Air Pollution and Meteorological Conditions Significantly Associated With Vernal Keratoconjunctivitis Exacerbations

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Purpose. Vernal keratoconjunctivitis (VKC) is a severe chronic allergic inflammation of the ocular surface with episodes of acute exacerbations, that primarily affects children and young adults. Although the etiology and pathogenesis of VKC remain unclear, studies have suggested that environmental factors may be involved. This study aims to investigate the association between exposure to meteorological and environmental factors and the incidence of VKC exacerbations.

Methods. This study was conducted in southern Israel, which is a semi-arid, hot, and dry climate with frequent dust storms. Patients diagnosed with VKC were recruited for the study. VKC exacerbations were identified as the need for medical intervention. Pollutants measured included nitrogen dioxide (NO_2), ozone (O_3), particulate matter (PM_{10} and $PM_{2.5}$), sulfur dioxide (SO_2), relative humidity (RH), temperature, and solar radiation (SR). To assess the association between VKC exacerbations and exposure to different pollutants, a case-crossover analysis was conducted. We also stratified the analysis by sex, age, ethnicity, immigration status, and social state score.

Results. Our results demonstrated that the pollutants NO_2, O_3, and PM_{10} were associated with VKC exacerbations with odds ratio (OR) = 2.17 (95% confidence interval [CI] =1.40 to 3.04), OR = 2.28 (95% CI = 1.30 to 3.39), and OR = 1.89 (95% CI = 1.06 to 2.74). Other pollutants $PM_{2.5}$, temperature, and solar radiation were also independently associated with incidence of exacerbations with OR = 1.15 (95% CI = 0.87 to 1.50), OR = 1.75 (95% CI = 1.16 to 2.65), and OR = 1.37 (95% CI = 1.01 to 1.63) and had varying effects in different demographic strata.

Conclusions. The environmental parameters, NO_2, O_3, PM_{10}, $PM_{2.5}$, temperature, and solar radiation were found to be significantly associated with VKC exacerbations, with NO_2, O_3, and PM_{10} showing the strongest associations. Our findings suggest that environmental factors should be considered when developing strategies to prevent and manage VKC exacerbations.

Keywords: air pollution, meteorological, ozone, particular matter, nitric oxide, vernal keratoconjunctivitis (VKC) epidemiology, Israel, prevalence, diagnosis

Vernal keratoconjunctivitis (VKC) is a severe chronic allergic inflammation of the ocular surface, with episodes of acute exacerbations. It is an important cause of visual debilitation and impairment of quality of life in children and young adults in certain parts of the world, such as the Mediterranean areas, Central and West Africa, the Middle East, Japan, the Indian subcontinent, and South America.[1–3] The hallmark of the disease is the presence of giant papillae at the upper tarsal conjunctiva (tarsal form) or at limbus (bulbar form). Intense itching, tearing, burning, and photophobia are the main ocular symptoms. Chronic recurrent inflammation can cause long-term visual impairments, such as corneal ulcers, as well as the development of cataract or glaucoma, and permanent visual loss. Early diagnosis and treatment are crucial to prevent recurrence of exacerbations and their consequences.[4–6]

Epidemiological studies have suggested different risk factors that may influence the occurrence of VKC. Patients have a family history of atopic diseases in 49% of cases. These patients may also have a medical history of other atopic conditions, including asthma (26.7%), rhinitis (20%), and eczema (9.7%).[5,7,8] It has been found that exposure to the sun and wind containing dust and pollen can aggravate the disease.[2] Therefore, its prevalence in hot, dry, and tropical regions is much higher. The disease is known to be usually seasonal, with more than 60% of patients with seasonal recurrence. The disease outbreaks usually lasting from the beginning of spring until autumn. The predominance in these months, of the higher temperatures, dry climates, and air pollution highlights the probable role of environmental factors on the VKC pathogenesis.[8–10]

Previous studies have shown that ambient air pollution can trigger allergic conjunctivitis. Air pollution is a recognized risk for many diseases, including cardiovascular, respiratory diseases, and lung cancer, and it significantly impedes the general health of young children. The World Health Organization (WHO) estimates that approximately 1 in 10 deaths in children under the age of 5 years is caused by air pollution.[11] The pathological mechanism by which airborne particles affect human health is yet to be fully understood. Air pollutants include particulate matter (PM) and other pollutants, including nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO), and ozone (O_3). Only a few studies have evaluated the association between air pollution and ocular allergic diseases.[11–13]

