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Air Pollution and Tear Lactoferrin among Dry Eye Disease Modifications by Stress and Allergy: A Case–Control Study of Taxi Drivers

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Abstract: Few studies have explored the possible associations between air pollution and tear lactoferrin (Lf) levels, a non-invasive biological marker of ocular surface diseases, among taxi drivers, while none have explored the modifications by stress and allergic tendencies in the relationship. We recruited 1905 taxi drivers with dry eye disease (DED) and 3803 non-DED controls in Liaoning, China, in 2012–2014. After physical examination and questionnaires were recorded, ocular surface was measured and tear Lf was determined by electrophoresis. Air pollutants and humidity were estimated by measured concentrations from monitoring stations. Conditional logistic regression models were employed to examine the associations of air pollutants and humidity with tear Lf levels. Among taxi drivers with stress or allergic tendencies, an IQR (26 μg/m^3, 10 μg/m^3) increase in PM_{10} and NO_2 levels elevated the adjusted odds ratio by 1.89 (95% CI, 1.19 to 3.08) or 1.77 (95% CI, 1.06 to 2.90); and 2.87 (95% CI, 1.60 to 3.58) or 2.93 (95% CI, 1.64 to 3.83), respectively. In contrast, humidity was inversely associated for taxi drivers with stress [0.51 (95% CI, 0.38 to 0.64)] or allergic tendencies [0.49 (95% CI, 0.11 to 0.84)]; and for taxi drivers without stress [0.33 (95% CI: 0.17, 0.39)] or without allergic tendencies [0.39 (95% CI, 0.19 to 0.59)]. Tear Lf was negatively associated with each quartile of PM_{10} or NO_2 exposure, and low humidity. PM_{10}, NO_2, and low humidity were inversely associated with Lf levels, especially for DED taxi drivers with stress and allergic tendencies.

Keywords: air pollution; dry eye disease; lactoferrin; taxi drivers

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Citation: Hao, W.; Kong, F.; Song, W.; Zhang, L.; Xu, X.; Ren, Z.; Li, J.; Yu, F. Air Pollution and Tear Lactoferrin among Dry Eye Disease Modifications by Stress and Allergy: A Case–Control Study of Taxi Drivers. *Atmosphere* **2022**, *13*, 2003. https://doi.org/10.3390/atmos13122003

Academic Editors: Francesca Costabile and Daniele Contini

Received: 4 July 2022
Accepted: 21 November 2022
Published: 29 November 2022

1. Introduction

As a major global public health problem, climate change and pollution impact human health and mortality [1]. Recently, the Chinese government has implemented increasingly specific policies to reduce air pollution [2,3], and affected people have established self-help to prevent respiratory illnesses and cardiovascular ailments [4]. Unfortunately, fewer protection measures are provided regarding ocular surface health, despite ocular surface being continuously exposed to climate change and pollution [4].

As the most common ocular surface disease, dry eye disease (DED) causes ocular discomfort due to the abnormal amount or quality of tear fluid involving oxidative stress and inflammation mechanisms [5]. Although DED is not cause life-threatening, it seriously interferes with vision-related quality of life [5]. Particularly in China, the prevalence of DED continues to increase and was as high as 17–21% (from 2008 to 2010) [6]. However, studies on the association of air pollution with DED face two main challenges: (1) There is no uniform diagnostic standard for DED [7]: The questionnaires for symptoms can induce under-reporting due to homeostatic mechanisms of the ocular surface, or over-reporting due to individual sensitivity [8]. The clinical tests are not specific for one subtype [9]; and (2) Most are cross-sectional studies which do not establish the dose-response relationship between DED and exposure, and the modification of potential factors between air pollution and DED is not evaluated [10].

Thus, this study selected a specific occupation (taxi drivers) experiencing long-term outdoors exposure; collected air pollution data two years before diagnosis; and matched age and sex through a case-controled study, to explore whether covariates (especially stress and allergic tendencies) can conduct the modifications in the relationship between air pollution and DED (i.e., aggravating DED risk). Next, we wanted to further analyze whether lactoferrin (Lf) was a non-invasive biological marker of chronic exposure to specific pollution and ocular surface disease risk [11], stratified by covariates.

2. Materials and Methods

2.1. Study Participants

First, based on the 2012–2014 total gross domestic product (GDP) of each city provided by the Liaoning Provincial Bureau of Statistics, we divided all the 14 cities into three socio-economic zones: low (a total annual GDP of less than RMB 100 billion), medium (a total annual GDP of RMB 100 billion to RMB 600 billion), and high (a total annual GDP of more than RMB 600 billion). There are eight cities (Benxi, Chaoyang, Liaoyang, Fushun, Dandong, Huludao Tieling, and Fuxin) in Liaoning that belong to the low socio-economic zones, four cities (Anshan, Yingkou, Panjin, and Jinzhou) that belong to the middle socio-economic zones, and two cities (Shenyang and Dalian) that belong to the high socio-economic zones. To maximize the inter-city gradients of interest, and to minimize the correlation between pollutants, we selected 6 cities from these three socio-economic regions as sample selection regions based on 2012–2014 air pollution measurements.

Second, between 1 January and 31 December 2014, 8758 individuals from six cities provided information related to their physical examination, socioeconomic status, and behavioral habits, and were classified according to the Ocular Surface Disease Index (OSDI). According to the inclusion criteria, 7611 drivers entered the next step of examination or treatment. Cases had to have at least two of the following three signs in at least one eye: (a) corneal fluorescein staining (CFS) [12]; (b) tear break-up time (TBUT) [13]; and (c) Schirmer's test [14] with anesthesia. Controls were selected from enrolled taxi drivers without DED, and were matched to cases by age and sex.

We recruited a final total of 1905 participants with DED (case group) and 3803 participants without DED (control group) from the 7611 taxi drivers (Figure 1 Flow chart). After measurements of visual acuity and slit lamp examinations were taken, we collected unstimulated tears of these taxi drivers using a capillary tube, and quantified their Lf levels by electrophoresis [15]. Tear Lf levels were detected using a Human lactoferrin ELISA kit from Biovision Chemicals, Inc. (San Francisco, CA, USA). We put 10 µL of saline into the conjunctival sac with a micropipette ring cap. Tear fluid samples were stored at −80 °C until analysis. The Lf detection limit of this test is 4 ng/mL. The concentration of Lf was measured twice, and the average value of the two measurements was used as the concentration of Lf protein. All study procedures and protocols were approved by the medical ethics committee of China Medical University [Approval number: SCXK_LN CMU 2013-0222].

