Air Pollution Associated Dry Eye Disease May Be Increased by Qi Stagnation in Young: A Nested Case-Control Study in Liaoning, China

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Abstract

Background: Little information exists regarding the interaction of Qi stagnation and air pollution on young's dry eye disease (DED) in fixed area with an epidemic threat. The aim of this study is to assess the modification by Qi stagnation on the associations of exposure with DED in Chinese young.

Methods: A nested case-control study was conducted in Chinese young population aged 17-20 years, within a cohort of He Eye Health screening project. All cases newly diagnosed ($n = 576$) were matched to controls ($n = 576$) by age and sex. Logistic regression model was used to assess the odds ratio (OR) and 95% confidence interval (CI) of DED for exposure to different air pollutants in terms of an interquartile range (IQR) increase in exposure level, adjusted for potential confounders.

Results: In single-pollutant model, the DED ORs (95% CI) for the 20th to 40th percent of quintile (vs. lowest) were 2.64 (1.66, 4.18) for PM_{2.5}, 1.70 (1.09, 2.66) for PM₁₀, for the highest quintile (vs. lowest) were 1.74 (1.13, 2.66) for CO, and 1.57 (0.98, 2.51) NO₂. In contrast, the odds ratios for the highest quintile (vs. lowest) were 0.23 (0.07, 0.78) for O₃. Corresponding estimates were higher among Stagnant qi constitution [OR_{PM10} = 1.69 (1.08, 2.16), OR_{CO} = 1.93 (1.19, 3.54)] than Balanced constitution [OR_{PM10} = 1.29 (0.79, 2.05), OR_{CO} = 1.70 (1.09, 3.43)] for PM₁₀ and CO₂, respectively. In addition, O₃ was inversely associated for Stagnant qi constitution [0.67 (0.23, 1.90)] and Balanced constitution [0.51 (0.08, 1.40)].

Conclusion: Exposure to ambient PM_{2.5}, PM₁₀, CO and NO₂ was positively associated with DED in Chinese young population. Qi stagnation might amplify the association of exposures to PM₁₀ and CO with DED.

1. Introduction

Currently, many people in China suffer from serious dust-haze pollution that detracts from their ability to live in full health [1]. The government has implemented increasingly special policy to reduce air pollution, and the individuals have established self-help to protect their cardiovascular and respiratory system [2-4]. Unfortunately, there is no public health intervention taken to protect ocular surface health, despite ocular surface is lastingly exposed to air pollutants in China [4]. Chronic exposure to air pollution causes various symptoms of ocular surface disorders, such as ocular discomfort, abnormal tear structure, and ocular surface inflammation [5-7]. As a common disorder of the ocular surface, dry eye disease (DED) causes ocular discomfort, fatigue, and visual disturbances, interfering with quality of life for millions of people worldwide, with varying severity [8]. Chronic inflammation and environmental exposures have been associated with DED, which is also public health problem affecting vision related quality of life [9]. The biological pathway may be related with alteration of autophagy activity in human corneal epithelial cell line [10]. Because the rapid increase in prevalence of DED is unlikely to be attributable to genetic changes only, environmental factors largely contribute to the development and aggravation of DED. The environmental factors include both physical and social environmental exposures. However, little

information exists regarding the interaction of physical environment (air pollution) and social environment (Qi) on DED.

Air pollution is main physical environment factor. An ecologic study suggested that short-term exposure of airborne particulate matter (PM), especially that less than 2.5 μm in diameter ($\text{PM}_{2.5}$), induced acute ocular surface diseases by altered activation of autophagy in a time-dependent manner [10]. Meanwhile, a cross-sectional study in China suggested that nitrogen dioxide (NO_2), high-temperature, wind velocity and low-humidity increased the prevalence of DED, especially for women and old people [11]. Despite less than 10% of time spent outdoors for these people, air pollutants exposure may be undeniably hazardous for human ocular surface and conjunctivitis [11-13]. A mouse dry eye model showed PM_{10} induced apoptosis by increasing TNF- α , NF- κB -p65 and NF- κB expressions in the cornea, and abnormal differentiation and proliferation of the ocular surface [14]. Thus, it is urgent to assess the association of exposure to a wide variety of individual-level air pollutants with DED of young in their respective fixed area. Thus, we need to assess the association of exposure and the key component of air pollution in the development of DED, so as to develop more effective measures of prevention and intervention.