The Negev region is located in the southern part of Israel, it is characterized by unique environmental exposure of sandstorms and increasing pollutant levels that were shown to impact human health. The abundance in solar radiation and low humidity with moderate exposure to industrial pollution make it an ideal area to study the effects of environmental factors on health. Research of the Negev region has revealed a correlation between air pollution and hospitalizations for cardiovascular causes, asthma attacks, and more.[14]

We hypothesized that exacerbations of VKC were significantly associated with exposure to air pollution in the Negev region of southern Israel. The combination of this unique geographic location and our ability to create a population-based cohort due to the high percentage of the population in the southern region of Israel insured by Clalit Health Services can allow us to investigate this association between exposure to meteorological and environmental factors and incidence of VKC exacerbations in a way that has not been previously done, in order to hopefully help prepare for expected peaks in VKC incidence and to provide recommendations for populations that are at higher risk for VKC.

Methods

Clinical Setup

This retrospective observational population-based study was conducted by the Negev Environmental Health Research Institute (NEHRI), in collaboration with the Soroka University Medical Center (SUMC) Clinical Research Center and Ophthalmology Department. SUMC is a large, 1100 bed medical facility that serves a population of over 1.25 million residents in the southern region of Israel. It is the only hospital in the area, and is part of Clalit Health Services, which covers over 70% of the Negev population. The Clalit database contains detailed information on patients' medical history and primary care records, including demographic information, socio-economic status, geographic location, diagnoses, laboratory results, medications, and visits to healthcare providers. The area of Southern Israel has a semi-arid climate with hot and dry summers and mild winters, during which dust storms are common. Therefore, the Negev Desert provides an ideal natural laboratory to explore the impact of climate on health, with its unique environment, moderate exposure to industrial pollution, and developed medical facilities.

Study Population

The study population for this research was selected from patients registered with the Clalit Health Maintenance Organization (HMO) and living in the southern district of Israel between 2000 and 2021. Patients diagnosed with VKC were recruited for the study. Patients with VKC were identified based on recorded physician diagnosis (International Classification of Diseases, Ninth Revision [ICD-9]) of VKC. To ensure the accuracy and reliability of our cohort, we implemented manual verification of patient files for age outliers, including few months old patients as well as very old patients or where concerns regarding their diagnosis were present. Furthermore, we conducted a sensitivity analysis by cross-referencing the VKC diagnoses with data on acceptable drug delivery during VKC exacerbations. This additional verification step revealed a high level of concordance, with over 95% of cases demonstrating a match between the diagnosis and the appropriate medication administered. VKC exacerbations were defined as the need for medical intervention, which included several criteria. These criteria encompassed various scenarios where patients with VKC required medical attention. First, we identified referral to the emergency department with VKC exacerbation diagnosis assigned by an ophthalmologist, pediatrician, or emergency department (ED) doctor. Second, we identified admission to the ophthalmology department with VKC exacerbation diagnosis and, third, we identified referral to an ophthalmologist, pediatrician, or family physician outside the hospital to a patient with VKC exacerbation diagnosis. This allowed for the accurate identification and characterization of VKC exacerbation events, which were used in the analysis to assess the association between environmental exposure and VKC risk. The subjects were excluded from the analysis if their HMO records indicated that they had moved out of the Negev area during the study period, or if there was a lack of clinical or demographic data in their electronic files. This ensured that the study sample consisted only of individuals who were residents of the Negev area and had complete data available for analysis.

Data Collection

In this study, demographic and clinical data were collected for each participant from electronic medical records. This included information such as age, gender, ethnicity, and number of VKC exacerbations. Social state score was identified using data published by the Israeli Central bureau of statistics 2018 for each municipality based on 14 variables, including average monthly income, median age, percentage of families with $\geq$4 children, and more.

Exposure to ambient environmental factors was determined based on the subjects' residence addresses. The pollutants measured included NO_2, O_3, PM_{10} and $PM_{2.5}$, SO_2, relative humidity (RH), temperature, and solar radiation (SR). These levels were recorded by monitoring stations managed by the Ministry of Environmental Protection (MoEP) and were assigned to the study participants based on an average of the levels measured at 5 proximal monitors within a 20 km radius of their residence. The ambient environmental levels of pollutants, temperature, and humidity are recorded every 5 minutes. This model incorporates daily satellite remote sensing data at a 1 km spatial resolution. Levels of NO_2, SO_2, and O_3 were reported by the MoEP and meteorological services. Meteorological conditions, including temperature and RH, were based on readings from monitors in the area. All exposure variables were verified for the defined exposure window period of 2 to 7 days prior to the event. This exposure window is based on previous research showing potential effects up to 7 days prior to an event.[13]

Statistical Analysis

Descriptive statistics were used to summarize the demographic characteristics of the study population and the levels of environmental pollutants. Mean with standard deviations (SDs) or median with interquartile ranges (IQRs) values were calculated for each variable depending on the normality of the data.