2.2. Air Pollution Exposure Assessment

The average ambient concentrations of $PM_{2.5}$, PM_{10}, O_3, SO_2, CO and NO_2 were obtained as previously described [16]. For CO and O_3 exposure, we calculated the average 8-h concentration, and calculated the average 24-hour concentration for other pollutants. We obtained the average daily concentrations of these pollutants for 2012 to 2014 from the Liaoning Provincial Meteorological Bureau database using AirData (http://www.zhb.gov.cn/ (accessed on 21 September 2017)). In the selected 6 cities, each district of each city had a municipal air monitoring station, which was used to record the concentration of daily ambient air pollutants and relative humidity. All data was collected by the hour. Since taxi drivers work outdoors all year round, we used the air pollutant concentration in each district to estimate the daily average concentration of air pollutants in the city where participants were located, then added these data together to calculate the monthly average concentration of aggregate exposure for each taxi driver.

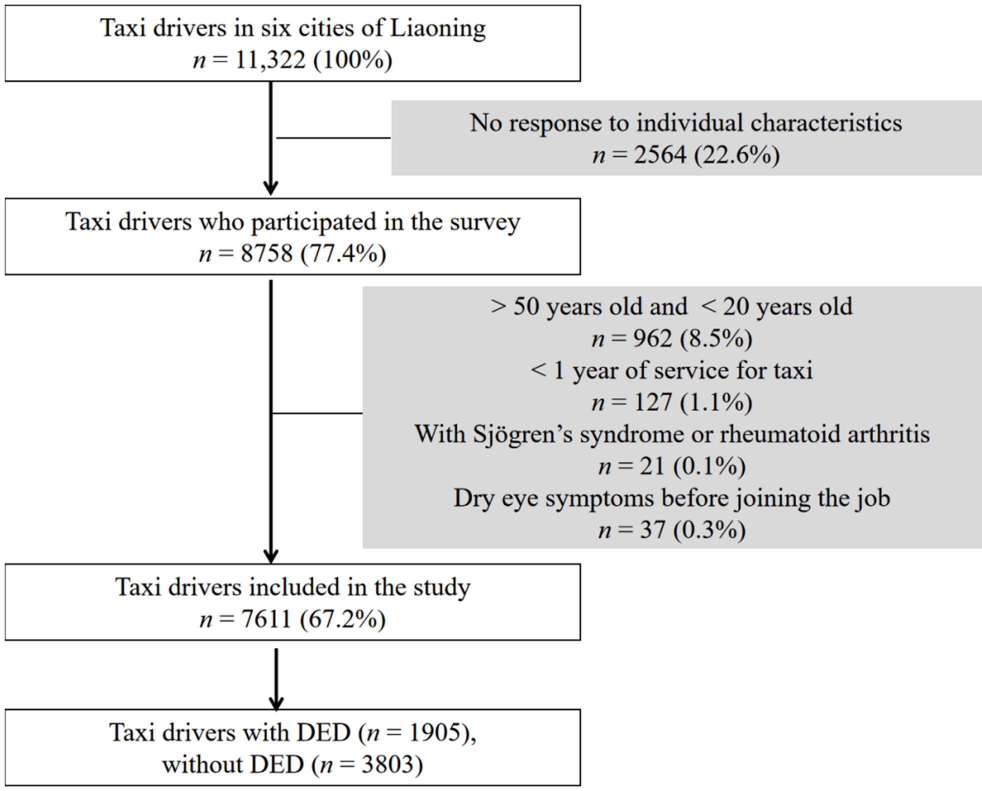

Figure 1. The flow chart of cases and controls selection.

2.3. Covariates

We collected the characteristics of taxi drivers (gender, age, BMI, chronic diseases, allergies, smoking, drinking, eye surface status), as well as details of their socioeconomic status (education, income, business style, work intensity, and family pressure). Chronic stress was obtained through the Occupational Stress Scale [17] and Life Stress Interview [18].

2.4. Statistical Analysis

We used Q–Q plots to test data for normality, and used Bartlett's test for unequal variances to detect data for homogeneity. For continuous variables with normal distribution, we calculated the mean ± standard deviation (SD) by *t*-test; for non-normal distribution variables, we calculated the median and interquartile range (IQR) by the Wilcoxon rank–sum test. For categorical variables, we used contingency tables and the Chi-square test to describe the differences in distribution. Because tear Lf levels belonged to a skewed distribution, a logarithmic transformation on tear Lf was performed. We then calculated the geometric means and their 95% confidence intervals (CI) for the ln-transformed Lf (Ln-Lf). In our data, $PM_{2.5}$ was highly correlated with PM_{10} ($r = 0.825$), which increased some potential variance inflation and deviation in the statistical model. In the multivariable models, logistic regression was used to evaluate whether selected covariates interfered with the association between air pollution and DED risk. If the covariate is significantly related to the effect ($p < 0.05$); or if the adjusted odds ratio (aOR)—calculated by increasing an IQR of each air pollutant concentration—has changed by more than 10%, then the covariate is included into the model analysis. In the conditional logistic regression model, the likelihood ratio test is used to compare the effects of including and excluding the moderating variables in order to analyze whether there is a potential moderating effect. If the *p*-value of the difference level in the likelihood ratio test is less than 0.1, then this latent variable can be considered to have a moderating effect. In this study, only stress and allergies were found to meet this standard, so only these two adjustment variables were used for stratification and OR (95% CI) calculations. We used exposure (pollutants or humidity) levels below the 25th percentile as the reference category (baseline level), and used logistic regression to estimate associations with Lf in exposure quartiles, adjusting for covariates. Data were analyzed by SPSS 20.0 (IBM SPSS, Inc., Chicago, IL, USA).

3. Results

3.1. Characteristics of the Subjects Exposed to Air Pollution

Table 1 showed the physical examination and basic work statuses of 8758 taxi drivers who agreed to participate in this study. However, considering the influence of working age and participant age on the incidence of DED, we deleted 13% (1147) of taxi drivers. Compared with the included 7611 taxi drivers, there was no statistical difference in demographic variables. Figure 1 was a flow chart of case and control selection.

