



Effects of Ambient Exposure to Nitrogen Dioxide on Outpatient Visits for Psoriasis in Rapidly Urbanizing Areas

Yu Wang^{1,2*}, Changchang Li^{3†}, Zengliang Ruan⁴, Rouxuan Ye⁵, Bin Yang^{1,2*}, Hung Chak Ho^{6,7,8*}

¹ Department of Dermatology, The First Affiliated Hospital of Jinan University, Guangzhou 510630, China

² Department of Dermatology, Dermatology Hospital of Southern Medical University, Guangzhou 510091, China

³ STD Control Department, Dermatology Hospital of Southern Medical University, Guangzhou 510091, China

⁴ Department of Epidemiology and Health Statistics, School of Public Health, Southeast University, Nanjing 210096, China

⁵ Department of Biostatistics, Bioinformatics & Biomathematics, Georgetown University, Washington, DC 20007, USA

⁶ Department of Anesthesiology, School of Clinical Medicine, The University of Hong Kong, Hong Kong

⁷ Healthy High Density Cities Lab, Faculty of Architecture, The University of Hong Kong, Hong Kong

⁸ Department of Urban Planning and Design, The University of Hong Kong, Hong Kong

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* Corresponding Authors:

Hung Chak Ho
hcho21@hku.hk
Bin Yang
yangbin1@smu.edu.cn

† These authors contributed equally to this work

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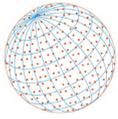
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ABSTRACT

Rapid development and urbanization can increase ambient exposure to NO₂ and its health risks in individuals. However, the association between NO₂ exposure and outpatient visits of patients with psoriasis has rarely been reported, though psoriasis is a major skin disease in rapidly urbanizing areas with high population densities. This study applied a time-stratified case-crossover design to investigate the effect of short-term exposure to ambient NO₂ on outpatient visits for psoriasis from 2014 to 2020 in Guangzhou, China (n = 62,305). A subgroup analysis was performed to evaluate NO₂ impacts on vulnerable subpopulations. Our results showed that the NO₂ concentration during the study period was lower than that of the level II threshold from China (PRC) but higher than that set by the WHO, indicating moderate air quality. However, a 10-μg m⁻³ increase in NO₂ concentration could still be associated with 3.1% higher outpatient visits for psoriasis (adjusted RR of lag 0 day: 1.031 [CI: 1.025, 1.037]). NO₂ exposure can also pose long-term risks. Additionally, NO₂ impacts on psoriasis may be independent of other pollutants. Adjusting for PM_{2.5}, SO₂, O₃, and meteorological factors, a 10-μg m⁻³ increase in NO₂ was associated with RRs of 1.043 [CI: 1.033, 1.053], 1.022 [CI: 1.014, 1.031], and 1.022 [CI: 1.014, 1.031] at lag 0, lag 1, and lag 2 days, respectively. NO₂ risks were higher among older individuals (age ≥ 60 years) and those with medical insurance [adjusted RRs: 1.045 (CI: 1.023, 1.066) and 1.047 (CI: 1.036, 1.058)]. Being a major pollutant in rapidly urbanizing areas with high population densities, NO₂ emission could be a crucial factor in psoriasis, although the daily pollution level was not above the air quality thresholds. Challenges associated with air quality control and health disparity create a necessity for the enhancement of health and environmental policies to reduce local and regional emissions (e.g., traffic-related pollution), and vulnerable subpopulations should be targeted.

Keywords: Air pollution, Nitrogen dioxide, Psoriasis, Outpatient visits



1 INTRODUCTION

Nitrogen dioxide (NO₂) exposure can originate from traffic-related emissions and regional pollution (Zhang and Batterman, 2013). NO₂ exposure is a critical determinant of community health because of its remarkable impact on the global disease burden (Cohen *et al.*, 2017). Owing to the co-influences of climate change, urbanization rate, and population growth, the short-term impacts of NO₂ exposure on human health have increased significantly, especially for those living in developing countries (Cohen *et al.*, 2017). Specifically, a rapidly urbanizing area with a high population density can be conducive to the development of various unstable air quality conditions. NO₂ concentrations can vary between weekdays and weekends owing to varying traffic patterns and industrial emissions. The large population of migrants in a megacity could also affect health practices and environmental awareness regarding acclimation and self protection. Therefore, NO₂ and its associated health risks should be investigated.