A case-crossover analysis of the patient-level data was performed to assess the association between VKC exacerbations and exposure to different pollutants. This study design is well-suited for investigating the effects of transient exposures on rare events, such as the development of VKC exacerbation. In this design, each participant serves as his/her own control, allowing for within-person comparisons of exposure levels between periods with and without the outcome of interest. This eliminates the need for a separate control group, and reduces the potential for confounding due to individual-level characteristics that do not vary over time. The case-crossover analysis compared the 7 days prior to the VKC exacerbation, as the hazard period, to a 7-day period prior to each control times, beginning with the same weekday. In total, there are 4 control times, including 1 and 2 weeks prior to the VKC exacerbation and 1 and 2 weeks after the VKC exacerbation as the control period.

For each participant, the levels of each pollutant were calculated over the study period. For each pollutant, we converted the scale to 0 to 1, whereas the maximum measurement for the patient received the number 1 and the minimum measurement received the number 0, we performed this mathematical procedure for each patient. The odds of developing VKC were then calculated for each pollutant, comparing the odds ratio (OR) during periods of maximum to minimum exposure represents the maximum effect of the pollutant for each patient. by using conditional logistic regression. This allowed for the calculation of ORs and 95% confidence intervals (CIs) for each pollutant, along with corresponding *P* values. To reveal possible vulnerable subpopulations, we stratified the analysis by sex, age groups, and Bedouin-Arab versus Jewish ethnicity. All analyses were performed using R software version 4.2.2.

Results

Descriptive Statistics

The study population comprised 6024 patients with a diagnosis of VKC. Most of the population were male patients (62.4%), 59.8% were of Arab-Bedouin origin, and 40.1% were Jewish. The subjects were, on average, 13.5 years old at the time of their index VKC case onset. The mean social state score was 3.97 of 10, whereas a large proportion of the population (41.2%) had a score under 2, which corresponds to 60% of the population being Bedouin-Arabs who are known to represent the lowest stratum of the socioeconomic status (SES), the vast majority of the population (95.0%) are non-immigrants. VKC exacerbations occurred on average 4.08 times for each patient (Table 1). Environmental factors are described in Table 2, including pollution levels averaged over all monitoring stations during the study period of 2000 to 2021. Over the years of the study, NO_2 levels averaged 8.45 parts per billion (ppb), O_3 38.4 ppm, PM_{10} average levels were 39.3 µg/m^3 with maximum levels reaching 448. The average levels of $PM_{2.5}$ were at a 19.9 µg/m^3, SO_2 ppm was 1.62, and RH was 65.2% during the study years. As per the study protocol, all subjects had a residential address recorded in the database. A seasonal analysis of the annual VKC exacerbations, demonstrated in Figure 1, showed an apparent peak in the months between April and August over the years, especially between 2006 and 2016 when more than 30% of exacerbations occurred between those months. In recent years, the incidence of cases appeared to be more scattered throughout the year, nevertheless, they were still more abundant during the mentioned above months.

Table 1. Demographic Characteristics of the Study Population – 6024 Patients Diagnosed With Vernal Keratoconjunctivitis (VKC) in Southern Israel During the Study Period 2000 to 2021

Subjects' Characteristics	VKC Cases (N = 6024)
Age, y	
Mean (SD)	13.5 (8.6)
[Minimum, maximum]	[1.95, 57.3]
<5	1069
5–15	3208
>15	1747
Male gender	3760 (62.4%)
Ethnicity	
Jews	2414 (40.1%)
Bedouin	3604 (59.8%)
Other	6 (0.1%)
Social state score	
Mean (SD)	3.97 (3.43)
<2	2480 (41.2%)
2–5	2362 (39.2%)
>5	1183 (19.6%)
Immigration status	
Never immigrated	5723 (95.0%)
Immigrated before 1989	160 (2.7%)
Immigrated in 1989 and later	141 (2.2%)
VKC exacerbations	
Mean (SD)	4.08 (3.96)
Median [Q1, Q3]	3.00 [1.00, 5.00]