Table 1. Baseline characteristics of taxi drivers included (n = 7611) and not included (n = 1147).

Baseline Characteristics	Included n (%)	Not Included n (%)	p-Value
Male sex	7276 (95.6)	1092 (95.2)	0.92
Day-time drivers	4156 (54.6)	617 (53.8)	0.78
<CNY 5000/month	5480 (72.0)	848 (73.9)	0.80
≧10 h/day	4353 (57.2)	630 (54.9)	0.53
Smoking	6667 (87.6)	1015 (88.5)	0.98
Alcohol	4818 (63.3)	760 (66.3)	0.83
Allergic tendencies *	2658 (35.1)	413 (37.6)	0.89
Obesity	4346 (57.1)	650 (56.7)	0.59
Iron deficiency anemia	2679 (35.2)	414 (36.1)	0.77
Hypertension	3889 (51.1)	571 (49.8)	0.65
Hypercholesterolemia	2839 (37.3)	472 (41.2)	0.70
Hypertriglyceridemia	3311 (43.5)	535 (46.6)	0.72
High blood sugar	1659 (21.8)	221 (19.3)	0.42
Self-employed	571 (7.5)	83 (7.2)	0.97
Education (college)	175 (2.3)	7 (0.6)	0.50
Stress (occupation and family) *	6439 (84.6)	1000 (87.2)	0.90

* Total numbers were not equal to 7611 and 1147 for these characteristics due to missing data.

Figure 2 shows the distribution of the annual mean pollutant concentration in the included taxi drivers before DED diagnosis date from the 6 cities of Liaoning. The concentration range of these pollutants varied widely between district gradients for $PM_{2.5}$ (34–119 μg/m^3), PM_{10} (25–155 μg/m^3), O_3 (29–256 μg/m^3), SO_2 (5–70 μg/m^3), CO (512–2433 μg/m^3) and NO_2 (12–61 μg/m^3). Compared with Chinese National Ambient Air Quality Standards or WHO standards, PM levels exceeded WHO guidelines in all districts of these 6 cities. Other pollutants, such as O_3, SO_2 and NO_2 levels also exceeded WHO guidelines at 43.1%, 76.1% and 52.5%, respectively. The variation range of relative humidity was from 45% to 90% (Supplementary Table S1).

Supplemental Table S2 shows Spearman's correlation air-pollutant averages. The correlation coefficients showed only moderate correlations observed between air pollutants. The strongest correlation among coefficients was seen for $PM_{2.5}$ and PM_{10} (r = 0.825).

Table 2 shows the distributions of sociodemographics, socioeconomic characteristics, habits and clinical examination of taxi drivers with DED compared to controls. The 25.0% (1905/7611) among enrolled taxi drivers with DED was diagnosed by clinicians. The 1905 DED were matched 1:2 to 3803 controls by age and gender. Among the variables, the distributions of shift drivers (day-time) (59% vs. 49%), allergies (43% vs. 32%), non-self-employment (96% vs. 91%), and occupational and family stresses (90% vs. 77%) were higher in taxi drivers with DED than those in taxi drivers without DED. There were statistical differences in other categorical variables between cases and controls. In addition, tear Lf levels (0.69, 95% CI: 0.67–0.71) in taxi drivers with DED were significantly higher than those (0.41, 95% CI: 0.39–0.43) in taxi drivers without DED. The TBUT values (2.65 ± 1.94 s) in cases were significantly lower than those (4.51 ± 2.36 s) in controls; moreover, the mean values of both groups were below 7 s in both eyes. There was no statistically significant difference in mean (SD) values of OSDI score, CFS and Schirmer's test between cases and controls.

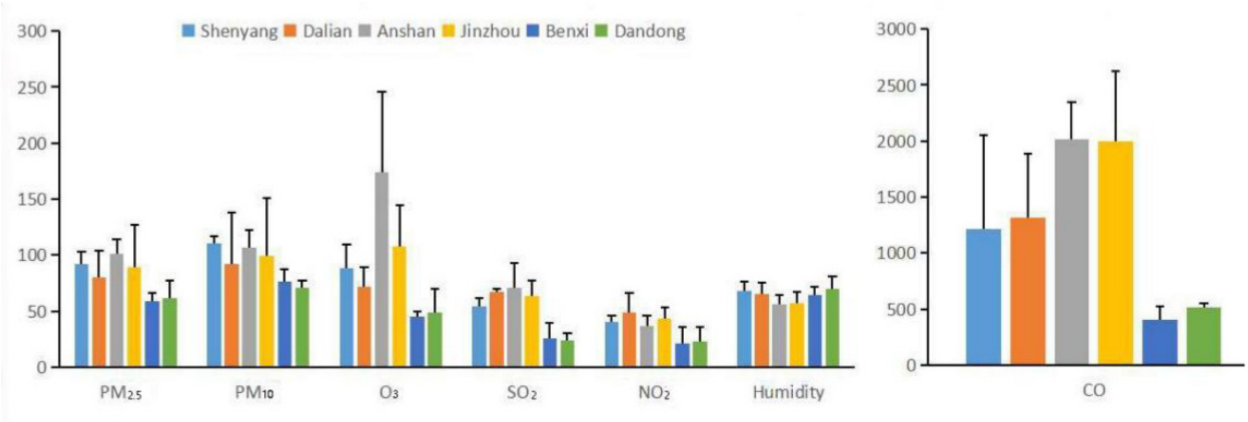

Figure 2. Air pollution concentrations (μg/m^3) and humidity (%) in the six cities of Liaoning, China, from 2012 to 2014.

Table 2. Characteristics of taxi drivers with or without DED (*n* = 5708).