Being the largest organ of the human body, the skin can be exposed to air pollutants from the external environment under different weather conditions. When the amount of air pollution exposure exceeds the resilience threshold for self protection, it may result in skin diseases (Szyszkowicz *et al.*, 2010; Xu *et al.*, 2011; Li *et al.*, 2016; Liu *et al.*, 2018; Ren *et al.*, 2019; Chao *et al.*, 2021; Zhang *et al.*, 2021). Thus, the effects of NO₂ exposure on skin diseases have received increasing attention. Understanding the relationship between NO₂ and psoriasis is of particular concern because psoriasis is a major skin disease in rapidly urbanizing areas with high population densities.

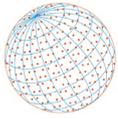
1.1 NO₂ and Psoriasis

Psoriasis is a chronic inflammatory disease with a high risk of recurrence. More than 100 million individuals worldwide suffer from psoriasis (WHO, 2016; Mehrmal *et al.*, 2021). Psoriasis not only affects one's skin condition, but also causes multiple comorbidities. Previous studies found that an individual with psoriasis could be at greater risk of developing cardiovascular disease, metabolic disease, psoriatic arthritis, inflammatory bowel disease, depression, kidney disease, and malignancy (Takeshita *et al.*, 2017). These comorbidities may result from the complex pathogenesis of psoriasis, including factors associated with genetic predisposition, immunologic conditions, socio-demographic characteristics [e.g., mechanical stress (Binitha *et al.*, 2013), infection (Fry and Baker, 2007), drug intake (Balak and Hajdarbegovic, 2017), smoking (Richer *et al.*, 2016), and alcohol consumption (Adisen *et al.*, 2018)]. Recent studies have found that air pollution can be an additional factor associated with an increased risk of developing psoriasis (Hancox *et al.*, 2004; Lønnberg *et al.*, 2016; Richer *et al.*, 2016; Liaw *et al.*, 2017; Kardes, 2019; Nikam *et al.*, 2019; Wu *et al.*, 2020).

Specifically, photolysis (or photodissociation) from NO₂ may affect the condition of the skin (Cibella *et al.*, 2015; Fussell and Kelly, 2020), thereby further inducing allergic and immunologic skin diseases, including atopic dermatitis and chronic eczema (Kim *et al.*, 2017; Schnass *et al.*, 2018), as well as other chronic and inflammatory skin diseases, such as acne vulgaris (Liu *et al.*, 2018). Although the pathophysiological mechanisms between NO₂ concentration and inflammatory skin diseases have not been fully explored, a study reported that short-term exposure to low concentrations of NO₂ could affect the epidermal barrier function in individuals with atopic eczema, leading to a change in the structure of the skin surface (Eberlein-Konig *et al.*, 1998). Therefore, NO₂ exposure may aggravate skin diseases via irritants or oxidative stress, as well as disturb the cutaneous microbiome (Araviiskaia *et al.*, 2019), thereby inducing psoriasis in individuals.

1.2 Missing Linkages: NO₂ and Psoriasis in Rapidly Urbanizing Areas with High Population Densities

Despite the fact that psoriasis and the impact of NO₂ on skin diseases could pose health risks, no studies have reported the association between ambient NO₂ exposure and psoriasis in rapidly urbanizing areas with high population densities, such as Guangzhou, China. This gap in research is of high concern, as the prevalence of psoriasis among adults could vary according to race and geographic region (Li *et al.*, 2012; Parisi *et al.*, 2013). A systematic review found that the difference in prevalence among children and adults due to geographic variations (Norway) could range from 0% to 2.1% and 0.91% to 8.5%, respectively (Parisi *et al.*, 2013). Considering the urbanized state



of these regions and the associated rapid development, this variation should be given more attention.

Industrial development and urbanization have been key factors in NO₂ pollution in rapidly urbanizing areas with high population densities. A high population density also increases the exposure to NO₂, thereby resulting in increased healthcare burdens. Therefore, understanding how NO₂ could influence the occurrence of psoriasis in rapidly urbanizing areas with high population densities is crucial for global health.

1.3 Temporal Variations in NO₂ Concentrations and Psoriasis Occurrences

Due to urbanization and industrial development, NO₂ can only be reduced but not completely removed from a high-population-density environment (Soares *et al.*, 2021). Although some regions have applied clean-air policies for pollution control, temporal variations (e.g., seasonal change, anthropogenic haze) could increase NO₂ concentrations from low-to-moderate or moderate-to-high levels. Although the average concentration of NO₂ across this area may be lower than the World Health Organization (WHO) or national thresholds, the health impacts may still be significant. Some studies have found significant impacts of low levels of air pollution on health risks (Olmo *et al.*, 2011). Therefore, the impacts of NO₂ on psoriasis may be considerable, even if the air pollution does not exceed the set limits. This is because psoriasis may be more sensitive to environmental changes than other diseases. The unstable conditions associated with rapidly urbanizing areas and the underestimated problem of citizens' unawareness could increase the risk of psoriasis among the people living in this city.