Case-Crossover Analysis

Analysis of cumulative association of VKC with maximum exposure as compared to minimum exposure pollutants' levels (exposure parameters range between 0 and 1 for each patient), are demonstrated in Figure 2. Most pollutants were independently associated with VKC exacerbation, specifically NO_2, O_3, PM_{10}, $PM_{2.5}$, temperature, and SR with ORs = 2.17 (95% CI =1.40 to 3.04), OR = 2.28 (95% CI = 1.30 to 3.39), OR = 1.89 (95% CI = 1.06 to 2.74), OR = 1.15 (95% CI = 0.87 to 1.50), OR = 1.75 (95% CI = 1.16 to 2.65), and OR = 1.37 (95% CI = 1.01 to 1.63), respectively. In addition, SO_2 is also likely to be adversely associated with VKC.

We further examined a possible impact of pollutants by three demographic strata and by RH and temperature (Fig. 3). A stratified analysis of cumulative association of VKC

Table 2. Ambient Pollutants Among the Study Population in South Israel During the Study Period of 2000 to 2021 Averaged Over all Monitoring Stations, by Residence Location

	Ambient Daily Exposure Description	Individual Span (Minimum to Maximum Exposure)
NO_2, ppb		
Mean (SD)	8.45 (3.96)	5.24 (3.32)
Median [Q1, Q3]	7.68 [5.66, 10.4]	4.50 [3.00, 6.70]
[Minimum, maximum]	[1.33, 49.0]	[0, 45.0]
O_3, ppm		
Mean (SD)	38.4 (12.2)	12.1 (7.16)
Median [Q1, Q3]	37.2 [31.4, 42.6]	11.0 [8.00, 14.5]
[Minimum, maximum]	[8.00, 126]	[0, 101]
PM_{10}, µg/m^3		
Mean (SD)	39.3 (15.6)	27.9 (15.3)
Median [Q1, Q3]	37.2 [29.2, 47.1]	25.5 [16.5, 36.5]
[Minimum, maximum]	[6.50, 448]	[0, 426]
$PM_{2.5}$ levels, µg/m^3		
Mean (SD)	19.9 (8.37)	15.5 (10.3)
Median [Q1, Q3]	18.3 [14.2, 23.4]	12.8 [8.50, 20.0]
[Minimum, maximum]	[2.00, 80.4]	[0, 72.0]
SO_2, ppm		
Mean (SD)	1.62 (8.33)	1.60 (16.4)
Median [Q1, Q3]	1.25 [0.80, 1.90]	0.84 [0.47, 1.42]
[Minimum, maximum]	[0.33, 528]	[0, 125]
RH, %		
Mean (SD)	65.2 (12.9)	22.2 (13.4)
Median [Q1, Q3]	67.1 [58.9, 73.5]	19.5 [11.5, 30.5]
[Minimum, maximum]	[6.50, 98.0]	[0, 84.5]
Temperature, °C		
Mean (SD)	20.1 (5.56)	4.91 (3.09)
Median [Q1, Q3]	21.0 [15.3, 25.2]	4.25 [2.50, 6.50]
[Minimum, maximum]	[2.50, 32.5]	[0, 30.5]
SR, W/m^3		
Mean (SD)	34.8 (11.9)	12.9 (11.1)
Median [Q1, Q3]	34.0 [26.8, 44.3]	9.50 [5.00, 17.5]
[Minimum, maximum]	[3.00, 96.5]	[0, 89.0]

