite these considerations, the
15
16 106 diagnosis of dry eye DE is frequently often ignored in overlooked in the clinics and ~~the concept~~ has
17
18 107 not yet been widely accepted in China ~~as well~~. When clinically identifying DE, in addition to the
19
20 108 primary auxiliary examinations, including measurement of visual acuity, external examination, as
21
22 109 well as and slit-lamp biomicroscopy ~~(Su Zhou SIX SIX Technological Development Co., Ltd,~~
23
24 110 ~~China),~~^[25] further diagnostic tests should be performed to assess evaluate the extent of ocular
25
26 111 surface damage (e.g., staining with rose bengal, lissamine green, or fluorescein dye), tear film
27
28 112 instability (e.g., tear breakup time (BUT) test), as well as and the aqueous tear flow (e.g., schirmer
29
30 113 test)^[36] of a given patient. It has ~~been recently been~~ reported that ~~the~~ DE symptoms, as evaluated
31
32 114 subjectively in a patient questionnaires, ~~occurred occurs~~ in about 2 approximately 21% of the the
33
34 115 adult population within China, ~~and the authors also found that~~ Furthermore, it was found that
35
36 116 psychological the depression was is associated with DE, in particularly when the sign symptoms
37
38 117 occurred in an older aging patient populations from Beijing recently^[47,58]. Although there are many
39
40 118 population-based survey studies of dry eye DE in the world have been performed globally,^[69,740] ~~it~~
41
42 119 has not the nature of this disorder has not been well documented there are few in within Chinese
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44 120 populationsa. We t Therefore, we ~~Therefore we~~ carried out conducted Although there are so many
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46 121 population based survey of such condition,^[9,10] large scale and population based dry eye
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48 122 epidemiologic studies on the discrepancy are limited in China. So we conducted performed an
49
50 123 extensive survey the present survey in order to to determine examine the lack of correlation
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2 124 between the subjective presentation of DE signsymptoms,ymptoms and two objective clinical
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4 125 tests of DE, within selected Chinese patient groups. In additionAdditionally, Secondly we and
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6 126 analyzeanalysed the associationcorrelation of smoking and environmental humidity into the
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9 127 incidence of dry eyeDE-as well.

11 128 METHODS

12
13 129 The study wasA population-based, and cross-sectional study was performed performedon
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15 130 patients living in northeast China conducted, during from July to August, 2007. It-The study was
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17 131 carried out in two rural districts, of Zhuanghe and Dawa, which were-are located about
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19 132 approximately 377km km and 177km km from our hospital respectively, respectively.
20
21 133 EspeciallyIn particular, tThe Zhuanghe district is located near the Bohai Sea, while the Dawa
22
23 134 district in-is inland. The majority of the inhabitants fromin both-either districts were-work as
24
25 135 farmers. All of the people living in these communities were-iswere officially registered by-withby
26
27 136 name, gender, and age at-through the local government's office, which-ensuringed that the
28
29 137 boundaryies of the communities and the-size-of-the population sizedensity of each of the
30
31 138 communityies were known beforeat the beginning of the start-of-the the study-started. Home
32
33 139 visits ss wasere performed according to these registration lists, and-a self-administered
34
35 140 questionnaire was distributed. All of the enrolled subjects were aged 12 and over, and-or older
36
37 141 were and were selected by-via cluster sampling, and-Subject choices were confirmed by
38
39 142 door-to-door visitation. Excluding After iReligible residents were deemed ineligible and excluded
40
41 143 from study population owingduefor reasons including-to death, moving out of the town, nursing,
42
43 144 or hospitalization. aAA total of 2600 eligible residents from 1300 households were identified,
44
45 145 and the valid responses were obtained from 2262 residents, with the-a mean age of 48 (range:
46
47 146 12-88) years (926 men and 1336 women; response rate, 87%). If the-a subject was unwilling to join
48
49 147 this-the study, or did not receive all the tests outlined in our diagnostic protocol, one-an invalid
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51 148 response was recorded. The-sSubjects who had clearwith a documented history records aboutof