Characteristics	Cases (*n* = 1905), *n* (%) or Mean ± SD	Controls (*n* = 3803), *n* (%) or Mean ± SD	*p*-Value
Sex			0.940
Males	1822 (95.6)	3636 (95.6)	
Females	83 (4.4)	167 (4.4)	
Age			0.948
21–30	446 (23.4)	887 (23.3)	
31–40	882 (46.3)	1740 (45.8)	
41–50	577 (30.3)	1176 (30.9)	
BMI			0.213
<18.5	130 (6.8)	422 (11.1)	
18.5~23.9	689 (36.2)	1213 (31.9)	
24~	1086 (57.0)	2168 (56.9)	
Shift drivers			0.033
Day-time	1128 (59.2)	1871 (49.2)	
Night-time	777 (40.8)	1932 (50.8)	
Myopia			0.904
No	1775 (93.2)	3567 (93.8)	
Yes	130 (6.8)	236 (6.2)	
CNY/month			0.500
<5000	1393 (73.1)	2722 (71.6)	
5000~8000	396 (20.8)	757 (19.9)	
8000~	116 (6.1)	324 (8.5)	
Working h/day			
8~10	853 (45.8)	1468 (38.6)	0.206
≥10	1052 (55.2)	2335 (61.4)	

Table 2. *Cont.*

Characteristics	Cases (n = 1905), n (%) or Mean ± SD	Controls (n = 3803), n (%) or Mean ± SD	p-Value
Smoking			
Never	236 (12.8)	354 (9.3)	0.236
Former	1667 (23.7)	3449 (26.3)	
Current	1667 (63.5)	3449 (64.4)	
Alcohol			0.320
No	607 (31.9)	1373 (36.1)	
Yes	1296 (68.1)	2430 (63.9)	
Allergic tendencies			0.011
No	1090 (57.3)	2578 (67.8)	
Yes	813 (42.7)	1225 (32.2)	
Hypertension			0.514
No	942 (49.5)	1784 (46.9)	
Yes	961 (50.5)	2019 (53.1)	
Hypercholesterolemia			0.143
No	1106 (58.1)	2426 (63.8)	
Yes	798 (41.9)	1377 (36.2)	
Hypertriglyceridemia			0.069
No	961 (50.5)	2232 (58.7)	
Yes	942 (49.5)	1571 (41.3)	
High blood sugar			0.276
No	1448 (76.1)	3039 (79.9)	
Yes	455 (23.9)	764 (20.1)	
Self-employed			0.026
No	1821 (95.7)	3442 (90.5)	
Yes	82 (4.3)	361 (9.5)	
Education			0.151
≤High school	1869 (98.2)	3712 (97.6)	
College	34 (1.8)	91 (2.4)	
Stress events (occupation and family) during the 2 years [a]			0.000
No	183 (9.6)	870 (22.9)	
Yes	1720 (90.4)	2932 (77.1)	
Ln-Lf (mg/mL) [b]	0.41 (0.39–0.43)	0.69 (0.67–0.71)	0.000
OSDI score	9.11 ± 8.05	8.40 ± 12.11	0.206
CFS	1.06 ± 0.98	0.98 ± 0.42	0.152
TBUT (sec)	2.65 ± 1.94	4.51 ± 2.36	0.021
Schirmer's test (mm/5 min)	12.10 ± 7.66	10.85 ± 7.09	0.089
Hb (g/L)			
Male	116 ± 12	119 ± 13	0.081
Female	105 ± 11	110 ± 12	0.069

[a] Includes decrease in income, severe traffic penalties, separation/divorce, offspring, loss of school or job, serious health problems, or death of family member or close relative. [b] Values are presented as median (Q1–Q3). OSDI = Ocular Surface Disease Index, CFS = corneal fluorescein staining, TBUT = tear break-up time.

3.2. The Relationship between PM_{10}, NO_2, Humidity and DED

Table 3 shows the aORs and 95% CI for associations between air pollutants, humidity (an increase in IQR), and the occurrence of DED in the single-factor and multi-factor models. In the single-factor model, PM_{10} (1.32, 95% CI: 1.15, 1.70) and NO_2 (2.61, 95% CI: 1.67, 3.56) were positively correlated with DED after adjusting for other covariates. Humidity (0.44, 95% CI: 0.54, 0.34) was inversely correlated with DED. The multi-factor model also showed the same related trend as in the single-factor model, although the CI range was increased. Therefore, there was a strong association between pollutants (PM_{10} or NO_2), humidity, and DED, apart from affecting the changes in the effect estimation.

Table 3. Adjusted ORs (95% CI) for DED associated with an IQR increase of air pollutants and humidity.

	Single [a]	**Multi** [b]
$PM_{2.5}$	1.01 (0.98, 1.02)	—
PM_{10}	1.32 (1.15, 1.70) *	1.33 (1.07, 1.90) *
O_3	0.98 (0.78, 1.19)	0.95 (0.76, 1.21)
SO_2	1.10 (0.63, 1.81)	1.08 (0.54, 1.72)
NO_2	2.61 (1.67, 3.56) *	2.64 (1.30, 4.37) *
CO	1.08 (0.78, 1.82)	1.04 (0.62, 2.16)
Humidity	0.44 (0.54, 0.34) *	0.40 (0.83, 0.27) *

OR (95% CI) was estimated for an IQR increase in $PM_{2.5}$, PM_{10}, O_3, SO_2, NO_2, CO and humidity. * $p < 0.05$. [a] Single-pollutant model: adjustment for all the potential covariates in Table 4. [b] Multi-pollutant model: PM_{10} + O_3 + SO_2 + NO_2 + CO + humidity. Further adjustment for the effects of the other air pollutants on the base of single-pollutant model.

Figure 3 show the relationship between PM_{10}, NO_2, humidity and DED after adjusting for other variables; these were stratified by the four factors of stress, allergies, self-employment or shift work, on the basis of each IQR increase in conditional logistic regression. The stratifications were based on the variables in Table 2 that had statistically different distributions between DED and non-DED. Among taxi drivers with stressful events, or with allergic tendencies, each IQR (26 μg/m^3) increase in PM_{10} was positively statistically associated with the risk of DED, with an aOR of 1.89 (95% CI, 1.19 to 3.08) or 1.77 (95% CI, 1.06 to 2.90). Similarly, each IQR (10 μg/m^3) increase in NO_2 was positively associated with DED with an aOR of 2.87 (95% CI, 1.60 to 3.58) or 2.93 (95% CI, 1.64 to 3.83). In contrast, an inverse association of DED with an IQR (15%) increase in humidity was shown in taxi drivers without stress, or without allergies, with aORs of 0.33 (95% CI, 0.17 to 0.39) or 0.39 (95% CI, 0.19 to 0.59), respectively.