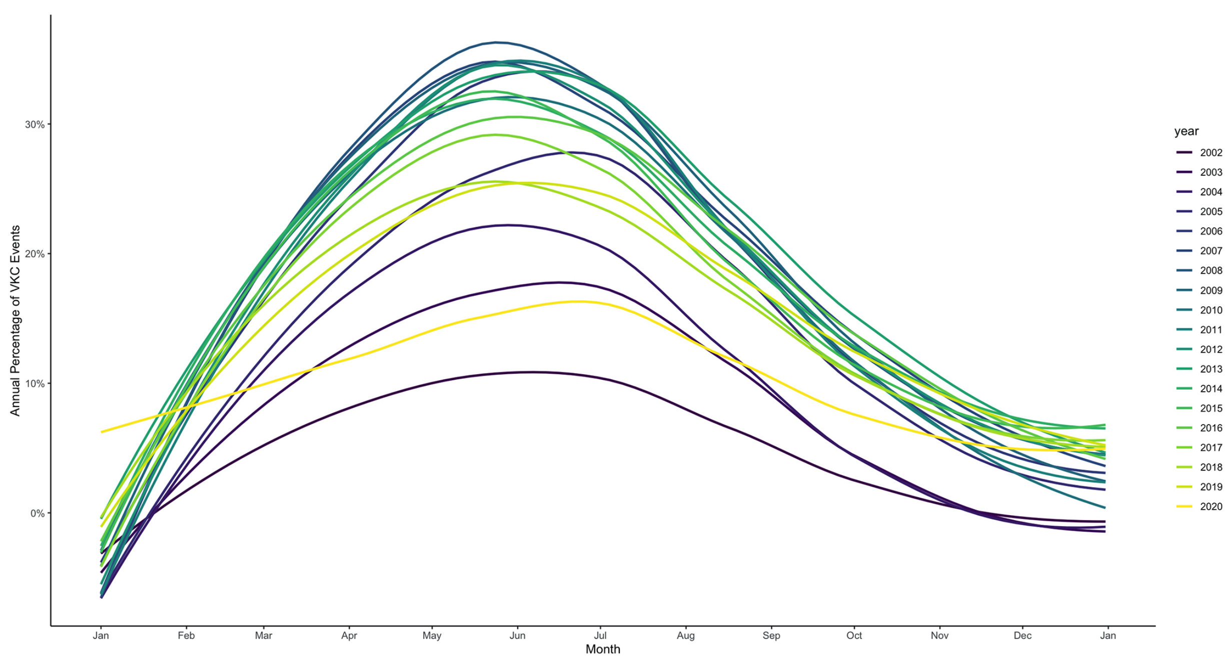

Figure 1. Seasonal plot illustrating the occurrence and variation of vernal keratoconjunctivitis (VKC) exacerbations over different seasons during the study period.

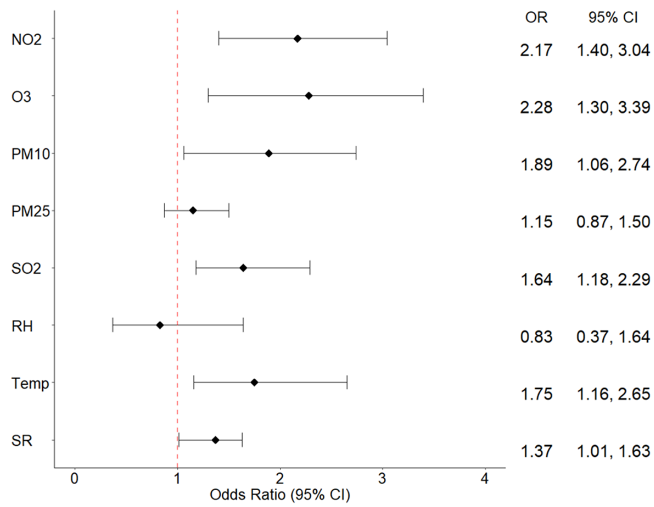

Figure 2. Association between ambient exposure to pollutants at residence location and vernal keratoconjunctivitis (VKC) exacerbations.

with maximum exposure as compared to minimum exposure pollutants' levels (exposure parameters range between 0 and 1 for each patient). The stratified findings indicated a higher impact of NO_2 on Bedouins featured by OR = 1.05 (95% CI = 1.00 to 1.12). Ozone showed a significant impact on female subjects, patients between ages 5 and 15 years, and Jews with OR = 1.12 (95% CI = 1.04 to 1.20), OR = 1.13 (95% CI = 1.06 to 1.19), and OR = 1.17 (95% CI = 1.08 to 1.26), respectively. Furthermore, Jews, older patients (>15 years old), or very young patients (<5 years old) were more likely to be affected by PM_{25} with higher OR estimates 1.08 (95% CI = 1.01 to 1.16), OR = 1.12 (95% CI = 1.02 to 1.22), and OR = 1.12 (95% CI = 1.00 to 10.25). Moreover, Bedouins were found to be more susceptible to exacerbations when exposed to PM_{10} with OR = 1.05 (95% CI = 1.00 to 1.11). Jews were found to be significantly affected by RH with OR = 1.07 (95% CI = 1.00 to 1.15). On the other hand, RH demonstrated a protective impact on Bedouins and male subjects with OR = 0.9 (95% CI = 0.84 to 0.96) and OR = 0.93 (95% CI = 0.88 to 0.99), respectively. Additionally, we conducted several sensitivity analyses to further strengthen the robustness of our results. First, we restricted the analysis to patients diagnosed by specialist ophthalmologists, ensuring a higher level of expertise and accuracy in the diagnostic process. Second, we considered only patients who received acceptable medical treatment specifically for VKC (Supplementary Table S1).