As social environmental factor, constitution is expressed by “Qi” in the theory of Traditional Chinese Medicine (TCM). Intriguingly, a multicenter cross-sectional study in Chinese young people, suggested that the occurrence of DED may be associated with Qi stagnation, which is known as one of eight imbalanced constitutions of healthy people in TCM [15,16]. Based on TCM theory, “Balance” is referred to as Qi (yin and yang) homeostasis, which ensures the mental and physical health in Chinese Han population [17]. “Qi” is understood as an invisible effect, which corresponds to energy or signaling in modern western medicine. As for “Qi stagnation”, it is regarded as a body state in which energy metabolism or signal transduction is blocked [18]. As an increased psychosocial stress, the prevalence of “Qi stagnation” is likely to increase among Chinese young people [15,19], yet the condition is often underrecognized and undertreated [16]. However, few studies have examined the possible interaction between air pollution and “Qi stagnation” on DED. The aim of this study was to explore whether air pollutants including particulate matter ($\text{PM}_{2.5}$ and PM_{10}), and gaseous pollutants (O_3 , SO_2 , CO and NO_2) is associated with increased risk of DED in a well-defined population of Qi stagnation.

2. Methods

2.1. Study design and participants

We conducted a nested case-control study of the association between air pollution and dry eye disease (DED) at 17-20 years of age from He University students. He University is the third largest private medical college in China with an undergraduate population of 8,412 (regular) from 23 provinces in China, which is located in the beautiful Qipanshan forest scenic area of Shenyang, with the best air quality all year round ($\text{PM}_{2.5}$: $4\mu\text{g}/\text{m}^3$, PM_{10} : $14\mu\text{g}/\text{m}^3$, O_3 : $42\mu\text{g}/\text{m}^3$, SO_2 : $10\mu\text{g}/\text{m}^3$, CO: $0.6\mu\text{g}/\text{m}^3$ and NO_2 : $15\mu\text{g}/\text{m}^3$). Since 2017, we have conducted a long-term study of He Eye Health (HEH) screening among freshmen enrolled once a year. The diagnostic check of study was conducted by expert physicians. All protocols were

approved by the medical ethics committee of He University [Approval number: IRB (2017) K004.01], and were in accordance with the World Medical Association Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects. Due to a continuing 2019-nCoV epidemic threat of novel coronaviruses, all students were forced to go home on holiday from January to July in 2020, and could not leave their respective communities under the control of the government. Until August 2020, most students were allowed to return to university. Thus, these students were exposed to air pollution from January to July in 2020, in their respective fixed areas.

We included students who lived in Liaoning and had no DED from the HEH screening visit in September 2019. We excluded students who had positive history of smoking, refractive surgery or contact lens wear, who used systemic medication, such as antianxiety, antidepressive, and antihypertensive medications. The enrolled students ($n = 6407$) read and signed an information and consent form before participating in this study, and attended the physical examination and completed the symptom questionnaires of the demographic information and daily custom, Qi stagnation and Ocular Surface Disease Index (OSDI). Then, we recruited 576 participants with DED (cases) and 576 without DED (controls) from 6407 students. Cases had to have at least two of the the following three signs in at least one eye: a) corneal fluorescein staining (CFS), b) tear break-up time (TBUT), c) Schirmer's test with anesthesia. Cases included all patients newly diagnosed with active DED. Controls were selected from enrolled students without DED, were matched to cases (1:1) by age and sex. Individual air pollution exposure of participants ($n = 1152$) was estimated using the measurements from the municipal air monitoring station, which was located 1000 meters from each participant's home.

2.2. Stagnant qi

The the enrolled students ($n = 6407$) with the Stagnant qi or Balanced constitutions were chosen through completion of a standardised questionnaire according to the constitution classification criteria (Table 1) confirmed by the Chinese Association of TCM. Then, based on Classification standard of TCM Constitution (ZZYXH/T157-2005) [15, 17-19], the Stagnant qi or Balanced constitutions were diagnosed by TCM doctors through the method of observation, hearing and questioning (main symptoms: introverted and unstable, melancholy and fragile, sensitive and suspicious, poor ability to adapt to mental stimulation, usually melancholy face, look more bored and unhappy; auxiliary symptoms: chest and hypochondriac fullness, or running pain, often accompanied by sigh, or belching hiccup, or pharyngeal foreign body sensation, or breast swelling pain, poor sleep, loss of appetite, palpitation, palpitation, forgetfulness, phlegm, more dry stool, normal urination, reddish tongue, thin white moss, fine pulse.)

