The Cumulative Impact of Air Pollution on Dry Eye Disease: Evidence from The Korea National Health and Nutrition Examination Survey (2017-2020)

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The Cumulative Impact of Air Pollution on Dry Eye Disease: Evidence from The Korea National Health and Nutrition Examination Survey (2017-2020)

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ABSTRACT

The Cumulative Impact of Air Pollution on Dry Eye Disease: Evidence from the Korea National Health and Nutrition Examination Survey (2017-2020)

Air pollutants can disrupt the tear film and damage the corneal epithelium, leading to significant discomfort and irritation. Despite this apparent vulnerability, establishing a direct association between pollution and dry eye disease at a population level has been challenging due to the complex interactions among various pollutants.

Cross-sectional data from the 7th and 8th Korea National Health and Nutrition Examination Survey (2017-2020) were analyzed alongside air pollution data from the National Ambient Air Quality Management Information System to investigate the relationship between environmental pollution and dry eye disease.

The Aggregated Air Quality Index and Cumulative Index of air quality were calculated for each region of residence based on key pollutants. Multiple logistic regression analysis assessed the impact of air pollutants on dry eye disease while adjusting for clinical, demographic, and meteorological factors. The number of high pollutant days within a year significantly increased the odds of artificial tear drop users(adjusted Odds Ratio = 1.04, P <0.001). The Cumulative Index effectively demonstrated the aggregated effect of multiple air pollutants on dry eye disease.

Keywords: dry eye disease, eye discomfort, air pollution.

1. Introduction

1.1. Research background

Detrimental effects of air pollution on human health have been extensively documented, with numerous studies linking exposure to air pollutants to a variety of health issues.[1,2] However, the impact of air pollution on ocular health has received relatively little attention[3]. Dry Eye Disease (DED) is a one such condition that significantly impairs quality of life through chronic discomfort, visual disturbances, which can worsen if left untreated.[4-6] Beyond its clinical implications, DED imposes a substantial economic burden due to healthcare costs, reduced work productivity, and the need for continuous treatment.[4,6] These considerations underscore the need to quantitatively assess the impact of environmental contributors to DED in order to effectively inform public and improve management strategies.

Although previous studies have suggested link between air pollution exposure and DED,[5,7-11] the key question that remains is whether this relationship can be reliably observed at a population level. Laboratory and localized studies have shed light on the effects of air pollution and provided valuable insights into pollutant impacts[8,10-11]. However, the fluctuating levels of air pollutants, the episodic nature of DED symptoms, and variations in individual exposure and susceptibility complicate efforts to fully understand the specific impact of air quality on DED.[12-14] In particular, the aggregated effects of multiple air pollutants and their cumulative impact on DED remain poorly understood, necessitating further investigation to better clarify these relationships.[8] Given the emerging evidence of the impact of air pollution on DED, it is essential to identify reliable measures of air quality exposure to understand their relationship with ocular health outcomes.

1.2. Aggregate indices of air pollutants

Air pollution significantly impacts human health, and quantifying this effect has led to the development of various indices. One widely recognized tool is the Air Quality Index (AQI), which provides a standardized measure of air quality based on the concentration of key pollutants like particulate matter ($PM_{2.5}$, PM_{10}), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO), and ozone (O_3).[15] The AQI is widely used to communicate the severity of pollution to the public, offering a clear and understandable assessment of air quality on a single scale. It was intended to be part of an alert system to the public. However, it primarily focuses on individual pollutants, which limits its ability to reflect the combined effect of multiple pollutants.[16]

To overcome this challenge, aggregate indices such as the Aggregate Air Quality Index (AAQI) and the Cumulative Index (CI) have been developed.[17,18] The AAQI integrates data from multiple pollutants into a single numerical value, offering a composite representation of overall air quality. Designed for ease of interpretation, the AAQI aligns with the National Ambient Air Quality Standards (NAAQS).

The CI aims to provide a more sensitive and comprehensive measure of pollution exposure.[18] This index effectively captures both the intensity and frequency of pollutant exposure, making it more suitable for assessing health impacts. Moreover, the CI is computationally efficient, allowing it to serve as a real-time alert system for public health risks. Its streamlined calculation process makes it an excellent candidate for rapidly assessing air quality, offering timely and comprehensive information on pollution exposure and its potential health risks.

1.3. Objectives

The objective of this study is to assess the impact of key air pollutants on the prevalence of DED in South Korea by integrating data from large-scale population surveys and environmental monitoring systems. By utilizing both the AAQI and CI, this analysis aims to evaluate how outdoor air pollutant exposure contribute to DED.