Recent studies have shown that short-term exposure to moderate adverse environmental conditions in the Pearl Delta River (PRD) (e.g., moderately cold or hot days, low-level air pollution) affects the health of individuals (Chen *et al.*, 2018; Ho and Wong, 2019; Zhang *et al.*, 2020; Cheng *et al.*, 2021). Due to changes in NO₂ concentrations, the magnitude of risks from low-to-moderate or moderate-to-high level increases could even be higher than those of a high-to-extremely-high level increase. Therefore, people living in cleaner environments under clean air policies may still be at high risk of NO₂ exposure. Since the above population may be less acclimatized to adverse conditions than those in highly polluted areas, the effects of moderate air quality on such populations should be investigated.

1.4 Objectives

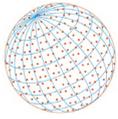
In this study, we developed a time-stratified case-crossover design to evaluate the association between ambient NO₂ and daily outpatient visits for psoriasis in Guangzhou, China. The objectives of this study were to: 1) evaluate the effect of NO₂ concentrations on outpatient visits for psoriasis and 2) identify subpopulations susceptible to NO₂ exposure.

2 METHODS

2.1 Study Area

Guangzhou was selected as the study area. Guangzhou is one of the largest cities on the Pearl Delta River (PRD). Owing to rapid economic development since the 1950s, there have been high rates of urbanization and industrialization across China (Zhang and Song, 2003; Chen *et al.*, 2014; Zhang, 2017). This development has enhanced the quality of life among the local population through the improvement of infrastructure and advanced technologies, while also creating an obvious environmental inequality and health disparity during the 21st century (Azimi *et al.*, 2019). Recent studies have found that industrial development and urbanization have induced significant air pollution across metropolitan areas in China, and the types of air pollution can range from very fine particles to toxic chemicals and heavy metals originating from various local sources, and result in regional impacts (Yuan *et al.*, 2020). Moreover, rural-to-urban migration in China dramatically increased the population density in metropolitan areas, which increased the population exposure to ambient air pollution and its related healthcare burdens (Gong *et al.*, 2012).

In particular, the PRD has been reported as an area with rapid development and industrialization. The level of air pollution has increased in the PRD owing to traffic emissions and regional impacts (Hou *et al.*, 2019). The population density has also increased because of local migration. Previous



studies have found that air pollution in the PRD has caused a significant increase in health risks (Lu *et al.*, 2016; Lin *et al.*, 2017; Wu *et al.*, 2019), and local governments have introduced clean air policies to reduce air pollution.

2.2 Health Data

We retrieved the daily records of outpatient visits for psoriasis between October 1, 2014, and December 31, 2020, from the Dermatology Hospital of Southern Medical University, Guangzhou, China. All visits were registered based on the 10th version of the International Statistical Classification of Diseases and Related Health Problems (ICD-10). Outpatient visits records was used because of the nature of medical care in China, where there is no necessity to pre-schedule medical appointments, thus allowing individuals to visit and revisit clinics instantly under various medical conditions, such as onset, aggravation, or relapse of diseases. The daily records of outpatient visits could be used to estimate whether psoriasis is due to the short-term effects of ambient NO₂ exposure.

The analytical dataset for this study was developed based on the following inclusion criteria (Fig. 1): (1) outpatient visits were recorded as ICD-10 L40 and (2) they were recorded as patients returning for follow-ups. The following exclusion criteria were also applied to retrieve medical records: (1) without age or residential information and (2) location of residence indicated as being “outside Guangzhou.”

This study was approved by the Medical Ethics Committee of the Dermatology Hospital, Southern Medical University, and complied with the Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects.

2.3 Environmental Data

Average daily concentrations of air pollutants between October 1, 2014, and December 31, 2020, were obtained from the Guangzhou Environmental Monitoring Center through its public sharing system. This included information on the following air pollutants: NO₂, SO₂, particulate matter with an aerodynamic diameter of 2.5 μm or less (PM_{2.5}), and daily 8-h maximum of O₃. The system automatically averaged daily records from 11 national air quality monitoring stations across Guangzhou. Daily records of relative humidity, temperature, and sunshine duration between study period were obtained from the China Meteorological Data Sharing Service System.