2.3. Signs of DED

2.3.1. OSDI

The enrolled students ($n = 6407$) were chosen by using a score on OSDI confirmed by the Outcomes Research Group at Allergan Inc. (Irvin, California). The OSDI includes 12-items. Each item is scored on a scale from 0 to 4 (0 = none of the time, 1 = some of the time, 2 = half of the time, 3 = most of the time, 4 =

all of the time). A score = [sum of the scores for all questions answered X 25] / total number of questions answered]. The scores indicate normal (scores 0-12), mild (13-22), moderate (23-32), and severe (33-100) DED.

2.3.2. CFS

CFS was measured by the National Eye Institute/Industry (NEI) grading scale as previously described [20]. The total CFS score ranges from 0 to 15, with higher scores indicating greater abnormality. The NEI grading scale consists of a grid that divides the corneal area into five sections, each of which is assigned a score between 0 and 3 depending of the amount and distribution of CFS.

2.3.3 TBUT

TBUT was performed using Lowther technique in each eye following a previous method [21]. A sterile fluorescein strip (Indicator, He eye Co., Shenyang, China) was moistened using nonpreserved saline. The time between a blink and the appearance of gaps in the tear film was tested in seconds. The time ranges from 0 to 7 seconds, with shorter times indicating greater abnormality.

2.3.4 Schirmer's test

After TBUT, the participant waited for 30 min, then performed Schirmer's test with anesthetic as previously described [22]. The Schirmer's test is measuring the total tear secretion (basic and reflex) in each eye, ranging from 1 to 7 mm in 5 minutes . The length of wetting of paper strips placed in the inferior cul de sac of the lower eyelid, with shorter lengths indicating greater abnormality.

2.4. Exposure assessment

The average ambient concentrations of PM_{2.5}, PM₁₀, O₃, SO₂, CO and NO₂ were obtained as previously described [23]. We obtained the average daily concentrations of these pollutants for each participant during seven months (from January 1, 2020 to July 31, 2020). The data were based on one of air pollution monitoring stations located within 1000 meters residence from each participant's home, and obtained using air pollution monitoring stations from National Climate Center in Ministry of Ecology and Environment of China by the use of AirData (<http://www.zhb.gov.cn/>). We estimated the average daily exposure for usual residence of each study participant, and then added the data together to calculate the monthly mean concentrations of the aggregate exposures. In addition, we calculated average 8-hr concentrations of CO and O₃ from these same monitors closest to each participant's home address. Because the participants were in own closed communities, we ensured that these average values were available during this study period.

2.5 Confounders

We assessed potential individual-level confounders and effect measure modifiers, including demographics and socioeconomic characteristics (eg, age, sex, body-mass index, parents' education

level), lifestyle factors (eg, myopia, time spent squinting at computer and cell phone, sleep, humidity), and “constitution” (defined as the unique TCM entity exhibiting individual’s biological feature and clinical presentation). To explore the potential role of “Qi stagnation” in the association between air pollution and DED, this variable was constructed from both behavioural and temperamental information estimated.

2.6. Statistical analysis

We used Chi-square test to compare the frequencies of baseline characteristics to the status of participants with DED and controls, used two-sample *t*-test to compare the values of OSDI score, corneal staining score, TBUT and the result on Schirmer’s test between two groups, and used 1:1 paired logistic models adjusting for all matching factors (age, and sex), to assess other influencing factors for the association between DED and each average air pollutant concentration (PM_{2.5}, PM₁₀, O₃, SO₂, CO and NO₂) assigned to each participant for the 7 months before diagnosis (study entry) date. For ease of interpretation, the “Time” was recorded (1 = cases, 2 = age and gender-matched controls), and the “Status” was recorded [1 = case group (virtual censoring group), 0 = control group]. The paired pair number (“ID”) was selected into “Strata” list box, and the influencing factors were selected into “Covariates” list box. We selected exposure level below the 20th percentile as the referent category (baseline level) for each pollutant.

Potential confounders were based either on actual articles from the medical literature [11,24-26]. We assessed potential confounders using a > 10% change for these risk factors such as, body-mass index (BMI), time spent at computer or mobile phone, myopia, parental education level, sleep, humidity, which could potentially confound the relationship between air pollution and DED. There were no factors confounding the associations between air pollution and DED. Thus, the final analysis did not include the above factors. The matching factors were age and sex in this final model. Furthermore, we assessed potential effect modifier (constitution) using likelihood ratio tests (LRTs) [27]. If the LRT differed at a significance level of < 0.10, we considered effect modification to be present. The effect modifiers according with this criterion included constitution. Data were analyzed with the use of SPSS software for Windows, version 20.0 (IBM SPSS, Inc., Chicago, IL).