2. Materials and Methods

2.1. Study design and population

Figure 1 provides an overview of the study's design and methodology. This cross-sectional study utilized data from the Korea National Health and Nutrition Examination Survey (KNHANES), conducted by the Korea Centers for Disease Control and Prevention. KNHANES employs a stratified, multistage clustered sampling method to represent the entire South Korean population, covering a range of demographic and socioeconomic groups[19]. For this study, data collected from 2017 to 2020 were analyzed, focusing on adults aged 40 to 80 who completed ophthalmologic examinations and provided relevant information for the study's covariates.

Air quality data were obtained from the National Ambient Air Quality Management Information System (NAMIS), which provides hourly measurements of six key pollutants (e.g., PM_{10}, $PM_{2.5}$, SO_2, NO_2, O_3, and CO).[20] A total of 421 monitoring stations located near residential areas were selected for analysis to accurately capture pollution exposure in densely populated regions. These stations were chosen after excluding those that showed inconsistencies or failed to meet quality standards (e.g., equipment malfunctions or operational issues). Meteorological data were also sourced from the Automated Synoptic Observing System (ASOS), managed by the Korea Meteorological Administration, ensuring comprehensive environmental data[21]. Quality control measures for air quality data included regular calibration of equipment and the automated exclusion of anomalous readings.

The study adhered to ethical standards outlined in the Declaration of Helsinki. The study procedures met the criteria for IRB exemption for human subject research and were approved by the Severance Hospital Institutional Review Board of Yonsei University Health System (IRB number: 4-2024-0910).

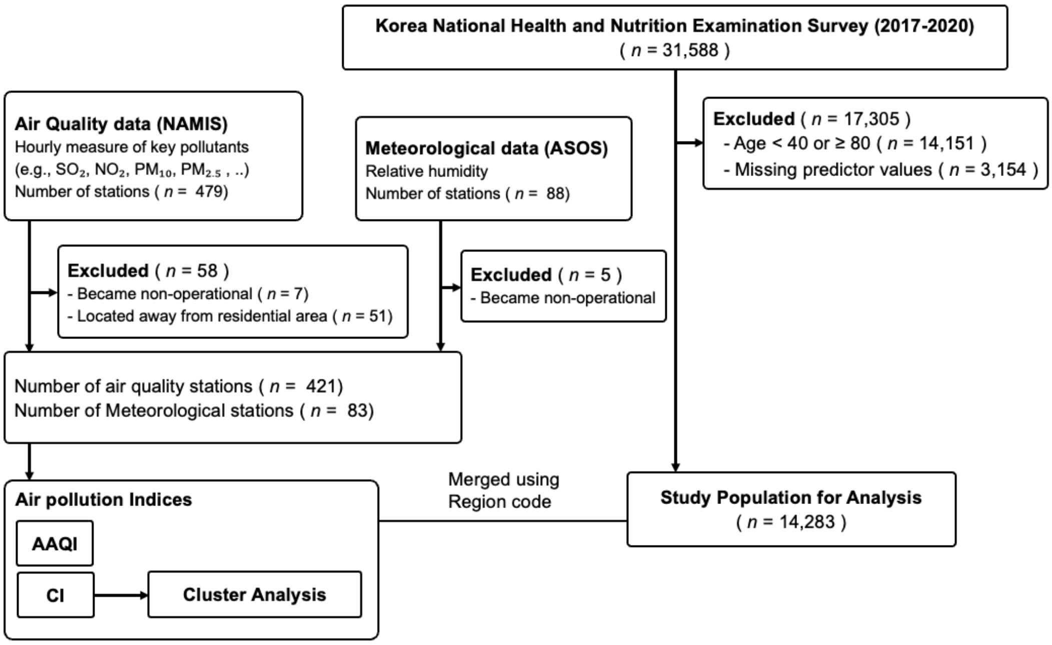


Figure 1. Overview of study participant selection and data analysis process

Abbreviations: ASOS = Automated Synoptic Observing System; NAMIS = National Ambient Air Quality Management Information System; AAQI = Aggregate Air Quality Index; CI = Cumulative Index

2.2. Calculation of aggregated indices and cluster analysis

The AAQI was calculated using the following formula:

$$I = \left(\sum_{i=1}^{n} \left(AQI_i \right)^{\rho} \right)^{\frac{1}{\rho}}$$

where AQI_i represents the AQI value for the i^{th} pollutant, and ρ was set to 2.5, as suggested by previous study.[17] The pollutants included in this calculation were PM_{10}, $PM_{2.5}$, SO_2, NO_2, O_3, and CO. The AAQI was averaged over each year and region to produce a composite metric that represents the overall annual air quality for each specific region. This annual regional AAQI was subsequently used as a quantitative regressor in further statistical analyses.