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2 149 ocular surface disease, ~~history~~ such as keratitis or conjunctivitis, were excluded.
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4 150 ~~Besides~~ ~~Also, Additionally,~~ the subjects were excluded if ~~these such~~ lesions were detected ~~by the~~ via
5
6 151 slit lamp (Su Zhou SIX-SIX Technological Development Co., Ltd, China) ~~at the scene~~ during initial
7
8 152 ~~visitation,~~ the corresponding subjects were excluded too. ~~With~~ After answering a self-administered
9
10 153 ~~questionnaire distributed by the investigators, all of the the~~ eligible subjects from the same
11
12 154 ~~community were afterwards then required to~~ brought to a central location ~~And then, a~~
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14 155 ~~self-administered questionnaire was distributed to the eligible subjects by the investigators. Next,~~
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16 156 ~~The~~ eligible subjects were requested to ~~come to a certain room for clinical investigation in each~~
17
18 157 ~~community with these blank questionnaires for investigation.~~ All the ~~research experiments~~ and
19
20 158 measurements adhered to the ~~tenets~~ ethical principles of the Declaration of Helsinki, ~~and the~~
21
22 159 ~~study was~~ and werewas approved by the Medical Research Ethics Committee of the First
23
24 160 Hospital of China Medical University. Written informed consent was obtained from all participants.
25
26 161 All subjects were first required to ~~do~~ fill out complete a questionnaire survey at the scene of
27
28 162 ~~the~~ about epidemiological investigation (the clinic) firstly, and then following this, their amount of
29
30 163 tear secretion volumes and tear film BUT values were recorded ~~at the scene of the epidemiological~~
31
32 164 investigation.
33
34 165 We evaluated dry eye DE symptoms using the ~~following~~ 7 questions developed and validated by
35
36 166 Gulati A et al. ^[47,811,912] ~~, which focus on The survey emphasized related~~ ocular discomforts,
37
38 167 including awareness, tearing, burning, blurring and fluctuating vision, irritation, foreign body
39
40 168 sensation, ~~as well as~~ and tired eyes (Table 1). Those subjects who identified a minimum of 3 out of
41
42 169 7 questions as positive were ~~labelled as~~ considered "symptom positive." ~~Additionally, s~~ Smoking
43
44 170 status was also recorded. ~~These~~ The above data were ~~was data were~~ jointly recorded by two
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46 171 investigators (RH, YDH) ~~together, who conducted an in house interview of these people during in~~
47
48 172 home interviews of prospective subjects.
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50 173 BUT: To avoid any interference, the BUT was performed before prior to other DE tests. Fluorescein
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2 174 filter paper (Tianjin Jingming New Technological Development Co., Ltd, China) was ~~wetted~~
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4 175 ~~moisturized and~~ placed on the eye ~~in order to~~ ~~smear~~ ~~coated~~ in the lower temporal side
5
6 176 of the bulbar conjunctiva. The subjects were advised to blink several times ~~in order to~~ ~~smear~~
7
8 177 ~~make sure the~~ ~~at the corneal surface~~ ~~became evenly~~ ~~of cornea-coated~~ ~~coated evenly with the~~ 2%
9
10 178 fluorescein ~~on the surface of cornea evenly~~. Then, tear film stability was measured ~~by using a slit~~
11
12 179 ~~lamp equipped with a cobalt blue filter, in order to~~ recording the time interval elapsed between
13
14 180 from the last complete blink ~~to and~~ the appearance of the first random dry spot ~~through, using~~
15