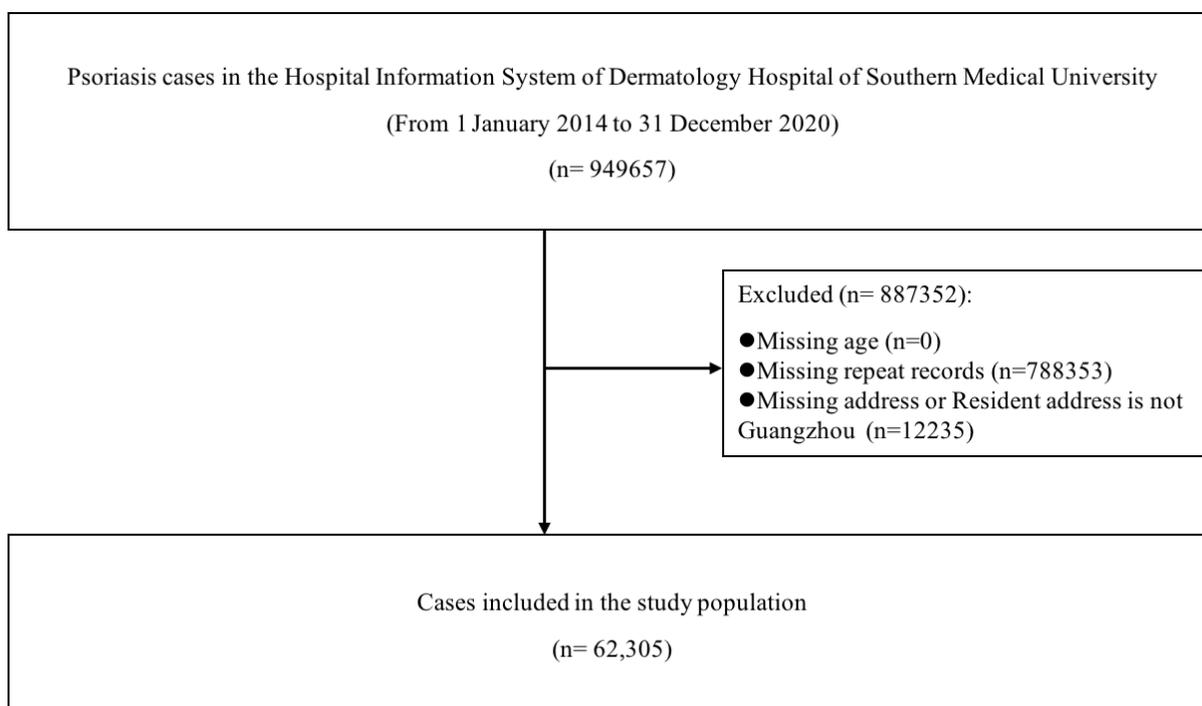
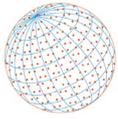


Fig. 1. Participant enrollment protocol.



2.4 Statistical Analyses

We employed a time-stratified case-crossover study design to estimate the association between NO₂ exposure and outpatient visits for psoriasis. Specifically, we identified the date of each visit as a “case” day and the same weekdays within the same month of the same year as “control” days. For example, if there was an outpatient visit on May 22, 2020, this was assigned as a “case” day while “control” days would be May 1, 8, 15, and 29, 2020. This design is commonly used in environmental health studies because of its ability to self-control for long-term trends, seasonality, weekday/weekend effects and holiday effects.

A three-stage analysis was conducted. First, we used a single-variable model to estimate exposure-lag-response associations between NO₂ and daily outpatient visits for psoriasis. We combined a conditional Poisson model and distributed lag nonlinear model to confirm whether linear or nonlinear associations existed between NO₂ and outpatient visits. A natural cubic spline function was applied, and a sensitivity analysis of the degrees of freedom from three to six was used. To estimate the lag effect of air pollution, we allowed a lag of 1 to 7 days. The model was adjusted for sunshine duration and relative humidity.

The second-stage analysis was conducted based on the confirmation of a linear or nonlinear relationship. We further applied a multiple-variable model that combined two or more air pollution variables in a regression to examine whether NO₂ effects on daily outpatient visits for psoriasis would be modified. All models were further adjusted for sunshine duration and relative humidity.

For the third-stage analysis, stratified analyses were conducted to examine the potential effect modification by age, sex, and medical insurance. Comparisons between subgroups were performed using meta-regression analysis and a two-sample z-test.

Relative risks (RRs) and 95% confidence intervals (CI) were reported for all models. The results are presented as the percentage of change in the number of daily outpatient visits for psoriasis per 10 micrograms per cubic meters ($\mu\text{g m}^{-3}$) increase in NO₂ concentrations. All data analyses were performed using packages “*gnm*” and “*dlnm*” in the R software (version 4.1.0). Statistical significance was defined as a two-sided p-value of < 0.05.

A sensitivity analysis has also conducted (Table S1) to test whether results reported based on $\mu\text{g m}^{-3}$ could be comparable with volume mixing ratio unit (ppb).