The CI was calculated as follows:

$$CI = \frac{\sum_{i=1}^{4} AQI_i \times \left(\frac{R_i^{\text{lower}} + R_i^{\text{upper}}}{2} \right)}{\frac{\sum_{i=1}^{4} AQI_i}{4}}$$

where AQI_i represents the AQI value for the i^{th} pollutant, R_i^{lower} and R_i^{upper} are the respective lower and upper bounds of exposure for that pollutant. The pollutants included in this calculation were PM_{10}, $PM_{2.5}$, SO_2, and NO_2. Due to the absence of reference values for the CI that could be used for clinical applications, Gaussian Mixture Models (GMMs) were employed to cluster the CI data. GMMs allowed for the identification of natural groupings within the CI distribution by fitting multimodal Gaussian distributions, facilitating the establishment of data-driven thresholds.

2.3. Multivariable regression analysis

2.3.1. Clinical definition of dry eye disease

Figure 2 provides a visual summary of the classification process used to define clinical DED based on survey responses. Classification was based on self-reported eye drop use and ocular condition diagnoses, assessed through two key survey questions: *"Are you currently using any eye drops? If so, please select all that apply"*, *"Have you ever been diagnosed with an ophthalmic condition? If so, please select all that apply."*

Participants were classified into four groups based on their use of artificial tears (AT) and diagnosis of DED, and then categorized as 'Clinical DED' or 'Non-DED'. The 'Diagnosed and Treated DED' group included those reporting both AT use and a DED diagnosis. The 'Probable DED profile' group included participants using AT without a DED diagnosis, often with other ocular conditions or no diagnosis. The 'Neither Diagnosed nor Treated as DED' group included participants with neither AT use nor a DED diagnosis. Lastly, participants using AT for non-DED conditions (e.g., glaucoma, diabetic retinopathy) were classified as 'Unlikely DED profile'. These subgroups were further analyzed to assess any potential biases that might affect the classification accuracy or study results.

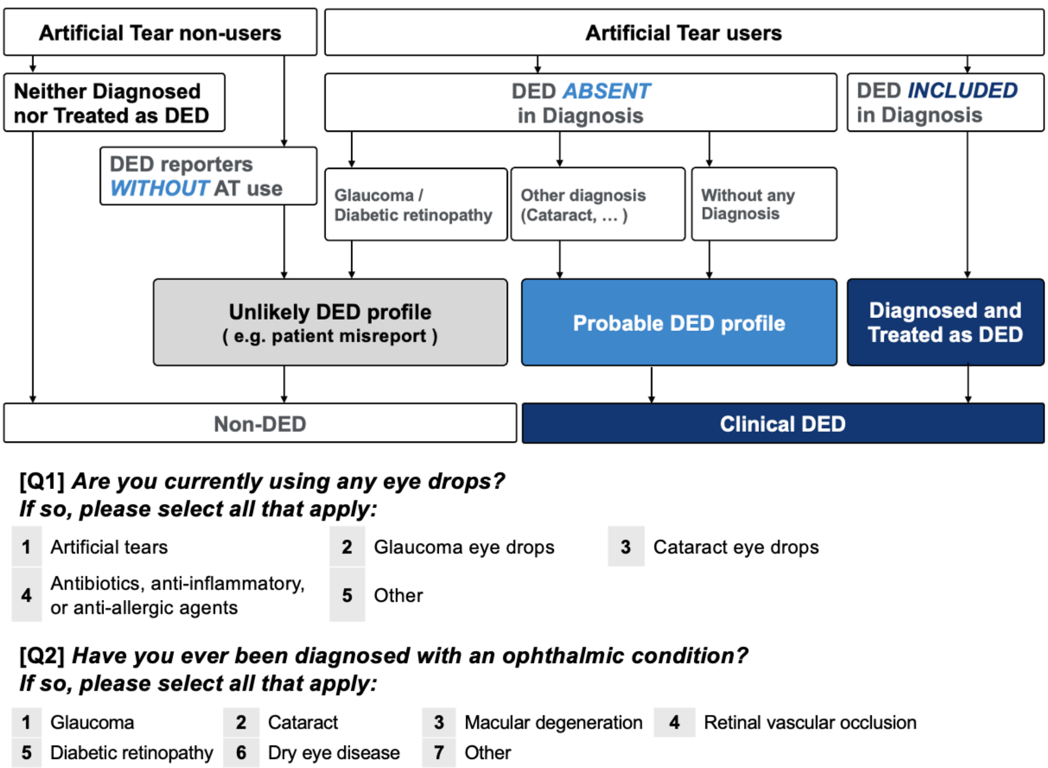


Figure 2. Clinical definition of dry eye disease

2.3.2. Predictors of dry eye disease

Several covariates were included in the multivariable regression model to account for potential confounders. These variables were selected based on prior studies[22,23], which identified them as key predictors of DED, as well as other factors that, while not part of earlier studies, could influence survey responses. The variables included were sex, age, subjective health status, unmet medical care needs, residential setting (urban or rural), diabetes, dyslipidemia, thyroid disease, ocular surgery, relative humidity, and wind speed. These factors have been shown to impact DED risk, and their inclusion in the model allows for a more accurate evaluation of the relationship between air pollution and DED.