3. Results

3.1. Study Subjects

Table 2 showed ocular test values at baseline and screening. Table 3 summarized the basic characteristics of DED and matched controls nested within the college students. We identified 576 cases of DED, and 576 controls matched 1:1 to cases by age and sex, which were selected from the enrolled (September 2019) in He University during the study period. Less than one-fifth (186) of the participants were classified as Qi stagnation. The study population was split by sex ratio according to 1:3 (male:female) between cases and controls. Although there was no significant difference in the ratio of Qi

stagnation between males and females from controls (23.1% vs. 18.7%), a larger percentage of males were considered Qi stagnation than females among cases (21.1% vs. 9.5%).

3.2. Air Pollution Concentrations

Table 4 showed that average ambient air pollution concentrations in the 7 months before the DED diagnosis date varied for participants. There were no significant differences in the Median air pollution concentrations between the Stagnant qi constitution and Balanced constitution for all pollutants.

Table 5 present Spearman's correlation air-pollutant averages in the 7 months. The correlation coefficients showed only moderate correlations observed between air pollutants. The strongest correlation among coefficients was seen for PM_{2.5} and PM₁₀ ($r = 0.825$).

3.3. DED

Table 6 demonstrated that the single and multi-pollutant models associations between air pollution (in quintiles) and DED diagnosis in the 7 months prior to diagnosis date/study entry among all cases and matched controls by the odds ratios (ORs) and 95% confidence intervals (CIs). The matching factors of age and sex were used to adjust all effect estimates.

In single-pollutant models, DED was not associated with the criteria pollutant SO₂. Additionally, PM_{2.5}, PM₁₀, CO and NO₂ were positively associated with DED. Specially, the strongest positive effect estimates among all participants for the association of ambient air pollution and DED were observed for PM_{2.5} [OR = 2.64 (95% CI: 1.66, 4.18)]. There were positive dose-response patterns between air pollution exposure (CO and NO₂) and DED odds. However, O₃ was inversely associated with DED. Specially, the inverse association in the 60th to 80th quintile of O₃ exposure had a considerable decrease in risk of dry eye symptoms than the in the lowest quintile [OR = 0.23 (95% CI: 0.07, 0.78)]. Also, there was inverse dose-response pattern between O₃ and DED odds.

Simultaneously, in multi-pollutant models, these results were generally consistent with those of the single-pollutant models, but most of effect estimates were attenuated. In contrast, for PM_{2.5} and CO, effect estimates were enhanced. Especially, in multi-pollutant models, the OR for the 20th to 40th percent of quintiles of PM_{2.5} exposure was 4.79 (95% CI: 1.94, 11.82).

3.4. DED stratified by Stagnant qi constitution

Table 7 showed that the Stagnant qi constitution was an effect modifier of the association between ambient PM₁₀, CO and DED ($p = 0.09, 0.10$) for the interaction on a multiplicative scale in single-pollutant models. Under stratification, we found no dose-response pattern. The effect estimates for the highest quintile of PM₁₀ exposure, compared with those of the lowest, were more pronounced among Stagnant qi constitution [OR = 1.69 (95% CI: 1.08, 2.16)] than among balanced constitution [OR = 1.29 (95% CI: 0.79, 2.05)]. But, A dose-response pattern was observed that the effect estimates for the highest quintile of CO

exposure, compared with those of the lowest, were more pronounced among Stagnant qi constitution [OR = 1.93 (95% CI: 1.19, 3.54)] than among balanced constitution [OR = 1.70 (95% CI: 1.09, 3.43)].

When stratified by different constitutions, the ORs previously observed in nonstratified models were less pronounced. The association between PM_{2.5}, NO₂ and DED was more pronounced among Stagnant qi constitution [OR = 1.77 (95% CI: 1.00, 3.11), OR = 1.90 (95% CI: 1.04, 3.47), for the highest vs. the lowest quintile of exposure] than among balanced constitution [OR = 0.99 (95% CI: 0.33, 2.99), OR = 1.39 (95% CI: 0.49, 3.94)], but based on LRT heterogeneity in the effect estimates was not statistically significant (p = 0.145, 0.130).

Under stratification on different constitutions, the strength of the inverse association was similar among both balanced constitution and Stagnant qi constitution for the association between O₃ and DED.