16 181 ~~The cobalt blue filter of slit lamp and filter which were standardized in all across the studies. We~~
17
18 182 ~~used standardized slit lamps at all visits. It is necessary to ensure the standardization of the~~
19
20 183 ~~equipments. For example, the same type slit lamps should be used.~~
21
22
23 184 Schirmer-I test: To avoid ~~the~~ ocular irritation caused by the test strip from interfering with ~~to~~ other
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25 185 examinations, ~~by from the test strip,~~ the Schirmer's test was the final test performed ~~at the~~
26
27 186 ~~end~~ during patient evaluation. Tear secretion test filter paper (Tianjin Jingming New Technological
28
29 187 Development Co., Ltd, China) measuring 35mm mm in length, with a bend at 55mm mm, was
30
31 188 used. ~~At o~~ One minute ~~after following the application of~~ topical ~~anesthesia~~ anaesthesia (200m
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33 189 ml:800m mg, oxybuprocaine hydrochloride eye drops, ~~santan~~ Santan, Japan), the filter paper was
34
35 190 placed at the junction of the medial 2/3 and lateral 1/3 of the lower lid in the fornix. In addition, the
36
37 191 test was carried out ~~in under~~ dim illumination and ~~under~~ standardized conditions of temperature
38
39 192 and humidity (temperature and humidity were maintained at 20-25°C and 45-65%, respectively).
40
41 193 ~~For example, the indoor temperature and humidity should be kept by air condition at 20-25°C, and~~
42
43 194 ~~45%-65% by air condition respectively. Then~~ ~~Then~~ ~~Following this~~ ~~Then~~, the length of wet amount of
44
45 195 moisture present on the filter paper ~~wetting~~ was recorded ~~after at~~ 55m min ~~after paper application~~.
46
47 196 ~~After that~~ ~~Afterwards,~~ the subjects were asked to blink normally. ~~the subjects were requested to~~
48
49 197 ~~keep their eyes open. The definition of p~~ Positive clinical findings in our study were defined as a
50
51 198 patient having both a: both s Schirmer II test result of was less than 100mm mm per 55m min and a
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1
2 199 tear film BUT value was of less than 10 s^[103]. ~~We defined the s~~Subjects with normal BUT and
3
4 200 Schirmers scores, ~~but and without any reported symptoms of DE, signs as were~~ considered defined
5
6 201 as normal group the control group. ~~And if T~~he sSubjects ~~with with both~~ abnormal BUT and
7
8 202 Schirmers scores, ~~as well as reported symptoms of DE signs, the DE group was labeled~~ were
9
10 203 labelled defined as the ~~as~~ DE group. ~~And then~~ Finally, the ~~s~~subjects ~~with the~~ producing
11
12 204 disagreement in consistencies ~~between the~~ symptom occurrence ~~of signs~~ and clinical findings, ~~was~~
13
14 205 were regarded to as the discrepancy. ~~The subjects with the disagreement between the occurrence~~
15
16 206 of symptoms and clinical findings, was regarded to the discrepancy.
17
18 207 All ~~data~~ analyses were analyze analysed performed by in using SPSS (version 19.0). ~~and~~ The data
19
20 208 ~~were~~ expressed as ~~the~~ median values (min-max). Regression analysis was performed to adjust for
21
22 209 gender, age, smoking status and geographical geographical region location. The Pearson Chi-square
23
24 210 test was used to assess the proportions proportional values for between the two cohorts, as well
25
26 211 as the influencing factors (gender and environment) in ~~the~~ subjects with positive clinical findings
27
28 212 statistically. The influencing factors (age) in those subjects, and the differences in Schirmer I test
29
30 213 and BUT values were analyze analyse by using the Kruskal--Wallis H test. A probability (p) P-values
31
32 214 of of ~~less than 0.05~~ was were considered statistically significant.