2.4 Statistical Analysis

Descriptive statistics were used to summarize participant characteristics and pollutant levels. Univariate analysis using the chi-square test and Cochran–Armitage trend test assessed the relationship between participant characteristics and DED. Multivariate logistic regression models were applied to evaluate the association between air pollution exposure and the prevalence of DED, adjusting for potential confounders. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were calculated to quantify the strength of associations between pollutant exposure and DED.

Data management and statistical analyses were performed using R (version 4.4.0, R Foundation for Statistical Computing ,Vienna, Austria). Cluster analysis, including threshold determination with the Gaussian Mixture Model (GMM), was performed in Python (Python Software Foundation, version 3.9.5) using the scikit-learn library.

3. Results

3.1. Characteristics of the study population

The study population comprised 14,283 participants, with 6,172(43.21%) men and 8,111(56.79%) women. The prevalence of DED was higher among women than men **(Table 1)**. There were few patients who missed medical care when needed (8.15%), compared to history of ocular surgery (17.80%), diabetes (12.41%), or dyslipidemia (26.98%).

Significant differences in DED prevalence were observed based on gender, age groups, subjective health awareness, and certain health conditions. Higher DED prevalence was significantly associated with being women, older age, poor subjective health awareness, and having a history of diabetes, dyslipidemia, thyroid disease, or ocular surgery ($P < 0.05$).

In contrast, there were no significant differences in DED prevalence related to missed medical care or region of residence. Overall, the prevalence of DED as previous definition was 15.75% (95% CI: 15.16% to 16.36%).

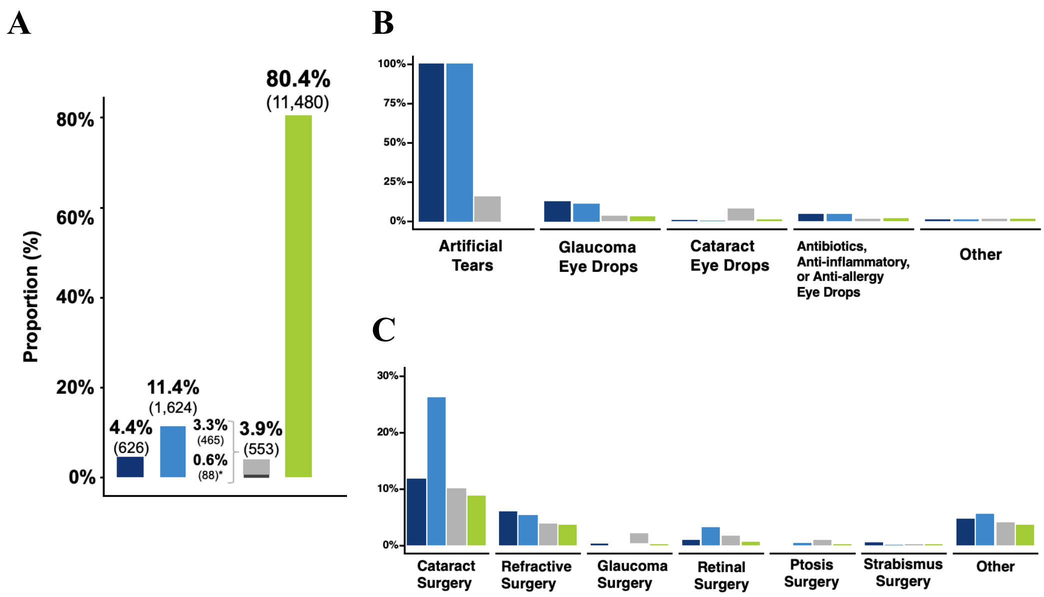
Table 1. Characteristics of the study population

Characteristics		**Participants (N = 14,283)**	**Participants With DED (N = 2,250, 15.75%)**	***P* value**
Sex, n (%)				
	Men	6172 (43.21%)	599 (9.71%)	
	Women	8111 (56.79%)	1651 (20.36%)	< 0.001[a]
Age Group, n (%)				
	40-49	3742 (26.20%)	402 (10.74%)	
	50-59	4024 (28.17%)	534 (13.27%)	
	60-69	4185 (29.30%)	767 (18.33%)	
	70-79	2332 (16.33%)	547 (23.46%)	< 0.001[b]
Region of residence (Rural), n (%)		2960 (20.72%)	457 (15.44%)	0.6[a]
Health satisfaction (Poor), n (%)		11386 (79.72%)	1616 (14.19%)	< 0.001[a]
Missed medical care, n (%)		1140 (8.15%)	197 (17.28%)	0.2[a]
Diabetes, n (%)		1773 (12.41%)	369 (20.81%)	< 0.001[a]
Dyslipidemia, n (%)		3853 (26.98%)	811 (21.05%)	< 0.001[a]
Thyroid disease, n (%)		693 (4.85%)	172 (24.82%)	< 0.001[a]
Ocular surgery, n (%)		2542 (17.80%)	708 (27.85%)	< 0.001[a]