3 RESULTS

3.1 Descriptive Summary

Our analytical dataset included 62,305 patients who met our inclusion criteria. The patient characteristics are shown in Table 1. Patient’s records in each year and each month are shown in Table S2. The average age of the patients was 37.8 ± 6.53 years. Of these patients, 56% were male and 82.1% had medical insurance. Furthermore, psoriasis vulgaris was the major cause of the outpatient visits. In addition, there was an equal proportion of outpatient visits during each season.

The average (\pm standard deviation) daily relative humidity, ambient temperature, and sunshine duration were $22.35 \pm 6.01^\circ\text{C}$, $79.82 \pm 11.2\%$, and 4.31 ± 3.76 h, respectively. The daily averages and standard deviations of the O₃, SO₂, NO₂, and PM_{2.5} concentrations were $178.04 \pm 97.23 \mu\text{g m}^{-3}$, $11.58 \pm 7.69 \mu\text{g m}^{-3}$, $45.72 \pm 19.25 \mu\text{g m}^{-3}$, and $35.37 \pm 20.75 \mu\text{g m}^{-3}$ respectively (Table 2). These concentrations were lower than the ambient air quality standards of Level II set by China’s PRC guidelines [GB 3095-2012] (O₃ = $160 \mu\text{g m}^{-3}$, SO₂ = $150 \mu\text{g m}^{-3}$, NO₂ = $80 \mu\text{g m}^{-3}$, PM_{2.5} = $75 \mu\text{g m}^{-3}$). Furthermore, the concentrations of NO₂ and PM_{2.5} were higher than the air quality standards set by the WHO (2021), whereas O₃ and SO₂ were lower than the set WHO values. This indicates moderate air quality in the study area.

3.2 Statistical Analyses

The first-stage analysis showed a linear relationship between NO₂ exposure and outpatient visits for psoriasis. A $10\text{-}\mu\text{g m}^{-3}$ increase in NO₂ concentration resulted in an RR of 1.031 [CI: 1.025, 1.037] at lag 0 day. A prolonged effect of NO₂ exposure was also observed. The RRs of lag 1 and lag 2 days were 1.013 [1.008, 1.018] and 1.013 [1.008, 1.018], respectively (Fig. 2).

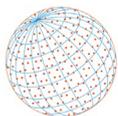


Table 1. Demographic characteristics of outpatient for psoriasis, 2014–2020 (N = 62,305).

Characteristics	Value
Cases, n	62305
Subtype of psoriasis	
Psoriasis vulgaris, n (%)	59001 (94.7%)
Psoriasis arthropathica, n (%)	3049 (4.9%)
Psoriasis pustulose, n (%)	775 (1.2%)
Psoriasis erythrodermicum, n (%)	521 (0.8%)
Age (years)	
< 60, n (%)	49633 (79.7%)
≥ 60, n (%)	12672 (20.3%)
Mean ± SD	37.8 ± 6.53
Sex	
Male, n (%)	34900 (56.0%)
Female, n (%)	27379 (43.9%)
Missing data	26 (0.5%)
Medical Insurance	
Yes, n (%)	51166 (82.1%)
No, n (%)	11139 (17.9%)
Presentation during March to May, n (%)	15684 (25.2%)
Presentation during June to August, n (%)	14979 (24.0%)
Presentation during September to November, n (%)	16139 (25.9%)
Presentation during January, February, and December, n (%)	15323 (24.6%)

Table 2. Descriptive environmental conditions in Guangzhou, 2014–2020.

Environmental Factor	Min.	P (25)	P (50)	P (75)	Max.	Mean ± SD
Weather conditions						
Daily mean ambient temperature (°C)	3.70	17.83	23.53	27.43	32.40	22.35 ± 6.01
Daily Relative Humidity (%)	27.67	73.67	81.67	88.00	99.67	79.82 ± 11.2
Daily sunshine duration (hours)	0.00	0.20	3.90	8.00	8.00	4.31 ± 3.76
Air pollutants concentrations						
Daily average concentration of CO (µg m ⁻³)	4.13	0.73	0.85	1.00	2.57	0.89 ± 0.23
Daily average concentration of O ₃ .8h (µg m ⁻³)	8.85	99.91	171.26	241.48	563.87	178.04 ± 97.23
Daily average concentration of SO ₂ (µg m ⁻³)	3.04	7.08	9.88	13.92	105.00	11.58 ± 7.69
Daily average concentration of NO ₂ (µg m ⁻³)	3.09	32.52	41.77	54.43	176.67	45.72 ± 19.25
Daily average concentration of PM _{2.5} (µg m ⁻³)	3.50	20.63	30.58	45.25	156.47	35.37 ± 20.75
Daily average concentration of PM ₁₀ (µg m ⁻³)	5.58	35.88	49.17	71.17	217.75	49.17 ± 28.43

P: percentile.