215 RESULTS

216 Of the 2262 subjects studied, 1710 subjects had sign symptoms presented with symptoms of DE and
217 1354 subjects had low BUT and Schirmers values Schrimers. Additionally, the discrepant ey group
218 contained 960 (302+658, 42.44%) subjects (42.44%), which is significant in statistics with significant
219 proportion difference (Pearson Chi-square test: $\chi^2=4.027$, $p = 0.045 < 0.05$) (; Table 2). Of the
220 1302 subjects with the demonstrating consistency between reported sign symptoms and measured
221 clinical findings Of the 1302 subjects with both symptoms and clinical findings being positive, 1052
222 are were within the DE group, positive and and others are the remainder accounted for the
223 normal control group negative. The sensitivity and specificity of DE identification based on subjects

224 ~~to subject~~ symptoms ~~for DE identification~~ were 77.70% (1052/1354) and 27.53% ~~respectively~~
 225 (250/908), ~~respectively~~, while the accuracy of ~~subjects' signs~~ subject ~~the subjects' perceived~~
 226 ~~symptomology~~ perception ~~for DE identification~~ ~~to disease~~ was 57.56% ((1052+250)/2262). ~~In~~
 227 ~~addition~~ Additionally, the positive predictive value and likelihood ratios were 61.52% (1052/1710)
 228 ~~and~~ 1.072 (77.70%/(1-27.53%)), ~~respectively~~, ~~and while the~~ negative ~~ones~~ predictive value and
 229 likelihood ratios were 45.29% (250/552) ~~and~~, 0.810 ((1-77.70%)/27.53%),
 230 ~~correspondingly~~ respectively.
 231 Logistic analysis showed that there was no relationship between ~~sign~~ symptom
 232 presentation and clinical findings in this study (OR = 1.112, p = 0.495 > 0.05). Moreover, gender
 233 (OR = 2.059, p < 0.0001), smoking status (OR = 2.263, p < 0.0001), and geographical region (coastal
 234 region ~~seaside and or backland~~ inland region) (; OR = 0.272, p < 0.0001) were risk factors for
 235 subjectively reported DE ~~subjective symptom~~ signs ~~symptoms~~, ~~other~~ ~~rather~~ ~~as well as~~ than age (OR
 236 = 1.400, p = 0.100 > 0.05).
 237 ~~For~~ ~~Of~~ the 1354 subjects with positive clinical findings ~~being positive~~, 622 out of 780 (87.12%)
 238 ~~females~~ ~~female subjects~~ ~~had presented with~~ related symptoms; while, 390 of 574 (89.51%) males
 239 ~~had presented with~~ related symptoms. Compared with males, females were more likely to
 240 ~~show~~ experience symptoms of DE ~~symptoms~~ signs ($\chi^2=12.193$, p < 0.0001). ~~At the same time~~ ~~Of~~
 241 patients living coastal region ~~seaside~~, ~~there were~~ 574 out of 820 (70.00%) subjects ~~with~~ presented
 242 with DE sign ~~symptoms~~ living in the ~~seaside~~ symptomology. ~~while~~ ~~On the contrary~~, the
 243 ~~percentage~~ ~~number~~ of symptomatic patients living ~~that in~~ backland inland was 89.51% (478 out of
 244 534 ~~(89.51%)~~ subjects). Thus, subjects ~~of living~~ backland inland ~~took~~ made up a higher proportion
 245 than ~~that of~~ ~~ose~~ living seaside ($\chi^2=35.528$, p < 0.0001). ~~Moreover~~ Furthermore, significant
 246 differences in whether subjects presented with DE symptomology were found to correlate with
 247 patient age ~~showed significant difference on whether there was DE sign~~ symptoms or not (Z=1.983,
 248 P = 0.047 < 0.05).

249 ~~There were remarkable differences in the~~ While values obtained for Schirmer II testing and tear
 250 film BUT ~~demonstrated remarkable difference among these~~ our three study ~~between the normal~~
 251 ~~groups, the discrepancy, and the subjects with both DE symptoms and positive clinical findings~~
 252 (Schirmer ~~II~~ test: $\chi^2=422.93$, $p<0.0001$; BUT: $\chi^2=264.85$, $p<0.0001$; Table 3) ~~(Table 3)~~.

253 DISCUSSION

254 DE or dysfunctional tear syndrome is one of the most frequent diagnoses in the practice of
 255 ophthalmology. ~~Its~~ Risk factors for the syndrome include age, sex (female gender), race, use of
 256 contact ~~lens wear~~ lenses, environmental conditions ~~with of~~ low humidity, systemic medications,
 257 and autoimmune disorders^[14].

258 Tear film components ~~include~~ contain ~~are composed of~~ meibomian lipids, ocular mucins and
 259 proteins, ~~and its~~ Tear film stability can be assessed via a number of approaches ~~developed~~ tools
 260 ~~designed~~ for clinical as well as research purposes, including evaluation of tear break-up time and
 261 non-invasive break-time; topographic and interferometric techniques; confocal microscopic
 262 methods; aberrometry; and visual function tests^[25]. In the present study, Schirmer II testing and
 263 BUT were performed. ~~As we know,~~ It is widely accepted that ~~the~~ measurements of tear
 264 hyperosmolarity ~~could be regarded as~~ are the “gold standard” for diagnosing DE, diagnosis^[25]
 265 ~~because as it~~ DE leads to cell apoptosis ~~ingives rise to the apoptosis of cells of~~ the conjunctiva and
 266 cornea, and triggers inflammatory cascades that contribute to further cell death, including the loss
 267 of mucin-producing goblet cells, which ~~exacerbating~~ exacerbates tear film instability.^[136] Sullivan
 268 ~~BD, et al reported that tear film osmolarity had the lowest variability among commonly used signs~~
 269 ~~of DE, and reductions in osmolarity preceded changes in symptoms during a 3-month therapy.~~^[17]
 270 ~~In addition, tear film osmolarity was proved to be the single best marker of disease severity across~~
 271 ~~normal, mild/moderate, and severe DE.~~^[18] However, it is difficult ~~hard to carry out on~~ such an
 272 approach es are difficult to perform under the conditions of epidemiological investigation ~~condition~~.
 273 Alternatively, BUT is also considered as the best top choice in clinical testing, ~~because as~~ it also

1
2 274 ~~to also~~ measures ~~the~~^{this} mechanisms ~~mentioned-discussed~~ above, ~~which with has~~ good overall
3
4 275 accuracy,^[149] and appears to be more repeatable ~~across patient visits (varies less from visit to visit)~~
5
6 276 than many other diagnostic tests.^[1529] As a result, BUT is a more suitable choice for epidemiological
7
8
9 277 investigation.