Abbreviations: DED = dry eye disease
a: χ^2 test   b: Cochran–Armitage trend test

3.2. Classification based on clinical definition

Figure 3 provides summary of the classification into four clinical groups. Of the population, 4.4% used AT and were identified as DED patients, while 80.4% neither used tears nor reported DED symptoms **(Figure 3A)**. The remaining two heterogeneous groups with discrepancies between self-reported AT use and diagnosis, included the 'Probable DED profile' (11.4%) and the 'Unlikely DED profile' (3.9%). The 'Unlikely DED profile' group showed a low proportion of AT use (15.9%), with other eye drops being used even less frequently **(Figure 3B)**. A higher proportion of individuals in the 'Probable DED group' reported having undergone cataract surgery (26.3%) compared to those in the group who both reported DED and used AT (11.7%) **(Figure 3C)**.



■ Diagnosed and Treated as DED
■ Probable DED profile
■ Unlikely DED profile
■ Neither Diagnosed nor Treated as DED

Figure 3. Clinical characteristics of subgroups

A, Classification based on self-reported artificial tear use and diagnosis. Significant number of people do not report themselves as DED, despite usnig AT (*light blue*). *AT users in the 'Unlikely DED profile' are less prominent (*dark grey*).

B, Relative proportion of eyedrop usage by subgroups. The low proportion of eye drop use in the 'Unlikely DED profile' suggests that the current clinical definition is less likely to underestimate clinical DED.

C, Relative proportion of ocular surgeries by subgroups. Considerable numbers of individuals who underwent cataract surgery and use AT did not report themselves as DED patients.

Abbreviations: DED = dry eye disease; AT = artificial tear

3.3. Characteristics of air pollutants and indices

Supplemental Figure 1 presents the distribution of hourly measured six air pollutants— PM_{10}, $PM_{2.5}$, SO_2, NO_2, O_3, and CO. Each pollutant displays a right-skewed distribution, with lower levels occurring more frequently and higher concentrations less frequently, a pattern also observed in the AAQI **(Figure 4A)** and the CI distribution **(Figure 4B)**. While 86.80% of the CI values cluster near the baseline of 200, 13.20% exceed this threshold. Two distinct clusters of higher values are modeled with a Gaussian distribution, with a decision boundary at a CI value of 447, marking the shift from moderate to severe pollution levels.

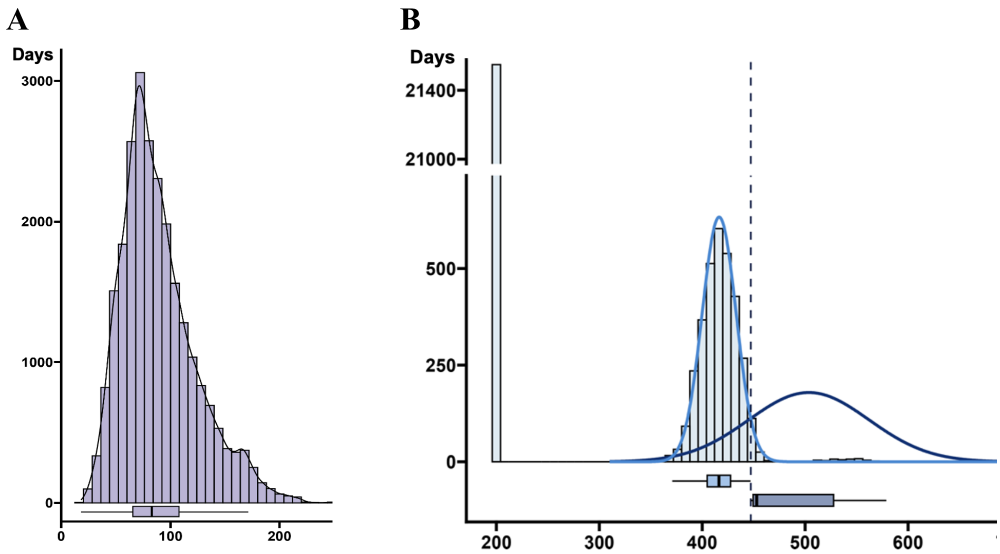


Figure 4. Distribution of AAQI and CI values.
A, Right-skewed distribution of AAQI. **B**, CI values clustered into three distinct groups, with a decision boundary at 447 marking the transition from moderate to severe pollution levels.
Abbreviations: AAQI = Aggregate Air Quality Index; CI = Cumulative Index

3.4. Multivariable logistic regression analysis

The multivariate logistic regression analysis demonstrated that each additional day with a CI exceeding 447 within a year was significantly associated with a 4% increase in the risk of developing DED (adjusted Odds Ratio [aOR] = 1.04; 95% CI: 1.02–1.06) **(Table 2)**. In contrast, a unit increase in the AAQI did not show a statistically significant association with DED (P = 0.83).