Based on these results, linear models were applied to determine the impact of multiple pollutants on outpatient visits for psoriasis. We found that the independent effect of NO₂ was highly stable, even when including other types of air pollutants (PM_{2.5}, O₃, SO₂) as confounders. Adjusting for SO₂, a 10-µg m⁻³ increase in the NO₂ concentration resulted in RRs of 1.035 [CI: 1.028, 1.042], 1.016 [CI: 1.010, 1.023], and 1.016 [CI: 1.010, 1.023] at lag 0, lag 1, and lag 2 days, respectively. Adjusting for O₃, a 10-µg m⁻³ increase in the NO₂ concentration was associated with a 3.3% increase in the number of outpatient visits for psoriasis (RR: 1.033 [CI: 1.027, 1.040]) at lag 0 days and 2% increased risk at lag 1 and lag 2 days. Adjusting for PM_{2.5}, a 10-µg m⁻³ increase in the daily NO₂ concentration was associated with RRs of 1.042 [CI: 1.033, 1.052], 1.022 [CI: 1.014, 1.030], and 1.022 [CI: 1.014, 1.030] at lag 0, lag 1, and lag 2 days, respectively. More importantly, the model adjusted for SO₂, O₃, and PM_{2.5} indicated RRs of 1.043 [CI: 1.033, 1.053], 1.022 [CI: 1.014, 1.031], and 1.022 [CI: 1.014, 1.031] at lag 0, lag 1, and lag 2 days (Table 3). This indicated that NO₂ was a dominant pollutant, and its effects on outpatient visits for psoriasis could be independent of other pollutants.

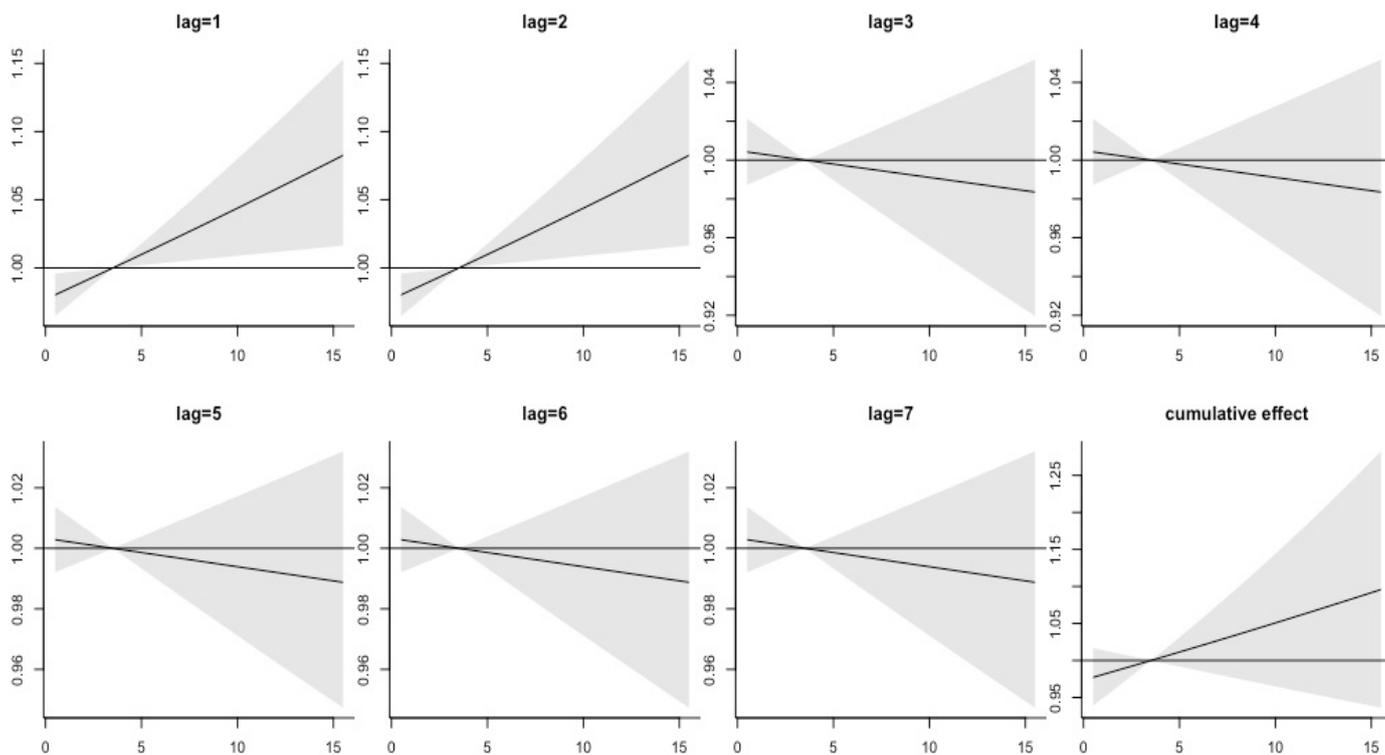
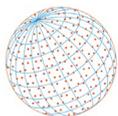