10
11 278 The numbers of patients comprising the discrepant group, those who did not report ~~are insensitive~~
12
13 279 ~~to the dry eye DE symptoms-signs/symptomology, with the discrepancy being is was~~ 42.44%. With the
14
15 280 ~~the~~ positive and negative likelihood ratio values both being close to 1 being (1.072 and 0.810
16
17 281 ~~respectively 0, respectively), (both close to 1), it is indicated was found~~ that the possibilities
18
19 282 possibility of correctly evaluating-identifying the disease-DE based on symptomology alone from
20
21 283 sign/symptoms both correctly and wrongly are basically the same with each other is equivalent to
22
23 284 the possibility of incorrectly identifying it.

24
25 285 Similarly, ~~as proved by~~ Schein OD^[1624], ~~it was~~ concluded that there ~~existed~~ exists distinguished
26
27 286 distinct differences between the chief symptomatic complaints of patients and ~~the~~ lab studies
28
29 287 results ~~-, making it so it seemed~~ difficult to distinguish such lesions ~~apparently~~. To our knowledge,
30
31 288 there are several reasons ~~for the behind the discrepancy-disparities found between-between~~
32
33 289 subjective sign/symptoms/subjective self-reporting and the clinical findings/measured clinical findings,
34
35 290 which that seems so are important to our vital to performing routine clinical work.

36
37 291 First, there ~~is~~ are gender differences. Chia EM et al. ~~insisted-reported~~ that women have a higher
38
39 292 tendency to show-develop the dry eye sign/symptom/symptomatic DE, which This finding may be
40
41 293 ~~related to~~ associated with the gender-related hormone levels,^[1722] as the androgen pool of
42
43 294 non-autoimmune dry eye DE patients with Meibomian glands malfunctions (MGD) is significantly
44
45 295 depleted compared with that of non-MGD and control cases^[1823]. Our findings agree with the Chia
46
47 296 study and that female sex/gender is a risk factor for DE. This supported our study. In the present
48
49 297 study, females were more likely to show DE symptoms.

1
2
3 298 Secondly, ~~the~~ environmental al conditions plays an important role in the development of DE.
4
5 299 ~~Predicted roles of environmental conditions, such as wind speed and relative humidity, on tear film~~
6
7 300 ~~stability agree with clinical observations. More importantly, For example, locally elevated~~
8
9
10 301 evaporation rates leads to hyperosmolar spots within the tear film and, ~~hence,~~ subsequent
11
12 302 vulnerability to epithelial irritation. In addition to evaporation rates, tear-film instability depends
13
14
15 303 on the strength of healing flow from the ~~neighboring~~ neighbouring regions of the eye that lie
16
17 304 outside the breakup region,^{f [1924]}. Many DE patients are sensitive to adverse environments, where
18
19
20 305 tear evaporation rates (TER) increases, due to a reverse correlation
21
22 306 with when environmental humidity is in the range of 5% to 70%. In fact, ~~with~~ TER is reduced to
23
24
25 307 zero at 70% relative humidity.^[2025] ~~In addition~~ Additionally, adult patients ~~with~~ exhibiting
26
27 308 mild-to-moderate dry eye DE and asymptomatic subjects of similar ages can both experience
28
29 309 acute exacerbation of the disorder, ~~after following exposing~~ exposure to a controlled
30
31 310 low humidity desiccating environment (5% relative humidity, ~~desiccating environment~~) for 2
32
33
34
35 311 hours.^[2126] ~~Moreover, Tesón M, et al reported that compared with a simulated standard condition~~
36
37 312 ~~of 23°C, 45% relative humidity, and 930 millibars of barometric pressure, a simulated in-flight~~
38
39 313 ~~condition of 23°C, 5% relative humidity, localized air flow, and 750 millibars will aggravate the~~
40
41
42 314 ~~symptom, the reduction in tear stability and volume.~~^[27] ~~These environmental conditions causes~~
43
44 315 ~~tear hyperosmolarity, because, although the water evaporates from the ocular surface at normal~~
45
46 316 ~~rates, it is from a reduced aqueous tear pool. Tear film hyperosmolarity causes hyperosmolarity of~~
47
48 317 ~~the ocular surface epithelial cells and stimulates a cascade of inflammatory events involving MAP~~
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50
51 318 ~~kinases and NFkB signaling pathways.~~^[1] ~~Therefore, to avoid tear film disruption and possible ocular~~
52
53
54 319 ~~surface damage, the environmental conditions of dry locations need to be improved or the tear~~
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56
57 320 ~~film should be protected against adverse environmental conditions.~~^[28] ~~Da~~ W ~~Wa~~ as ~~a~~