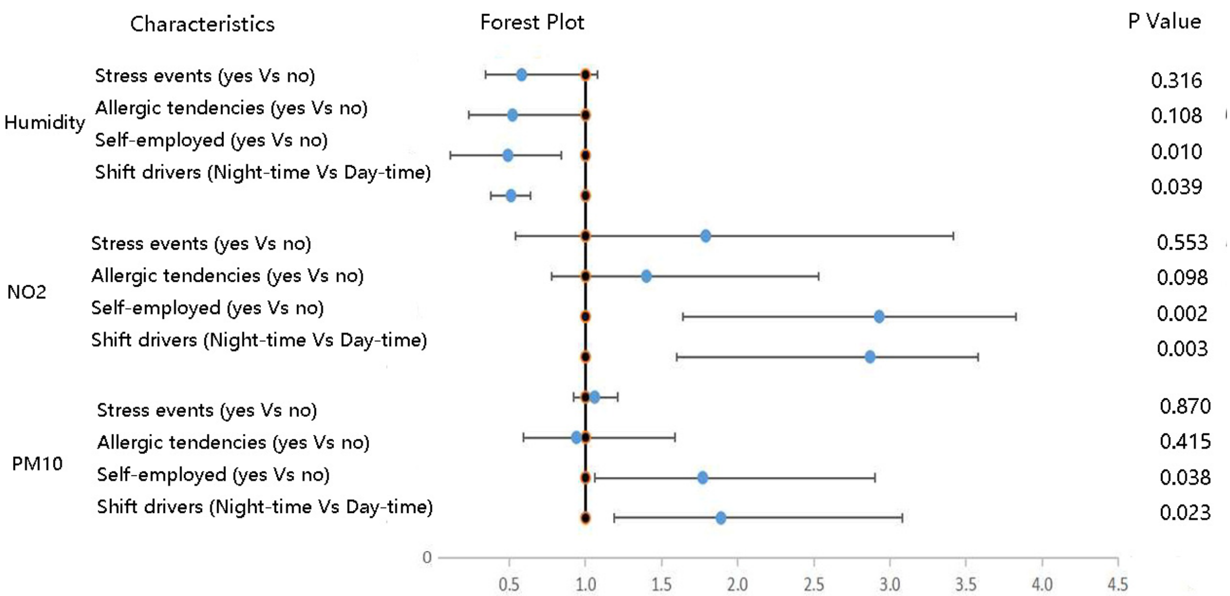

Figure 3. The forest diagram of adjusted odds ratio of PM_{10} (26 μg/m^3 increase), NO_2 (10 μg/m^3 increase) or humidity (15% increase) on dry eye disease, stratified by significant covariates.

Adjustment for all the potential covariates in Table 2 included characteristics of taxi drivers except for the stratification variables.

Tables 4 and 5 show the possible associations between PM_{10}, NO_2, or humidity and tear Lf levels, a prominent biomarker of DED.

Table 4. Association (adjusted β and 95% CI) between ln (Lf) (mg/mL) and PM_{10}, NO_2 or humidity for stress (no/yes).

	Quartile	**NO**				**Stress**			
		With DED (*n* = 183)		**Without DED (*n* = 870)**		**With DED (*n* = 1720)**		**Without DED (*n* = 2932)**	
		β (95% CI)	**R^2**	**β (95% CI)**	**R^2**	**β (95% CI)**	**R^2**	**β (95% CI)**	**R^2**
PM_{10}	1	Reference		Reference		Reference		Reference	
	2	0.113 (−0.398, 0.571)	0.11	−0.174 (−0.371, 0.123)	0.20	**−0.512 (−1.065, −0.041)**	0.31	−0.365 (−0.779, 0.051)	0.27
	3	−0.255 (−0.248, 0.770)	0.19	**−0.300 (−0.693, 0.013)**	0.23	−0.531 (−0.978, 0.086)	0.41	−0.538 (−1.163, 0.128)	0.48
	4	−0.315 (−0.642, −0.140)	0.14	−0.329 (−0.756, 0.105)	0.09	**−0.912 (−1.374, −0.413)**	0.59	**−0.586 (−0.888, −0.300)**	0.33
NO_2	1	Reference		Reference		Reference		Reference	
	2	0.020 (−0.654, 0.693)	0.02	−0.030 (−0.800, 0.737)	0.02	**−0.445 (−0.744, −0.151)**	0.29	−0.086 (−0.400, 0.261)	0.06
	3	−0.049 (−0.673, 0.579)	0.09	−0.301 (−0.802, 0.198)	0.14	**−0.495 (−1.089, −0.094)**	0.30	−0.131 (−0.994, 0.720)	0.12
	4	−0.451 (−0.920, 0.020)	0.30	**−0.525 (−0.997, −0.049)**	0.39	**−0.668 (−1.141, −0.199)**	0.49	**−0.329 (−0.613, −0.039)**	0.15
Humidity	1	Reference		Reference		Reference		Reference	
	2	**0.288 (−0.419, 0.994)**	**0.12**	**0.616 (−0.344, 1.561)**	**0.48**	**1.309 (0.095, 2.507)**	**0.62**	**0.139 (−0.142, 0.416)**	**0.11**
	3	0.777 (−0.207, 1.772)	0.52	0.971 (0.507, 1.430)	0.42	1.373 (−0.036, 2.626)	0.80	0.616 (−0.432, 1.724)	0.49
	4	1.070 (−0.148, 2.159)	0.76	**1.897 (0.494, 3.020)**	0.84	**1.994 (1.572, 2.303)**	0.92	**1.734 (0.872, 2.659)**	0.82

Values with $p < 0.05$ are indicated in bold, underlined text. R^2: Coefficients of determination; adjusted for all the potential covariates in Table 4 including BMI, chronic diseases, allergies, smoking, drinking, eye surface status, education, income, business style, work intensity, and family pressure. Contrast with taxi drivers exposed to level 1 (PM_{10}, NO_2 or humidity) to level 2, 3 or 4 (2 vs. 1; 3 vs. 1; 4 vs. 1). 1 = below the 25th percentile; 2 = between the 25th and 50th percentiles; 3 = between the 50th and 75th percentiles; 4 = above the 75th percentile.