4. Discussion

We provided a nested case-control study of its kind to assess the potential associations between air pollutants and DED within Chinese young people aged 17-20 years. The main strength of our study was that physical-social environment interactions between Stagnant qi constitution and the key component of air pollutants (PM₁₀ and CO) on the risk of DED. The risks of other air pollutants on DED were mutually adjusted to estimate their independent associations by using multi-pollutant model. This multi-pollutant model was used to explain the mutual confounding between pollutants, but, if these multi-pollutants were highly correlated, a number of potential variance inflation and bias is often possible [27,28]. We provided both single- and multi-pollutant model results, due to uncertainty about which model inducing the least-biased estimates. In this sample, a dose-response relationships were observed between air pollutants exposure [CO and NO₂ (positive), O₃ (inverse)] and DED odds. But, no consistent association was observed between PM_{2.5}, PM₁₀, SO₂ and DED., which could be related to perturbing mechanisms of tear homeostasis [8].

Although we observed no consistent association between PM and DED, we found a positive correlation between PM exposure and DED. Moreover the correlation between PM_{2.5} and DED was significantly compared with PM₁₀ exposure. This could be the reason that polycyclic aromatic hydrocarbon (PAH) level in PM_{2.5} from indoor dust at Chinese public places accounted for 71.5% of total particulate PAHs [29]. Ambient particle concentrations are primarily from combustion products (coal combustion and biomass burning), secondarily from diesel vehicle emissions [30]. Recently, an experimental study has shown that PM_{2.5} exposure slightly inhibit autophagy in the early stage, but activated autophagy in the late stage by homeostatic alteration between accelerating apoptosis and inhibit proliferation in human corneal epithelial cells [10]. Experimental studies have also shown that PM significant impaired human ocular health. It is the reason that heavy metals and PAHs are not only adsorbed on the surface of PM but also deeply encrusted in its structure [31,32]. The results of a previous study of combustion products were consistent with the hypothesis that diesel exhaust particles may be linked to cytotoxicity and

inflammatory responses because both have induced oxidative stress in human conjunctiva cells [33]. Also, we noticed that our analysis for PM_{2.5} and PM₁₀ was not consistent with one previous human epidemiological study reporting no association between short-term PM exposure and DED in the multivariate conditional logistic regression analyses [34], and suggesting the complex sources may represent PM_{2.5} and PM₁₀ as nonspecific pollutants, and leading to a failure in the relevance.

The positive associations between exposure to CO (or NO₂) and DED were consistent with other available evidence. Ambient CO and NO_x together in China in this setting are considered a surrogate of traffic emission, due largely to incomplete combustion inside motor engines [34]. NO₂ itself could acidify the tears and caused a decrease in tear break-up time [35,36], moreover, CO inhalation could lead to an increase in arterial and venous diameters, retinal blood flow velocity, and fundus pulsation amplitude in a placebo-controlled study [37].

Also, we observed a consistent inverse association between O₃ and DED, which is not consistent with the previous study, which reported increased O₃ levels were associated with dry eye symptoms in the Korean population [5]. It is the reason that ambient O₃ and NO₂ levels are bonded by chemical coupling, and the formation of O₃ needs to deplete nitrogen with the help of sunlight [38,39]. Consequently, when exposed to high levels of NO₂, the individuals usually undergoes a low exposure to O₃, and especially along high-traffic areas [40].

There was no consistent association between SO₂ and DED in this study, which was consistent with other epidemiological studies [5,34]. These studies also estimated that SO₂ was not associated with symptoms or diagnosis of DED. This was related to the decreasing SO₂ levels, due to the worldwide use of fuel with low sulfur content [41].

To reduce differential misclassification of “Qi stagnation” to some extent, we blindly assigned “Qi stagnation” status to case and air pollution exposure status. In addition, for study eligibility, we matched cases and controls on age and sex, and “Qi stagnation” status were diagnosed before recorded air pollution exposure. Moreover, a person’s Qi state is very difficult to change in a short time [16].

Limitations to the present study include the small sample size. This raised the possibility that findings were attributed to chance and hence need to be replicated. We did not consider seasonal and daily variations in air pollutants, and not collect other potential confounders, such as wind and temperature. Because of the severe air pollution in China, our findings were probably not well-suited for reflecting the integrated population from developed countries in North America and parts of Europe, due to their good air quality. Nevertheless, our analysis may provide valuable references for some developing countries. Heavy air pollution caused DED, which may lead symptom like Qi stagnation indirectly. Thus, we need to indicate causal relationships between Qi stagnation and exposure of air pollutants and DED.

In summary, our results showed positive associations between PM_{2.5}, PM₁₀, CO, NO₂ and risk of DED. The Stagnant qi constitution might increase the association between PM₁₀, CO and DED.