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2
3 321 ~~backland~~being an inland location, generally has lower atmospheric humidity ~~in the atmosphere,~~
4
5 322 which leads to distinctive ~~dry eye~~DE symptoms~~signs~~symptomology, ~~for as~~ increasing the
6
7 323 periocular humidity has been demonstrated to have a significant positive impact on ocular comfort
8
9
10 324 in DE patients ~~with dry eye.~~^[2279] ~~On the other hand~~Additionally, Sayin N, et al. reported that
11
12 325 cigarette smoking ~~seems~~appears to affect ~~the~~ Schirmer score values, TBUT values, and the
13
14 326 hexagonal cells of the corneal endothelium,^[23830] which ~~further supported~~supports our results.
15
16
17 327 The lack of correlation between objective clinical findings and subjective symptomatic reporting is
18
19 328 not an uncommon one-issue of signs and symptoms not correlating is not uncommon in many
20
21 329 diseases. ~~For example, Early detection of glaucoma is often difficult due to as it is frequently~~
22
23 330 asymptomatic course in the during the initial stages of the disease. ~~and~~ Thus, studies have shown
24
25 331 that and a large number the majority of glaucoma cases are not diagnosed ~~at~~ until later stage of
26
27 332 the disease progression has occurred.^[249] In a study performed by Uchino M's study, ~~that~~
28
29 333 ophthalmic findings revealed short BUT and corneal staining accompanied by normal Schirmer test
30
31 334 values,^[253034] while, we found ~~the a~~ discrepancy in DE between subjective ~~sign~~symptom~~symptom~~
32
33 335 reporting and measured clinical findings with ~~the accordance of~~ regard to BUT and Schirmer test ~~in~~
34
35 336 DE values. Similarly, no consistent relationship was found between
36
37 337 common signs and symptoms of self-reported symptoms of DE and objectively measured clinical
38
39 338 findings in the EU and United States. ~~Moreover, signs~~ As symptomology alone ~~are is~~
40
41 339 insufficient for the diagnosis and management of DE, it is arguable that ~~and argue for~~ a consensus
42
43 340 of clinical signs is needed that to better reflect all aspects of the disease.^[26312] As a result Thus,
44
45 341 having a combined test ~~combination of testing~~ and set criteria for diagnosis and differentiation of
46
47 342 DE is an important part towards of the improving ongoing research in dry eye future DE research.
48
49 343 Additionally, in the subjects with producing positive clinical ~~findings~~ findings being positive,
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3 344 symptomatic the subjects with complaints of DE signsymptoms had were found to be accompanied
4
5 345 by less-reduced tear secretion volumes and lower tear film stability values, which suggested-
6
7 346 suggests the existence of a “latent stage” in DE. Sullivan BD, et al. also reported that the initiation
8
9
10 347 and progression of DE is multifactorial and, which further supports the rationale for redefining DE
11
12 348 severity on the basis of a continuum of clinical signsymptomfindings.^[2748] In this study, we ranked
13
14
15 349 all subjects according to the severity of the amount of reduction in tear secretion and tear film BUT
16
17 350 values, we tried to rank all subject. Subjects were classified as having:s: 1. No
18
19
20 351 signsymptomspresentation of symptoms or without-measured clinical findings; 2. The-
21
22 352 discrepancyDisparity between -DE symptoms-signsymptom presentation and positive or negative
23
24 353 measured -clinical findings; and, 3. Symptomatic of DE signsymptoms with with positive measured
25
26 354 clinical findings being positive.
27
28 355 A-fFuture longitudinal studyies wasill be needednecessary to follow DE lesion progression in
29