Table 2. Impact of air pollutants on dry eye quantified by aggregated indices

	Model with AAQI		**Model with CI**	
Variable	adjusted Odds Ratio[a]	*P* value	adjusted Odds Ratio[a]	*P* value
Sex (women)	2.24 (2.02, 2.49)	<0.001	2.24 (2.02, 2.49)	< 0.001
Age (10-y increase)	1.26 (1.20, 1.32)	<0.001	1.26 (1.20, 1.32)	< 0.001
Ocular surgery	2.10 (1.88, 2.34)	<0.001	2.10 (1.88, 2.34)	< 0.001
AAQI[b]	1.00 (0.99, 1.01)	0.83		
Days CI > 447[c](in 1 year)			1.04 (1.02, 1.06)	< 0.001

Only key predictors are shown. Models adjusted for sex, age, subjective health status, unmet medical care needs, residential setting, diabetes, dyslipidemia, thyroid disease, ocular surgery, and yearly averages of relative humidity and wind speed.

[a] values are adjusted for all the variables included in the model.
[b] a unit increase in the annual average value of the AAQI
[c] number of days in a year when the CI exceeded 447
Abbreviations: AAQI = Aggregate Air Quality Index; CI = Cumulative Index

4. Discussion

The primary finding of this study is that air pollution, as measured by the CI, is significantly associated with an increased risk of DED. This result adds a novel perspective to the existing body of research, which primarily focuses on individual pollutants.[1-2,7-8]. Previous studies in environmental health often rely on multivariate regression models to evaluate the effects of individual pollutants, despite the high correlation between different pollutant.[7,8] Such correlation can lead to unstable model coefficients, making the results less reliable and difficult to interpret.[24] Our approach mitigates this issue by employing a mixture model within a multivariate logistic regression framework, effectively avoiding the problem of multicollinearity and providing a more accurate representation of pollution's cumulative effects.

Notably, just 10 additional high-pollution days per year raised the odds of developing DED by 48% (aOR = 1.48; 95% CI: 1.22–1.79)—a risk comparable to a decade of aging **(Table 2)**. By moving beyond traditional single-pollutant models, our findings illuminate the cumulative burden of environmental factors on ocular health, marking a significant step forward in understanding pollution's impact.

Most epidemiological studies average pollutant concentrations over long periods, which may dilute the effect of transient but severe pollution episodes, because there are more hours when pollutant levels are at baseline (**Supplemental Figure 1**). The integration of CI into population-level studies sets a new benchmark for evaluating environmental risks. Our approach is particularly valuable in ocular health, where brief but intense pollution spikes may have nonlinear impacts on the tear film and ocular surface.[10,11] Since the ocular surface has natural defenses—like tear production and blinking—that mitigate brief, low-level exposures [25-27], relying solely on long-term averages risks underestimating the impact of short-term events. By using the CI, we capture both cumulative exposure and periods of elevated pollutants, allowing for a more accurate reflection of pollution's effects on the eye. This approach enables detection of subtle but clinically significant impacts that simpler averaging methods might miss.

In recent years, significant debate has arisen regarding the extent to which $PM_{2.5}$ transported from China affects the air quality of neighboring countries, including South Korea.[28] Prevailing southwesterly and westerly winds drive the transboundary movement of pollutants, as evidenced by satellite imagery (MODIS-AOD), atmospheric modeling systems (CAMS), and back-trajectory analyses[29], with visualizations such as the PM2.5 forecast model from the Japanese Weather Association (Supplemental Figure 2) clearly illustrating this phenomenon[30]. Individual efforts alone cannot mitigate such large-scale environmental risks, making international collaboration indispensable. Multi-governmental funding and coordinated policy initiatives are essential for reducing emissions and addressing the economic and health-related costs of transboundary air pollution. This study contributes to these efforts by demonstrating a quantifiable link between air quality and DED prevalence, providing actionable data to guide policy and resource allocation.

An unexpected challenge during this study was the inability to include qualitative clinical measures, such as the ocular surface disease index (OSDI) or the standard patient evaluation of eye dryness (SPEED) questionnaire, which could have provided a more detailed assessment of symptom severity. While this represents a limitation, it is largely a matter of resource allocation; employing such measures would have required significantly more funding, which is often constrained in population-level studies. However, upon reviewing the clinical classifications, we found that the potential bias was minimal, as shown in Figure 3. The number of patients classified as 'Unlikely DED profile' (Figure 3A) and those reporting the use of other drugs (Figure 3B) represent possible margins of error, but these numbers are relatively small. Considering these factors and the reasonable patterns observed in Figure 3, the prevalence estimates derived in this study can be regarded as robust and appropriate within the scope of available resources.