The association of VKC exacerbation probability and exposure to the study's pollutant parameters, as displayed in Figure 4, interestingly demonstrates a nonlinear association in cases such as PM_{10}, RH, temperature, ozone, and SR where the effect decreases after a certain level of pollutant, hence, maximal levels of pollutant do not necessarily cause the maximal effect.

Discussion

The main goal of this study was to investigate the association of VKC exacerbation probability and exposure to environmental pollutants and factors. This study has demonstrated that exposure to environmental factors, such as air pollutants, temperature, and SR, is associated with increased risk of VKC exacerbations in the South Israel. This supports earlier studies that showed that the levels of air pollutants were associated with an increase in hospital emergency visits, outpatient visits, and overall VKC exacerbation prevalence.[3,11,12,15] Of the environmental parameters examined, NO_2, O_3, PM_{10}, $PM_{2.5}$, temperature, and SR were found to be significantly associated with VKC exacerbations, with NO_2, O_3, and PM_{10} showing the strongest associations. The mechanisms regarding the effects of air pollutants on VKC exacerbations are not well known. These pollutants are strong irritants, oxidant pollution is typically initiated by NO production which its primary source is from motor vehicles and burning fuel, and additionally from emissions of construction sites, agricultural burning, and household activities such as burning wood. NO is then converted to NO_2 followed by the generation of O_3. All of these pollutants can directly damage the ocular surface by reducing the pH of the lacrimal fluid or by oxidization. Hot weather and strong winds can enhance these effects leading to instability of the ocular surface.[16] Moreover, it has been hypothesized that atmospheric pressure, minimal humidity, and wind speed may have direct mechanical effects on the ocular surface and could thus increase the incidence of ocular surface complaints. O_3 can cause severe irritation of the respiratory tract mucosa, and the effects are also apparent on the ocular mucosa.[13]

Our results showed that higher levels of both PM_{10} and $PM_{2.5}$ in the environment are associated with an increased risk of VKC exacerbations, partially in contrary to a previous study that found only PM with a larger diameter (PM_{10}) to have a significant impact on the number of outpatient visits for conjunctivitis, hypothesizing that this might be due to coarse PM, causing stronger foreign body sensations, whereas fine PM is easily cleaned from the ocular surface with tears, without inducing ocular discomfort.[15] Furthermore, the study identified differences in susceptibility to VKC exacerbations influenced by different demographic factors, such as sex, age, and ethnicity. The different lifestyle and occupational conditions may also contribute to the differences in susceptibility among each demographic group. For example, the study revealed that Jews, older patients, and younger patients were more likely to be affected by $PM_{2.5}$, whereas Bedouins were found to be more susceptible to exacerbations when exposed to PM_{10}.