30 356 asymptomatic subjects the symptomless, to see what happens, in order to find out the lesions
31
32 357 progression. The rank may represent the lesions progression. MoreoverFurthermore, we should
33
34 358 pay more attention needs to be devoted towards following to the subjects that present with a
35
36 359 discrepancy subjectsbetween symptomatic reporting and measured clinical findings - a group
37
38 360 which has historically been stage (2), which are tended to be ignoreddisregarded in DE research.
39
40
41 361 It was widely consideredaccepted that the-increaseing in-subject age is closely related to the
42
43 362 severity of the DE signsymptomsymptomology. Recently, it has recently been reported that DE is
44
45 363 prevalent among young to middle-aged Japanese subjects who use visual display terminal userss.
46
47 364 An iincreased DE risk for DED was also noted in women aged over 30 years.^[2534] In this survey,
48
49 365 although, we found that the the age was not found to be a risk factor for symptomatic DE
50
51 366 signsymptoms in across all subjects; however, but in the subjects with positive clinical findings-being
52
53 367 positive, it did show we found that subject age did correlate significantly with whether there was a
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1
2 368 ~~presence of DE symptomology. significant difference on whether there was DE signs or not. The~~
3
4 369 ~~authors~~We suggested that this may be ~~due to~~influenced by the inclusion of ~~because of the~~
5
6 370 ~~discrepancy~~ subjects group in our analyses. ~~which may be due to the discrepancy, but there was a~~
7
8 371 ~~significant difference in the subjects with clinical findings being positive.~~
9
10 372 ~~As therapy strategies, we need to treat both signs and symptoms of the discrepancy subjects,~~
11
12 373 ~~because in this stage, Schirmer II test and BUT have already decreased, compared with the normal~~
13
14 374 ~~subjects in the present study. But we often ignore these conditions in clinics, due to the lack of~~
15
16 375 ~~symptoms or clinical findings. Currently, artificial tear emulsion may be an effective way to treat~~
17
18 376 ~~the signs and symptoms of DE in meibomian gland dysfunction (MGD) cases^[33]. On the other hand,~~
19
20 377 ~~Barabino S et al^[34] reported that the combination of hyaluronic acid and tamarind seed~~
21
22 378 ~~polysaccharide also could improve the symptoms of DE effectively.~~
23
24 379 ~~Even so, the~~Our study ~~had~~ ~~did~~ include some inherent limitations. For example, we did not test
25
26 380 tears osmotic pressure in ~~the~~ ~~our~~ diagnostic protocol, and did not directly evaluate the ocular
27
28 381 surface or the meibomian glands. ~~This study~~Our protocol also lacked some of the ~~other~~ additional
29
30 382 objective tests that can be used to evaluating ~~evaluate the~~ ocular surface. These limitations will be
31
32 383 ~~improved~~ addressed in our future studies~~y~~.
33
34 384 Our study findings suggested that there ~~were~~ ~~are~~ ~~so~~ many subjects that potentially suffer from DE
35
36 385 despite a lack of reported symptomology. ~~– without showing any sign~~ symptoms. The occupations
37
38 386 of the population examined in this study ~~are~~ ~~was~~ comprised mainly of farmers, ~~so we should~~ which
39
40 387 suggests that ~~pay~~ more attention should be paid to ~~the~~ ~~this~~ special group. ~~In addition~~ Additionally,
41
42 388 it is necessary to screen ~~in~~ those outpatients ~~with~~ possessing DE inducing factors, and future
43
44 389 interventions should focus on ~~the~~ discrepancy patients demonstrating discrepancies between
45
46 390 symptomology and measured clinical findings. Similarly, the Diagnostic Methodology
47
48 391 Subcommittee also concluded that the administration of a structured questionnaire to patients