Table 5. Association (adjusted β and 95% CI) between ln (Lf) (mg/mL) and PM_{10}, NO_2 or humidity for allergies (no/yes).

	Quartile	No				**Allergic tendencies**			
		With DED (*n* = 1090)		Without DED (*n* = 2578)		With DED (*n* = 813)		Without DED (*n* = 1225)	
		β (95% CI)	R^2	β (95% CI)	R^2	β (95% CI)	R^2	β (95% CI)	R^2
PM_{10}	1	Reference		Reference		Reference		Reference	
	2	0.010 (−0.277, 0.288)	0.05	−0.083 (−0.580, 0.412)	0.09	**−0.240 (−0.457, 0.028)**	0.17	−0.223 (−0.562, 0.117)	0.17
	3	−0.068 (−0.327, 0.252)	0.10	−0.117 (−0.377, 0.236)	0.11	**−0.489 (−0.761, −0.244)**	0.31	**−0.588 (−0.613, −0.072)**	0.16
	4	−0.148 (−0.316, 0.032)	0.16	−0.140 (−0.355, 0.024)	0.16	−0.751 (−1.597, 0.094)	0.46	−0.615 (−1.075, 0.157)	0.37
NO_2	1	Reference		Reference		Reference		Reference	
	2	−0.174 (−0.448, 0.109)	0.03	−0.207 (−0.441, 0.058)	0.10	**−0.336 (−0.616, −0.040)**	0.20	−0.199 (−0.654, 0.288)	0.19
	3	−0.432 (−0.551, 0.015)	0.06	**−0.382 (−0.863, −0.164)**	0.29	**−0.582 (−0.856, −0.230)**	0.34	**−0.446 (−0.715, −0.204)**	0.29
	4	−0.454 (−0.978, 0.049)	0.09	−0.551 (−0.984, 0.012)	0.33	−0.658 (−1.243, 0.046)	0.42	−0.507 (−1.102, 0.062)	0.39
Humidity	1	Reference		Reference		Reference		Reference	
	2	0.486 (−0.157, 0.921)	0.32	0.583 (−0.096, 1.055)	0.49	**1.054 (0.157, 1.956)**	0.59	0.751 (−0.020, 1.375)	0.50
	3	0.755 (−0.045, 1.533)	0.51	0.721 (−0.065, 1.420)	0.53	1.404 (−0.217, 2.977)	0.72	1.073 (−0.193, 2.212)	0.66
	4	0.994 (−0.051, 1.926)	0.61	**1.204 (0.020, 2.408)**	0.71	**1.470 (0.247, 2.619)**	0.74	**1.109 (0.329, 1.859)**	0.62

Values with $p < 0.05$ are indicated in bold, underlined text. R^2: Coefficients of determination; adjusted for all the potential covariates in Table 4 including BMI, chronic diseases, allergies, smoking, drinking, eye surface status, education, income, business style, work intensity, and family pressure. Contrast with taxi drivers exposed to level 1 (PM_{10}, NO_2 or humidity) to level 2, 3 or 4 (2 vs. 1; 3 vs. 1; 4 vs. 1). 1 = below the 25th percentile; 2 = between the 25th and 50th percentiles; 3 = between the 50th and 75th percentiles; 4 = above the 75th percentile.

3.3. Associations between Tear Lf and PM_{10}, NO_2, Humidity

Among non-DED taxi drivers without stress, tear Lf was significantly negatively associated with the 75th percentile (vs. the lowest) of NO_2 exposure (adjusted $\beta = -0.525$ mg/mL, 95% CI: -0.997, -0.049). In contrast, Lf was significantly positively associated with the 75th percentile of humidity (adjusted $\beta = 1.897$ mg/mL, 95% CI: 0.494, 3.020).

Among non-DED taxi drivers with stress, tear Lf was significantly negatively associated with the 75th percentile of PM_{10} exposure (adjusted $\beta = -0.586$ mg/mL, 95% CI: -0.888, -0.300), and NO_2 exposure (adjusted $\beta = -0.329$ mg/mL, 95% CI: -0.613, -0.039). In contrast, Lf was significantly positively associated with the 75th percentile of humidity (adjusted $\beta = 1.734\%$, 95% CI: 0.872, 2.659).

Among DED taxi drivers with stress, tear Lf was significantly negatively associated with the 25th to 50th percentile (adjusted $\beta = -0.512$ mg/mL, 95% CI: -1.065, -0.041), the 75th percentile of PM_{10} exposure (adjusted $\beta = -0.912$ mg/mL, 95% CI: -1.374, -0.413), and each quartile of NO_2 exposure (adjusted $\beta = -0.445$ mg/mL, 95% CI: -0.744, -0.151), (adjusted $\beta = -0.495$ mg/mL, 95% CI: -1.089, -0.094), (adjusted $\beta = -0.668$ mg/mL, 95% CI: -1.141, -0.199). In contrast, Lf was significantly positively associated with the 25th to 50th percentile (adjusted $\beta = 1.309\%$, 95% CI: 0.095, 2.507), and the 75th percentile of humidity (adjusted $\beta = 1.994\%$, 95% CI: 1.572, 2.303). There were inverse dose–response relationships between PM_{10} or NO_2 and DED odds, and a positive dose–response relationship between humidity and DED odds. Similar associations were observed among taxi drivers with allergic tendencies.

4. Discussion

The main strengths of this study include the demonstration of: (1) A positive association of PM_{10} or NO_2 with DED, and an inverse association of lower humidity with DED; (2) Positive correlation of potential factors including day-time, allergies, non-self-employment, and stress with DED. Moreover, stress or allergic tendencies increased DED risk from PM_{10}, NO_2 exposure, or from lower humidity; and (3) An inverse relationship between PM_{10}, NO_2, low humidity and tear Lf levels. The above associations between ambient factors on tear Lf levels were more pronounced among taxi drivers with stress or allergic tendencies than taxi drivers without stress or allergic tendencies.

4.1. Model Performance

Although epidemiological studies prove that acute and chronic exposures to air pollution have a negative impact on ocular surface health, there are statistical differences in the association of each pollutant on DED due to the different sources, intensity, exposure time, and dose calculation methods of air pollutants from different regions as well as study participants' characteristics [8,19,20]. This study only included taxi drivers with long-term exposure to outdoor pollution, who are low-income, high-stress, and disadvantaged groups in China, so the partial demographic bias could be avoided during the statistical analysis. Of course, this also limits the generalization of our results to the public, but at least further proves that air pollution is partly to blame for the increasing DED.