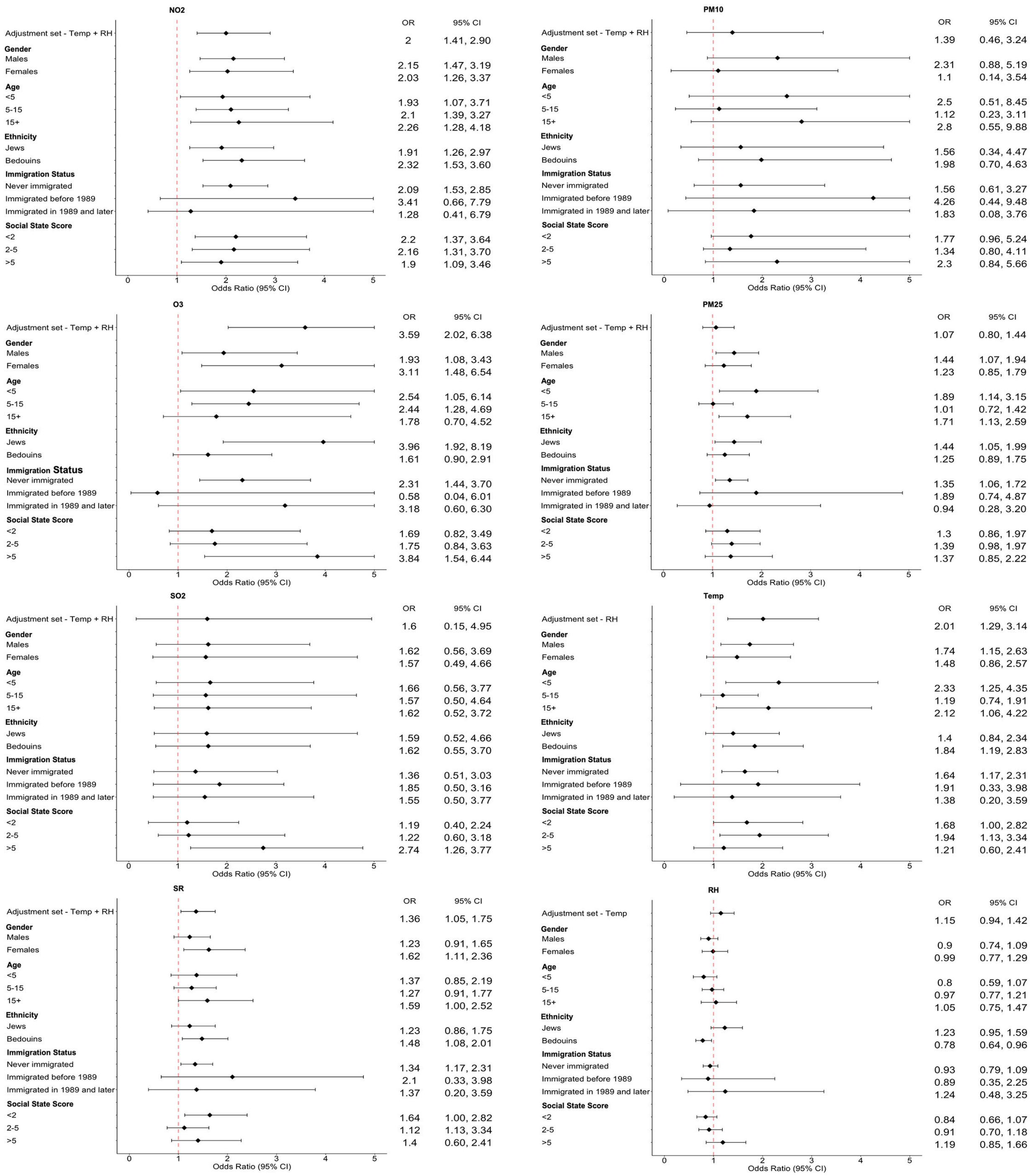

Figure 3. Stratified analysis of the association between ambient exposure to pollutants at residence location and vernal keratoconjunctivitis (VKC) exacerbations based on gender, age, ethnicity, immigration status, and socio-economic score.

The majority of a Bedouin-Arab population (over 25%) frequently reside in traditional tents or other temporary structures. This demographic is exposed to significantly higher levels of environmental factors throughout the year, including days with pollution that would typically confine individuals to their homes in other regions. Additionally, this population's lifestyle leads to exposures that even affect newborns and elderly individuals, who would typically experience minimal exposure while staying indoors in other locations, which may explain the mentioned effect on this population (PM_{10}).[17] The study also demonstrated a nonlinear association between VKC exacerbations and exposure to the pollutants, suggesting that the risk of exacerbations does not necessarily increase with each incremental increase in pollutant levels. This suggests that while exposure to higher levels of pollutants is associated with a greater risk of VKC exacerbations, the risk may not be greater for the highest levels of pollutant exposure. A reasonable