Another intriguing finding was that a higher number of participants fell into the 'Probable DED profile' category compared to those who had been formally diagnosed and treated for DED **(Figure 3A)**. This suggests that many individuals may experience symptoms severe enough to require AT use but do not seek formal medical diagnosis for treatment. This discrepancy raises concerns about public awareness of DED and underscores the need for educational efforts to help individuals recognize their symptoms and seek appropriate care. A similar trend was observed in population's report on ocular surgery. **(Figure 3C).** This suggests that patients may prioritize cataract-related concerns in multiple-choice settings, even when experiencing symptoms more indicative of DED. It is possible that some patients are unaware of newer treatment options, such as Intense Pulsed Light (IPL) therapy or thermal pulsation, which may alleviate their symptoms more effectively than AT alone.[31,32]

Despite the novel insights provided by this study, several limitations should be acknowledged. First, the reliance on self-reported data introduces the potential for recall bias and misclassification. The absence of clinical measures further limits the precision of symptom assessment. While efforts were made to minimize these biases, future research should incorporate objective diagnostic tools to improve precision. Second, the study design, which relies on data collected by year and province, works well at a population level but may not be applicable to individual cases. Lastly, as this study is cross-sectional, longitudinal research tracking pollution exposure and DED incidence over time would provide a more accurate understanding of the causal relationship between air pollution and DED.

5. Conclusion

This study concludes that the CI effectively demonstrates the combined impact of multiple air pollutants on DED and shows a strong association with DED prevalence. By integrating air quality indicators with survey data, the study quantifies the contribution of air pollutants to DED, detecting subtle but clinically significant impacts that conventional methods may overlook.

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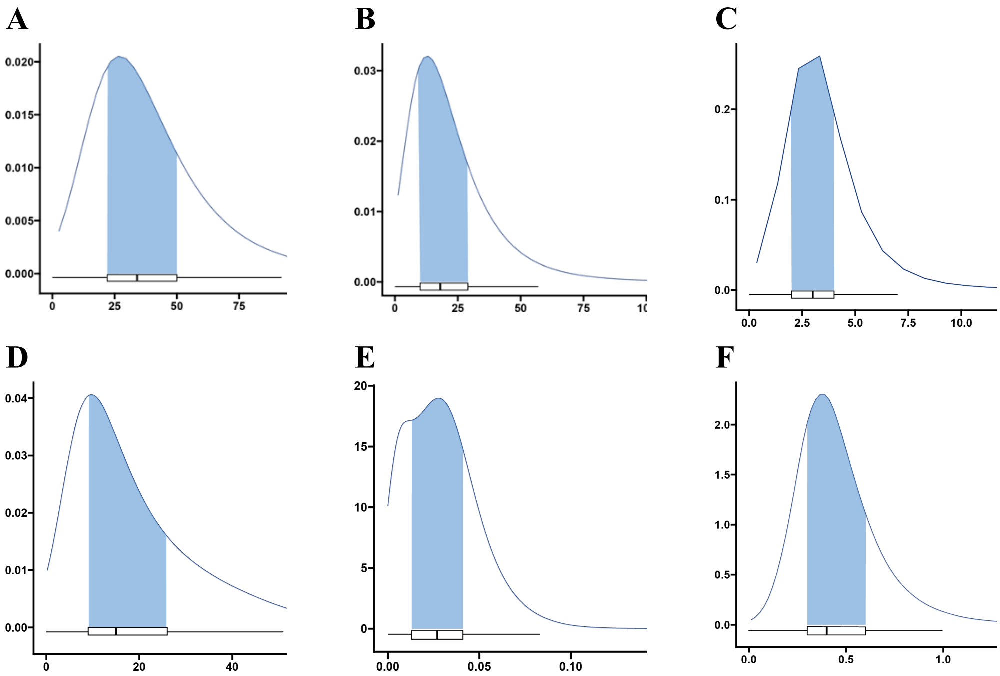
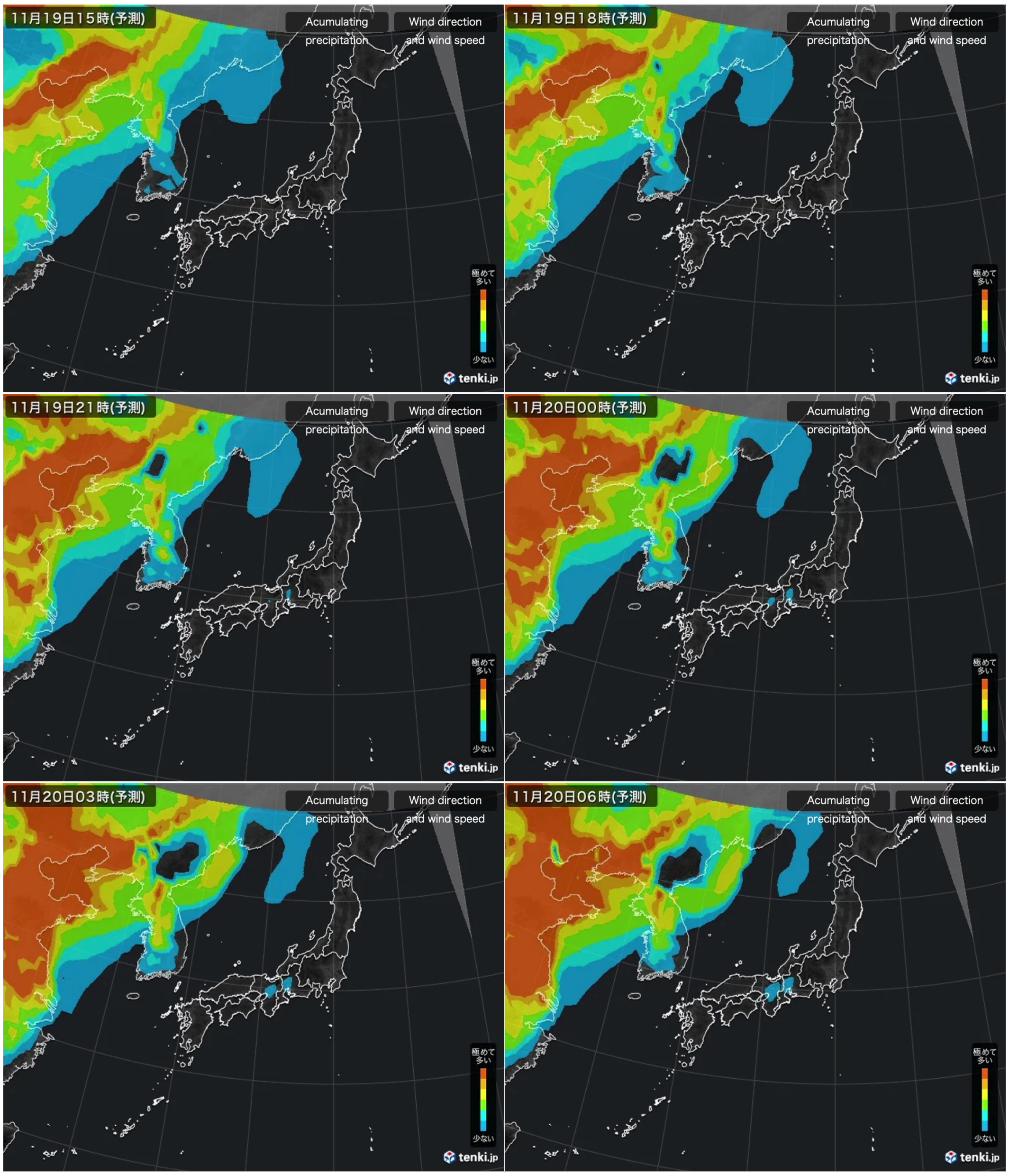
Appendices