1
2 392 presenting to ~~a~~the clinic provides an excellent opportunity for screening patients with potential
3
4 393 ~~dry eye~~DE disease.^[149]

5
6 394 In conclusion, the causes of DE is~~are a multi-stage disease related to multi factors~~multi-factorial,
7
8
9 395 and ~~influencing~~factors that influence the severity of ~~of~~ DE signsymptoms~~symptomology~~ included
10
11 396 gender, smoking, environment ~~as well as~~and age. ~~It~~Moving forward, it is of great importance to
12
13 397 make the progression of ~~the DE disease~~ clear, to put forward the pre-clinical phase concept and to
14
15 398 recogn~~ize~~ise the ~~discrepancy~~discrepancies found in many subjects, all of which may contribute
16
17 399 ~~favorably~~favorably to the prevention, diagnosis and treatment of DE.

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19
20
21 400 There ~~is no financial support and any~~were no conflicts of financial interest for this study.

22 23 401 Acknowledgments

24
25 402 This work was supported in part by Dr. Lei Liu, Dr. Yizhou Sun, and Dr. Jun Chen of the Department
26
27 403 of Ophthalmology, First Hospital of China Medical University.

28 29 30 404 Contributorship statement

31
32 405 Study concept and design: LC and RH. Acquisition of data: RH and YDH. Analysis and interpretation
33
34 406 of data: RH YDH and LC. Drafting of the manuscript: RH and KY. Critical revision of the manuscript
35
36 407 for intellectual content: LC. All authors have read and approved of the final manuscript.

37 38 39 408 Competing interests

40
41 409 There were no conflicts of financial interest for this study.

42 43 44 410 Funding

45
46 411 This research received no specific grant from any funding agency in the public, commercial or
47
48 412 not-for-profit sectors.

49 50 51 413 Data sharing statement

52
53 414 No additional data are available.

54 55 56 415 Authors' contributions

57
58 416 ~~Study concept and design: LC and RH. Acquisition of data: RH and YDH. Analysis and interpretation~~

1
2 417 of data: RH YDH and LC. Drafting of the manuscript: RH and KY. Critical revision of the manuscript
3
4 418 for important intellectual content: LC. All authors have read and approved of the final manuscript.
5

6 419 **Acknowledgments**
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8
9 420 ~~This work was supported in part by Dr. Lei Liu, Dr. Yizhou Sun, and Dr. Jun Chen in the~~
10
11 421 ~~investigation follow up in of the Department of Ophthalmology, First Hospital of China Medical~~
12
13 422 ~~University.~~
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59 537 **Table 1. Dry eye questionnaire ~~for used in~~ used in this survey.**

1. Do your eyes ever feel dry?
2. Do your eyes ever have tearing?
3. Do your eyes ever feel burning?
4. Do your eyes ever have blurring and fluctuating vision?
5. Do your eyes ever feel irritation?
6. Do your eyes ever feel foreign body sensation?
7. Do your eyes ever feel tired?

Possible answers to the questions were “none or rarely”, “sometimes”, and “often or all the time”. The positive signymptomsymptoms was were defined as having by the answers “sometimes” or “often or all the time”.

556 **Table 2. Reported the result of Discrepancy between DE symptoms signs and clinical**
 557 **findings.**

	Clinical findings		
	DE	<u>Controlnormal</u>	Total
DE	1052	658	1710
<u>Signsymptoms</u>	302	250	552
Total	1354	908	2262

558 *The discrepant group contained 960 (302+658, 42.44%) subjects ,which is significant in statistics
 559 (Pearson Chi-square test: $\chi^2=4.027$, $p = 0.045 < 0.05$). The sensitivity and specificity of DE
 560 identification based on subject symptoms were 77.70% (1052/1354) and 27.53% (250/908),
 561 respectively, while the accuracy of using the subjects' perceived symptoms for DE identification
 562 was 57.56% ((1052+250)/2262). The positive predictive value was 61.52% (1052/1710), while the
 563 negative predictive value was 45.29% (250/552).

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Table 3. Comparison of Schirmer I test and tear film break up time ~~The p~~Primary outcome variables of tear film BUT and Schirmer scores (Schirmer II) among the ~~three~~subject groups.

Sign symptoms	Clinical findings	Schirmer II test (mm)	BUT (s)
Normal	Normal	22.0 (2.0-30.0)	12.5 (0.0-30.0)
Discrepancy		15.0 (0.0-30.0)	9.0 (0.0-30.0)
DE	DE	5.0 (0.0-30.0)	4.0 (0.0-20.0)

*There were remarkable differences in the values obtained for Schirmer II testing and tear film BUT among our three study groups (Schirmer II test: $\chi^2=422.93$, $p<0.0001$; BUT: $\chi^2=264.85$, $p<0.0001$).

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	√ 1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	√ 2	Explain the scientific background and rationale for the investigation being reported
Objectives	√ 3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	√ 4	Present key elements of study design early in the paper
Setting	√ 5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	√ 6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case
Variables	√ 7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	√ 8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	√ 9	Describe any efforts to address potential sources of bias
Study size	√ 10	Explain how the study size was arrived at
Quantitative variables	√ 11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	√ 12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses

Continued on next page

Results		
Participants	√ 13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed <hr/> (b) Give reasons for non-participation at each stage <hr/> (c) Consider use of a flow diagram
Descriptive data	√ 14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders <hr/> (b) Indicate number of participants with missing data for each variable of interest <hr/> (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)
Outcome data	√ 15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <hr/> <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <hr/> <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures
Main results	√ 16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included <hr/> (b) Report category boundaries when continuous variables were categorized <hr/> (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	√ 17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	√ 18	Summarise key results with reference to study objectives
Limitations	√ 19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	√ 20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	√ 21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	√ 22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.