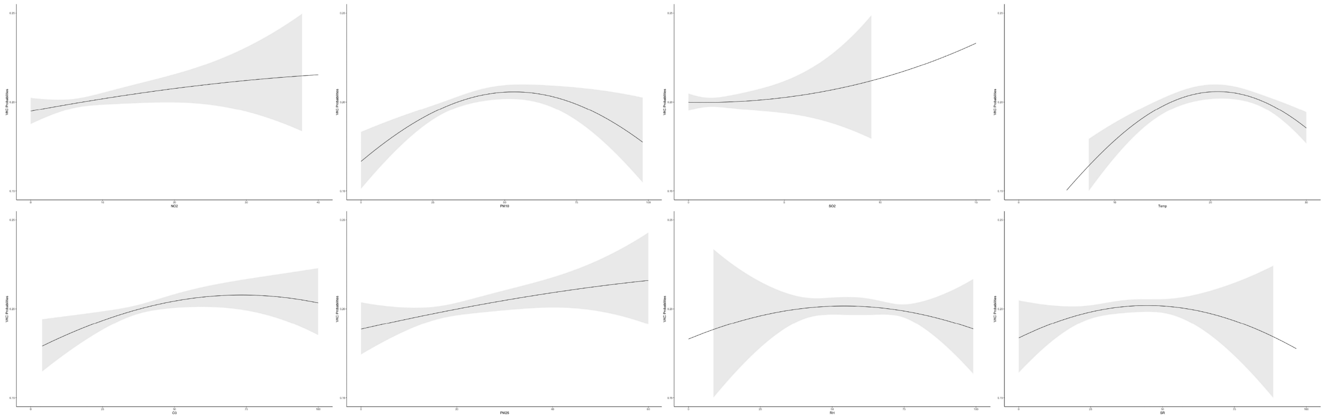

Figure 4. The A-linear association between different levels of ambient exposure to pollutants at residence location and vernal keratoconjunctivitis (VKC) exacerbations.

explanation for the decline in exacerbations at higher levels of exposure, for example with PM_{10} and temperature could be due to behavioral changes and adaptations done by the subjects as preventive measures in cases of strong sandstorms and days of excessive heat. By understanding the demographic characteristics of the people who are at a higher risk for exacerbations, targeted preventive measures can be developed. Patients at an elevated risk should take particular care to minimize their time spent in areas with expected high levels of risk associated environmental factors NO_2, O_3, PM_{10}, and high SR. It is also important to wear sunglasses and practice frequent hand, face, and hair hygiene, especially before going to bed. Furthermore, because VKC flare-ups are usually seasonal, special emphasis should be placed on prevention during the spring and summer months. In general, promoting education and awareness is essential. Developing educational materials and awareness campaigns specifically tailored to these populations can be highly valuable.[18]

The present study also has several limitations. One potential limitation of this study is clinical misdiagnosis; the diagnosis of VKC is based on clinical examination by a physician. This means that the diagnosis is subject to human error, and it is possible that some patients with VKC may have been misclassified. This could lead to an underestimation as well as overestimation of the true incidence of VKC in the population, which in turn could bias the study conclusion. To address this limitation, we performed a sensitivity analysis of the results in which only diagnoses given by an ophthalmologist were included, and diagnoses given by other healthcare providers, such as family doctors or pediatricians, were excluded. This analysis confirms that the results were robust and not affected by potential misdiagnosis by other healthcare providers. Another limitation of the study is a potential exposure misclassification, as a result of defining exposure to pollutants based on residency, without considering other factors that could modify exposure, such as behavior and time spent outdoors. This may not accurately reflect the true level of exposure to pollutants in the population. Given the fact that dust storms and increased pollution are common in the region, it would be fair to assume that people tend to alter their behavior during such events, in an attempt to lessen their exposure. Nevertheless, misclassification of this kind drives the study conclusions toward a null hypothesis, which did not occur in the current study. In addition, IgE sensitization data were not recorded, which did not allow us to isolate the pollutant exposure from allergen exposure or irritants.

Overall, this is a unique large-scale epidemiological environmental study of VKC in Israel that provides important insight into the environmental factors associated with VKC exacerbations and the differences in susceptibility among different demographic groups. As best we know, there have not been any studies that examined each individual before, during, and after an exacerbation, allowing a more accurate evaluation of the association to pollutant exposure. Our findings suggest that environmental factors should be considered when developing strategies to prevent and manage VKC exacerbations. Further research is needed to better understand the impact of environmental factors on VKC exacerbations and to identify effective strategies to reduce the risk of exacerbations in vulnerable populations.

Acknowledgments

Ethics Approval and Consent to Participate: The study was approved by the SUMC ethics committee, reference number 0064-22. All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. The ethics committee approval exempted the study from informed consent due to the retrospective data collection that maintained subject confidentiality. Informed consent was waived by the institutional review board at SUMC. Patient records were anonymized and de-identified prior to analysis.

Authors' Contributions: I.P. performed the data analyses presented in this manuscript. E.L., M.G., L.N., and E.T. contributed to the interpretation of the data. E.T. provided his clinical expertise in the Ophthalmological discipline. E.L. prepared the initial draft of the manuscript. All authors contributed to drafting of the manuscript and critical revision of the manuscript for important intellectual concepts. All authors read and approved the final manuscript for submission.

Availability of Data and Materials: The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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