We used a single-pollutant model to show that long-term PM_{10} and NO_2 exposure increased DED risk by 32% and 161%, respectively, while high humidity decreased DED risk by 56%. Although the results of the single-pollutant models were similar with the multi-pollutant models, we chose single-pollutant models to avoid multicollinearity due to high or moderate correlations between air pollutants, which may induce potential variance inflation and bias. Although the complex composition of pollution exposure can lead to $PM_{2.5}$ and PM_{10} being non-specific pollutants and weaken the correlation between them, the present study showed a high correlation between PMs, because automobile exhaust is currently the main source of air pollution in China [21]. Moreover, the enhanced correlations (PM_{10}, NO_2 and humidity) from the multi-pollution models compared to those from the single-pollution models, and other reduced correlations (O_3, SO_2 and CO) were noted. These ranges of confidence interval were wider, which also proved that the multi-pollution models were not appropriate in this study.

4.2. PM_{10} or NO_2 and Lower Humidity Were Risk Factors for DED

Increasing levels of tear film osmolarity is an indicator of DED. In one study of taxi drivers from Sao Paulo (Brazil), a negative association was found between $PM_{2.5}$ or NO_2 levels and tear film osmolarity levels within normal limits (316 mOsm/L) [22], which indicated the existence of an adaptive response when the ocular surface in individuals was exposed to air pollution. It should be noted that the average $PM_{2.5}$ levels (40 μg/m^3) in Sao Paulo is higher than the WHO levels (10 μg/m^3), but the value is lower than the Chinese standard (50 μg/m^3). In Liaoning, the average $PM_{2.5}$ levels is 80 μg/m^3.

If individuals initially are exposed to high levels of $PM_{2.5}$, tear osmolarity will increase and be prone to DED [10]. However, we did not find such a relationship between $PM_{2.5}$ exposure and DED in this study. This may be because $PM_{2.5}$ is unlikely to directly affect tear secretion and epithelial barrier function compared with PM_{10} [22], which may be due to the fact that heavy metals not only adsorb on the surface of PM, but also penetrate into the structure of PM [23,24]. In China, PM_{10} contains more heavy metal elements (S, Zn, Cu and Pb) than $PM_{2.5}$ (S and Pb) [25]. Therefore, these can exacerbate allergic reactions of PM as allergen carriers [26]. In addition, under long-term exposure to high concentrations, tear film osmotic pressure may be normalized to a certain extent [8].

The data for PM_{10} were not available in the study from Brazil. However, we demonstrated that PM_{10} was associated with DED, which was inconsistent with the results of a South Korean study. Although reflex tear may flush PM from the ocular surface, the annual PM_{10} level (84 μg/m^3) in China was higher than that in Korea (40 μg/m^3). Such high PM_{10} levels may be enough to induce DED [8].

In China, CO and NO_2 mainly come from automobile exhaust emissions due to incomplete combustion inside motor engines. Among Chinese taxi drivers, higher CO and NO_2 levels were positively associated with DED, but there was no statistically significant association between CO and DED. This problem may be related to CO assessment, because ambient CO concentrations have considerable spatial variability [27]. In contrast to the change of symptoms after NO_2 exposure, inhalation of CO can increase the diameter of arteries and veins, retinal blood flow velocity and fundus pulsation amplitude [28]. The indirect symptoms of ocular surface present in a delayed fashion [29]. For NO_2, this pollutant can acidify tears and reduce tear break-up time [30,31]. In this study, a negative correlation was found between exposure levels and DED. However, in the Brazilian taxi driver survey, there was no statistically significant difference. A possible explanation is the difference in NO_2 exposure levels between the two places (Brazil: 175 μg/m^3, China: 31 μg/m^3). The sensory receptor reactivity might adapt to high levels of air pollution and be reduced [32]. When NO_2 levels (less than 40 mg/m^3 in a hospital in São Paulo) were similar to our values, the results of significantly negative correlation were consistent with this study [31].

We also found a negative correlation between O_3 and DED, but with no statistical difference. However, in a Korean study, increased O_3 levels were associated with DED [8]. This inconsistent result was due to different O_3 background levels (Korea: 250 μg/m^3, China: 92 μg/m^3), participants' characteristics (Korea: population, China: taxi drivers), and different diagnostic criteria for DED (Korea: symptoms or diagnosis, China: OSDI, TBUT, CFS, Schirmer's test and Lf levels). Another possible explanation was that O_3 and NO_2 in the environment are coupled by chemical bonds, and the formation of O_3 needs to deplete nitrogen with the help of sunlight [33]. Thus, when exposed to high levels of NO_2, individuals typically experience lower O_3 exposure, especially in areas with heavy traffic [34].

There also are many controversies about the relationship between SO_2 and DED. Some studies reported positive association, [7,20] the others reported null association [8,35]. Our study also showed null association, which was related to the decreasing SO_2 levels due to the worldwide use of fuel with low sulfur content [36].

4.3. Stress or Allergies Increased the Risks of PM_{10}, NO_2 Exposure or Low Humidity on DED

The covariates listed (stress, allergies, driving during the day, and non-self-employment) may be potential risk factors for DED in taxi drivers. By taking each stratum with a single potential factor [37], and matching age and gender, we minimized the influence of confounding factors. However, the risks of PM_{10}, NO_2 exposure or low humidity on DED might be exacerbated in taxi drivers with stress or allergies.

Similar to other countries [38,39], in China today, taxi drivers are assigned as disadvantaged groups. Due to their low income (less than 5000 RMB/month) and high work intensity (more than 10 h/day), they feel stressed and irritable (e.g., due to traffic congestion), which increases traffic risks and the occurrence of various chronic diseases (anemia, hypertension, hypercholesterolemia, hypertriglyceridemia, high blood sugar), according on our study. Even if these taxi drivers pay attention to health protection, they are unavoidably exposed to air pollution for a long time due to their occupational characteristics [22].