Fig. 2. Lagged Effects of Per Unit Increase of NO₂ on psoriasis in Guangzhou, 2014–2020 (Without any adjusting factor). X axis indicates concentration of NO₂ ($\mu\text{g m}^{-3}$). Y axis indicates relative risk of NO₂ exposure.

Table 3. Increase of daily number of psoriasis cases associated with per 10 $\mu\text{g m}^{-3}$ increase of NO₂ concentrations and weather conditions with single-and multiple-pollutant models.

Environmental factors	aRR ^a Lag0	aRRLag1	aRRLag2
Single model			
Adjusted for O ₃ .8h	1.033(1.027, 1.040) ***	1.016(1.010,1.022) ***	1.016(1.010,1.022) ***
Adjusted for SO ₂	1.035(1.028, 1.042) ***	1.016(1.010,1.023) ***	1.016(1.010,1.023) ***
Adjusted for PM _{2.5}	1.042(1.033, 1.052) ***	1.022(1.014,1.030) ***	1.022(1.014,1.030) ***
Multiple model			
Adjusted for O ₃ .8h + PM _{2.5}	1.042(1.033, 1.052) ***	1.022(1.014,1.031) ***	1.022(1.014,1.031) ***
Adjusted for SO ₂ + PM _{2.5}	1.043(1.033, 1.053) ***	1.014(1.009,1.019) ***	1.014(1.009,1.019) ***
Adjusted for SO ₂ + O ₃ .8h	1.037(1.029, 1.044) ***	1.018(1.011,1.024) ***	1.018(1.011,1.024) ***
Adjusted for SO ₂ + O ₃ .8h + PM _{2.5}	1.043(1.033, 1.053) ***	1.022(1.014,1.031) ***	1.022(1.014,1.031) ***

^a aRR, adjusted relative risk, *** $\rho < 0.001$.

Stratified analyses were then performed. We found that the risk of NO₂ exposure could be higher among older individuals and individuals with medical insurance, with RRs of 1.045 [CI: 1.023, 1.066] and 1.047 [CI: 1.036, 1.058], respectively (Table 4). However, differences between the two subgroups were not significant.

4 DISCUSSION

This study conducted a case-crossover analysis to evaluate the effect of NO₂ concentrations on outpatient visits for psoriasis. This is the first study to investigate the association between short-term exposure to air pollution and psoriasis in rapidly urbanizing areas with high population densities. We found that short-term exposure to ambient NO₂ was positively associated with outpatient visits for psoriasis. NO₂ exposure also contributed to a prolonged effect on outpatient visits, with RRs of 1.042 [CI: 1.038, 1.053], 1.020 [CI: 1.018, 1.033], and 1.021 [CI: 1.012, 1.029]

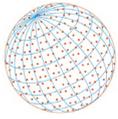


Table 4. Adjusted relative risk for psoriasis associated with per 10 $\mu\text{g m}^{-3}$ increase in NO_2 among subgroup populations in Guangzhou, 2014–2020.

Subgroups	aRR ^a Lag0 (95%CI)	p-value	aRRLag1 (95%CI)	p-value	aRRLag2 (95%CI)	P-value
Age groups						
≥ 60 years	1.045(1.023, 1.066) ***	0.277	1.020(1.006,1.034) ***	0.721	1.020(1.006,1.034) ***	0.721
< 60 years	1.037(1.026, 1.048) ***		1.021(1.012,1.030) ***		1.021(1.012,1.030) ***	
Sex groups						
Male	1.041(1.030, 1.053) ***	0.642	1.024(1.015,1.033) ***	0.220	1.024(1.015,1.033) ***	0.220
Female	1.040(1.022, 1.058) ***		1.015(1.003,1.027) ***		1.015(1.003,1.027) ***	
Medical insurance in Guangzhou						
Yes	1.047(1.036, 1.058) ***	0.115	1.026(1.017,1.035) ***	0.076	1.026(1.017,1.035) ***	0.076
No	1.028(1.007, 1.049) **		1.011(0.998,1.025)		1.011(0.998,1.025)	

^aaRR, adjusted relative risk, ** $p < 0.01$, *** $p < 0.001$.