Supplemental Figure 1. Distribution of six key air pollutants.
A, PM_{10} (µg/m³) **B,** $PM_{2.5}$ (µg/m³) **C,** SO_2 (ppb), **D,** NO_2 (ppb) **E,** O_3 (ppm) **F,** CO (ppm).
Each pollutant displays a pronounced right-skewed distribution, with lower concentrations occurring more frequently and higher levels less common.



Supplemental Figure 2. Hourly $PM_{2.5}$ forecast map for East Asia, updated every three hours. The transboundary movement of $PM_{2.5}$ pollutants from China to South Korea, driven by prevailing southwesterly and westerly winds.

Abstract in Korean

대기오염이 건성안에 미치는 누적 효과: 국민건강영양조사 (2017-2020)

대기 오염물질은 눈물막을 손상시키고 각막 상피에 손상을 줄 수 있어 심각한 불편함과 자극을 유발할 수 있다. 이러한 분명한 관계에도 불구하고, 다양한 오염물질 간의 복잡한 상호작용으로 인해 인구집단 수준에서 대기 오염의 건성안에 대한 영향을 직접적으로 평가하는 것은 어려운 과제로 남아있다.

이 연구는 대기오염물질의 건성안에 대한 영향을 조사하기 위해 2017 년부터 2020 년까지의 제 7 차 및 제 8 차 국민건강영양조사 자료와 국가 대기환경 정보관리 시스템의 대기오염물질 자료를 사용하여 대기오염과 건성안의 관계를 조사했다. 주요 대기오염물질들의 영향을 통합하여 보여주는 대기 지표를 계산하여, 다중 로지스틱 회귀 분석을 통해 연중 기준점 이상의 지표값을 나타내는 날의 수가 증가할수록 건성안의 발생 위험이 증가하는 것을 확인하였다.

핵심되는 말 : 건성안, 안구 건조증, 대기오염