As for identification of susceptible individuals [10], we collected information through questionnaires about whether participants had experienced asthma, allergic rhinitis, eczema and food allergy before working as taxi drivers. Although there was a certain recall bias here, we partially proved that underlying allergic tendencies increased DED risk in taxi drivers with chronic exposure to PM_{10}, NO_2, and low humidity.

4.4. Tear Lf Has Inverse Associations with PM_{10}, NO_2, and Low Humidity

Another major contribution of this study is the identification of the inverse associations between ambient factors (PM_{10}, NO_2, and low humidity) and tear Lf, especially for taxi drivers with stress or allergies. There were negative dose–response relationships between these ambient factors and Lf. To date, there are few studies on the relationship between air pollution and Lf. Regardless of animal experiments and epidemiological studies [40–42], the existing literature shows that air pollution transiently elevates Lf levels in the lung and nasal airways of healthy subjects, who face acute inflammatory reactions caused by short-term exposure. While our data is inconsistent with theirs, we found that more chronic exposure to airborne particulates and low humidity may be associated with decreased Lf levels in tears. To the best of our knowledge, there is no report similar to ours. Because healthy subjects will escape from the polluted environment after acute exposure, the body's compensation mechanism can restore Lf to normal [41,42]. Here, these taxi drivers had to be exposed outdoors for more than 10 h on average every day for their livelihood, and they rarely took breaks unless they were ill or had major issues at home.

A possible explanation is that iron and inflammatory homeostasis may cause changes in tear Lf, a natural glycoprotein, in acute and chronic exposures [11]. In the process of infection or inflammation caused by acute exposure eventually leading to oxidative damage, Lf levels may, in turn, increase in tears due to a transient recruitment of neutrophils, and increased production of Lf [43]. During irritation/cytotoxicity caused by chronic exposure, Lf may decrease due to low production of epithelial cells. Once the self-adjusting adaptive mechanism fails as a result of chronic exposure, it may induce tear hyperosmolarity and loss of goblet cells, and cause dry eyes to occur [22]. Another reason may be that the average Hb levels of taxi drivers (male: 118 g/L; female: 108 g/L) in this study was slightly lower than the standard levels of Chinese (male: 151 g/L; female: 129 g/L) [44].

Our results also show that the DED status modified the effect of air pollution exposure on the Lf biomarker; an iron-bound multifunctional cationic glycoprotein in different human fluids and secretions that exerts antibacterial, antioxidant, anti-inflammatory and immunomodulatory activities [11]. The difference of mean tear Ln-Lf levels between DED (0.41 mg/mL) and non-DED (0.69 mg/mL) taxi drivers may reflect the activity of DED after air pollution exposure. However, among other symptoms and clinical tests in this study, the results of the OSDI score, CFS and Schirmer's test were similar between DED and non-DED taxi drivers, with the exception of TBUT. This may be related to subjects adapting to long-term air pollution exposure, and subjects may have functional adaptations when air pollution worsens [22]. This again reflected these taxi drivers' insensitivity to dry eye symptoms and the specificity of Lf as a non-traumatic biomarker of DED in this study, but tear Lf is not a specific biomarker of DED. Moreover, Lf level may be modified in other ocular surface diseases due to infection [45] or airborne carbon black exposure [46].

When the examination was stratified by the potential role of stressful or allergic status, effect estimates for the ambient factors (per IQR increase in PM_{10}, NO_2, and low humidity)–tear Lf associations were stronger for taxi drivers with stressful or allergic status, which suggested that the dose-response relationship may be more intense in stressful or allergic conditions. Through further stratification, we found that DED may amplify the effect of ambient factors on Lf levels, but similar relationships were not found for non-DED subjects; this suggests that DED taxi drivers with stressful or allergic status may be more sensitive to Lf level changes after exposure to ambient factors.

4.5. Limitations

Our study had the following limitations. First, because of the lack of multiple time points, we could not claim to obtain the causal relationship between ambient factors and the results of concern. Nonetheless, robust associations of ambient factors with ocular surface injury indicate that there may be causal relationship. Second, the results of this study were limited to taxi drivers, and different results may be obtained from other professionals. Thus, the conclusions cannot be extended to the general population. Third, due to different driving ventilation habits (driver habitually could open their windows and others could close them when using air conditioning), the taxi drivers could have had different levels of exposure at the same level of air pollution. Fourth, each driver's individualized exposure was not recorded, thus, the exposure measurement may lead to exposure bias. Fifth, we could not investigate the etiology of DED (hyposecretion or hyper evaporation).

5. Conclusions

This case-control study supports the hypothesis that stress and allergic tendencies may increase the susceptibility of DED caused by long-term exposure to PM_{10}, NO_2, and low humidity in taxi drivers. Moreover, the aggravation caused by PM_{10}, NO_2, and low humidity may decrease tear Lf levels, especially for DED taxi drivers with stress and allergic tendencies.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/atmos13122003/s1. Table S1: Descriptive Statistic of air pollution concentrations ($\mu g/m^3$) and humidity (%) in the six cities of Liaoning, China, from 2012 to 2014; Table S2: Spearman correlation coefficients* between air pollutants; Table S3: Association of PM_{10}, NO_2 or humidity (per IQR increase a) and DED, stratified by significant covariates.

Author Contributions: F.Y., W.H. and F.K. wrote the main manuscript text. W.S. and L.Z. collected the data. Z.R. and X.X. analyzed the data. J.L. and F.K. prepared clinical tests. All authors have read and agreed to the published version of the manuscript.

Funding: The work was supported by "Liaoning BaiQianWan Talents Program" (Grant number: 2020-C122) and "Scientific Research Funding Project of the Education Department of Liaoning Province" (Grant number: LJKZ1390). The funding source did not have control of the design or analysis of the study publication.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of China Medical University (Approval number: SCXK_LN CMU 2013-0222 and 13 May 2012).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Acknowledgments: We would like to thank all members for their sincere cooperation in this long-term investigation, and thank the local taxi trade unions and environmental health staff for their strong support. Special thanks to the taxi drivers and their families. We are moved by their attitude of working hard under difficult circumstances. In fact, besides DED, we should pay more attention to the risk of air pollution for their other chronic diseases (hearing loss, anemia, hyperlipidemia, hypertension, diabetes, ventilation and respiratory diseases, etc.).

Conflicts of Interest: The authors declare no competing interest.

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