5. Conclusion

Our prospective cohort study suggested that Stagnant qi constitution might increase the susceptibility short-term exposure (PM₁₀ or CO) as associated with DED at young. Future studies require larger sample sizes to have sufficient statistical power to detect a significant interaction.

Declarations

Ethical Approval and Consent to participate

This study was approved by the medical ethics committee of He University [Approval number: IRB (2017) K004.01], and all participants have signed informed consents.

Informed consent was obtained from all parent and/or legal guardian of minors (under 18).

Consent for publication

Not applicable.

Availability of supporting data

The datasets generated during and analysed during the current study are available from the corresponding author on reasonable request for all interested researchers upon requests sent to the author's office. The initial contact for request should be addressed to the corresponding author's institution.

Competing interests

The authors declare that they have no conflicts of interest.

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Authors' contributions

XR He and FY conceived and designed the experiments. F Yu, J Li, C Yu, CH Yan and W Hao performed the experiments. F Yu, ZJ Ren and W Song analyzed the data. F Yu and W Hao wrote the paper. All authors read and approved the final manuscript.

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Tables

Table 1 Diagnostic standards for the Stagnant qi and Balanced constitutions

	Stagnant qi	Balanced
Main characteristics	Melancholy Sensitiveness	Energetic without any symptoms or characteristics of other constitutions
	Chest distending pain	
	Poor sleep	Good sleep
	Belching hiccup	Good appetite
Secondary characteristics	Poor appetite Poor memory Red tongue and white moss	Good memory

Table 2 Ocular test values of enrolled students at baseline and after the 12-month screening

	Baseline (September 2019)	Screening Outcomes (September 2020)	
		Case	Control
Number of eyes	12814	1152	1152
OSDI score	4.13 ± 3.84	32.09 ± 21.10	5.27 ± 3.81
CFS	1.06 ± 0.98	4.13 ± 2.82	0.98 ± 0.84
TBUT[sec]	4.51 ± 2.36	2.65 ± 1.13	4.46 ± 2.37
Schirmer’s test (mm/5 min)	12.11 ± 6.72	7.10 ± 3.96	10.80 ± 5.79

OSDI = Ocular Surface Disease Index, CFS = corneal fluorescein staining, TBUT = tear break-up time

Table 3. Characteristics of dry eye disease and matched controls ($n = 1152$)

Characteristics <i>n</i> (%)	All Cases Controls <i>n</i> = 576 <i>n</i> = 576		Stagnant qi <i>n</i> = 186 Cases Controls <i>n</i> = 72 <i>n</i> = 114		Balanced <i>n</i> = 966 Cases Controls <i>n</i> = 504 <i>n</i> = 462	
Sex						
Male	143(24.8)	143(24.8)	31(43.1)	33(28.9)	112(22.2)	110(23.8)
Female	433(75.2)	433(75.2)	41(56.9)	81(71.1)	392(77.8)	352(76.2)
Age						
17	39(6.8)	45(7.8)	2(2.8)	8(7.0)	37(7.3)	37(8.0)
18	268(46.5)	262(45.5)	31(43.1)	59(51.8)	237(47.0)	203(43.9)
19	187(32.5)	184(31.9)	23(31.9)	35(30.7)	164(32.5)	149(32.3)
20	82(14.2)	85(14.8)	16(22.1)	12(10.5)	66(13.1)	73(15.8)
BMI						
< 18.5	85(14.8)	94(16.3)	8(11.1)	18(15.8)	77(15.3)	76(16.5)
18.5 ~ 23.9	324(56.2)	334(58.0)	41(56.9)	70(61.4)	283(56.2)	264(57.1)
24 ~	167(29.0)	148(25.7)	23(31.9)	26(22.8)	144(28.6)	122(26.4)
Myopia						
No	266(46.2)	235(40.8)	39(54.2)	35(30.7)	227(45.0)	200(43.3)
Yes	310(53.8)	341(59.2)	33(45.8)	79(69.3)	277(55.0)	262(56.7)
Paternal myopia						
No	387(67.2)	395(68.6)	63(87.5)	85(74.6)	324(64.3)	310(67.1)
Yes	189(32.8)	181(31.4)	9(12.5)	29(25.4)	180(35.7)	152(32.9)
Paternal education level						
High school graduate	504(87.5)	494(85.8)	9(12.5)	29(25.4)	180(35.7)	152(32.9)
College degree	72(12.5)	82(14.2)				

Time at computer (cell phone)	505(87.7)	493(85.6)	62(86.1) 96(84.2)		442(87.7) 398(86.1)	
< 2 h/d			10(13.9) 18(15.8)		62(12.3)	64(13.9)
			66(91.7) 95(83.3)		439(87.1) 398(86.1)	
2 h/d ~	71(12.3)	83(14.4)	6(8.3)	19(16.7)	65(12.9)	64(13.9)
Sleep time						
< 8 h/d	111(19.3)	116(20.1)	12(16.7) 21(18.4)		99(19.6)	95(20.6)
8 h/d ~	465(80.7)	460(79.9)	60(83.3) 93(81.6)		405(80.4) 367(79.4)	
Areas with low humidity						
No	369(64.1)	365(63.4)	48(66.7) 76(66.7)		321(63.7) 289(62.6)	
Yes	207(35.9)	211(36.6)	24(33.3) 38(33.3)		183(36.3) 173(37.4)	

Table 4. Distribution of ambient air pollution concentrations averaged across a 7-month period

Air pollutant	Percentile distribution						
	Minimum	P_{20}	P_{40}	P_{50}	P_{60}	P_{80}	Maximum
Total population (1152)							
PM _{2.5} (µg/m ³)	13.70	41.36	44.17	47.80	53.30	62.10	99.47
PM ₁₀ (µg/m ³)	25.03	73.04	76.64	84.40	91.20	102.50	215.00
O ₃ (µg/m ³)	59.60	78.83	86.90	92.33	94.79	102.87	116.03
SO ₂ (µg/m ³)	5.47	18.47	24.70	26.43	29.77	42.33	80.17
CO(mg/m ³)	0.48	0.85	0.95	0.97	1.10	1.38	2.38
NO ₂ (µg/m ³)	11.70	25.67	31.00	31.23	34.30	43.40	60.43
Stagnant qi (186)							
PM _{2.5} (µg/m ³)	16.50	41.36	45.14	49.17	54.63	62.10	99.47
PM ₁₀ (µg/m ³)	39.90	73.00	76.66	83.90	91.30	102.50	166.13
O ₃ (µg/m ³)	63.00	78.21	86.67	90.37	93.80	99.90	116.03
SO ₂ (µg/m ³)	7.97	17.19	24.60	26.43	28.31	42.33	80.17
CO(mg/m ³)	0.48	0.89	0.97	0.99	1.12	1.38	2.38
NO ₂ (µg/m ³)	11.83	25.15	31.05	31.23	36.05	43.40	59.77
Balanced (966)							
PM _{2.5} (µg/m ³)	13.70	41.36	44.17	47.37	52.67	62.10	99.47
PM ₁₀ (µg/m ³)	25.03	73.07	76.64	83.90	90.67	102.50	215.00
O ₃ (µg/m ³)	59.60	78.83	86.90	92.33	94.79	102.87	116.03
SO ₂ (µg/m ³)	5.47	18.50	24.70	26.43	29.77	42.33	80.17
CO(mg/m ³)	0.48	0.85	0.95	0.97	1.10	1.38	2.38
NO ₂ (µg/m ³)	11.50	25.67	31.00	31.23	35.86	43.40	60.43

Table 5. Spearman correlation coefficients for the estimates of cumulative ambient criteria air pollutant concentrations.

Air pollutant	PM _{2.5}	PM ₁₀	O ₃	SO ₂	CO	NO ₂
PM _{2.5}	1	0.825	0.170	0.331	0.409	0.578
PM ₁₀		1	0.171	0.439	0.572	0.420
O ₃			1	-0.261	-0.210	-0.233
SO ₂				1	0.428	0.330
CO					1	0.763
NO ₂						1

Table 6. Conditional logistic regression estimated adjusted^a odds ratios (ORs) and 95% confidence intervals (CIs) for associations of dry eye disease with air pollutant concentrations

Air pollutant	Quintile	Single	Multi ^b
PM _{2.5}	1	Reference	Reference
	2	2.64 (1.66, 4.18)	4.79 (1.94, 11.82)
	3	1.80 (1.12, 2.92)	2.87 (1.17, 7.07)
	4	1.58 (1.00, 2.48)	2.29 (0.99, 5.23)
	5	1.85 (1.17, 2.93)	2.12 (0.91, 4.94)
PM ₁₀	1	Reference	Reference
	2	1.70 (1.09, 2.66)	1.37 (1.15, 1.90)
	3	1.19 (0.69, 2.06)	1.35 (1.12, 2.00)
	4	1.39 (0.90, 2.13)	1.54 (1.25, 2.14)
	5	1.44 (0.95, 2.18)	1.71 (1.35, 2.43)
O ₃	1	Reference	Reference
	2	0.54 (0.13, 2.01)	0.52 (0.21, 1.41)
	3	0.37 (0.17, 1.52)	0.35 (0.18, 1.72)
	4	0.36 (0.13, 1.23)	0.30 (0.09, 0.98)
	5	0.23 (0.07, 0.78)	0.25 (0.04, 0.61)
SO ₂	1	Reference	Reference
	2	1.22 (0.75, 1.98)	0.83 (0.44, 1.58)
	3	0.94 (0.59, 1.50)	0.89 (0.46, 1.71)
	4	0.92 (0.56, 1.51)	0.64 (0.30, 1.37)
	5	1.11 (0.69, 1.78)	1.07 (0.59, 1.92)
CO	1	Reference	Reference
	2	1.19 (0.78, 1.82)	1.54 (0.86, 2.76)
	3	1.23 (0.78, 1.93)	1.62 (0.92, 2.85)
	4	1.62 (1.00, 2.62)	2.12 (1.13, 3.99)
	5	1.74 (1.13, 2.66)	2.15 (1.03, 4.48)
NO ₂	1	Reference	Reference
	2	1.15 (0.82, 2.23)	0.97 (0.45, 2.09)
	3	1.19 (1.05, 2.71)	1.02 (0.52, 2.00)

4	1.45 (1.22, 3.13)	1.02 (0.52, 2.01)
5	1.57 (0.98, 2.51)	1.05 (0.51, 2.18)

^aAdjusted for the matching factors (age and sex)

^bMulti-pollutant model: SO₂ + PM₁₀ + PM_{2.5} + CO + NO₂ + O₃.

Table 7. Conditional logistic regression estimated adjusted^a odds ratios (ORs) and 95% confidence intervals (CIs) for associations of dry eye disease with air pollutant concentrations, stratified by constitution

Air pollutant	Quintile	Balanced constitution	Stagnant qi constitution	<i>P</i>
PM _{2.5}	1	Reference	Reference	
PM ₁₀	2	2.07 (1.05, 3.71)	2.23 (1.27, 3.90)	0.145
	3	2.11 (1.48, 4.25)	1.87 (1.04, 3.36)	
	4	0.92 (0.24, 3.61)	1.53 (0.87, 2.69)	
	5	0.99 (0.33, 2.99)	1.77 (1.00, 3.11)	
	1	Reference	Reference	
O ₃	2	1.80 (0.88, 3.20)	1.67 (1.02, 2.90)	0.085
	3	1.19 (0.44, 3.95)	1.26 (0.65, 2.47)	
	4	1.12 (0.31, 2.01)	1.66 (0.98, 2.82)	
	5	1.29 (0.79, 2.05)	1.69 (1.08, 2.16)	
	1	Reference	Reference	
SO ₂	2	0.48 (0.07, 1.45)	0.54 (0.12, 1.54)	0.332
	3	0.27 (0.03, 1.10)	0.37 (0.10, 1.45)	
	4	0.39 (0.05, 1.26)	0.48 (0.15, 1.53)	
	5	0.53 (0.08, 1.40)	0.67 (0.23, 1.90)	
	1	Reference	Reference	
CO	2	0.65 (0.15, 1.80)	1.24 (0.69, 2.24)	0.113
	3	0.96 (0.24, 1.93)	1.17 (0.67, 2.24)	
	4	0.50 (0.10, 1.42)	1.07 (0.60, 1.90)	
	5	0.56 (0.13, 1.33)	1.33 (0.75, 2.34)	
	1	Reference	Reference	
NO ₂	2	1.09 (0.34, 3.49)	1.38 (0.81, 2.38)	0.098
	3	1.50 (1.15, 2.71)	1.39 (0.95, 3.06)	
	4	1.69 (1.11, 3.24)	1.53 (0.91, 2.58)	
	5	1.70 (1.09, 3.43)	1.93 (1.19, 3.54)	
	1	Reference	Reference	
NO ₂	2	1.09 (0.67, 3.53)	1.40 (0.78, 2.53)	
	3	1.14 (0.37, 3.56)	1.64 (0.91, 2.97)	
	4	1.03 (0.23, 2.70)	1.56 (0.86, 2.84)	

5	1.39 (0.49, 3.94)	1.90 (1.04, 3.47)	0.130
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^aAdjusted for the matching factors (age and sex)

p-Value of likelihood ratio test comparing model fit with and without inclusion of interaction terms.

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