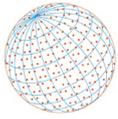
at lag 0, lag 1, and lag 2 days, respectively, with SO_2 , O_3 and $\text{PM}_{2.5}$ adjusted. Furthermore, the risk of NO_2 exposure was higher among older individuals and individuals with medical insurance. To the best of our knowledge, this is the first epidemiological study to demonstrate a link between various air pollutants and outpatient visits for psoriasis in China.

4.1 Strengths of the Study

The major strength of this study is our finding of a significant association between short-term exposure to NO_2 and outpatient visits for psoriasis. This result supports our hypothesis that the effect of NO_2 on psoriasis is acute because a $10\text{-}\mu\text{g m}^{-3}$ increase in NO_2 concentration (lag 0 day) was associated with a 3.1% (95% CI: 2.5–3.7%) increase in the number of outpatient visits for psoriasis. A previous study (Chao *et al.*, 2021) conducted in Xinxiang, China, reported that a $10\text{-}\mu\text{g m}^{-3}$ increase in NO_2 concentrations was associated with a 1.86% increase in the number of outpatient visits for multiple dermatologic diseases; for psoriasis, the increment risk of outpatient visits was 3.09% (95% CI: 1.26–4.92%). The study (Chao *et al.*, 2021) was conducted in an industrial city in North China with a relatively low population density, where the most considerable source of NO_2 was coal combustion (Zong *et al.*, 2018). Our study was conducted in rapidly urbanizing areas with high population densities in China, where NO_2 is mainly derived from vehicular- and household-related emissions (Shao *et al.*, 2009). Nevertheless, the impact of NO_2 exposure on outpatient visits for psoriasis was similar to that in an industrial city.

Our results provide some important findings. First, the study area reported an average daily NO_2 concentration lower than the critical standards set by the Chinese government, which is indicative of a cleaner environment. This suggests that the toxic effects of NO_2 could induce psoriasis, even though air pollution may not be at significantly high level. Furthermore, when we controlled for meteorological factors, our results indicated an independent effect of air pollution exposure. This further indicates that NO_2 exposure could be an environmental factor directly affecting skin conditions (psoriasis) of individuals other than known factors, such as temperature and humidity, although the NO_2 concentrations might not be higher than the critical level.

Further, from the results above, another strength of this study is the summary of the impacts from multiple air pollutant models. It should be noted that NO_2 can affect outpatient visits independently of other pollutants. This result is important because it demonstrates how a specific type of air pollutant could negatively affect skin conditions. When the skin conditions are weakened in multiple dimensions due to NO_2 exposure, it could increase the occurrence or recurrence risk of psoriasis within just few days. To protect individuals suffering from psoriasis, it is necessary to increase the knowledge, attitude, and practices (KAP) of patients to reduce their exposure to adverse environments with poor air quality. This also relates to our findings from the subgroup analysis, where we observed that older individuals aged ≥ 60 years were more vulnerable. Frail and pre-frail conditions as well as chronic diseases in older individuals may have already decreased skin barrier function and gradually deteriorated the epidermal immune response in these individuals, leading to a higher risk from air pollution (Chambers and Vukmanovic-Stejic, 2020); moreover, older individuals generally demonstrate lower knowledge and inappropriate practices to protect



themselves from environmental risks. Therefore, it is important to increase KAP among older individuals to increase their awareness of skin conditions and environmental issues.

Finally, the results for individuals with medical insurance are noteworthy. Increased visits by this group could have been due to an increased availability of health resources and financial support from insurance. This finding implies an economic disparity among individuals with psoriasis. Persons without medical insurance could be socioeconomically deprived and without the financial means required to re-visit clinics for official treatment. Further studies should focus on this subgroup to evaluate whether their health risks are underestimated.

4.2 Limitations

This study had several limitations. As psoriasis was classified based on ICD-10 codes, our analytical dataset did not include information on the severity of psoriasis. However, varying degrees of psoriasis may be induced by air pollution through different mechanisms. Further studies should use cohort data with information on the psoriasis severity to conduct a detailed longitudinal analysis for an evaluation of the impacts of air pollution.

Based on the outpatient records, we were not able to obtain details regarding residential addresses or daily behaviors such as time spent indoors or outdoors. These, however, may influence daily exposures to NO₂. Therefore, further studies should include relevant information to estimate the activity space of each individual. In addition, the patients' family histories could not be included because of imperfections in the hospital information system; thus, patients whose previous generation is free of the disease cannot be identified. However, as we focused on the temporal effects on each individual and applied a case-crossover study with self-controls that minimized problems from demographic information, our results are nonetheless appropriate for the purpose of this study.

In line with this issue, the use of air pollution data from monitoring networks should also be improved. Land use regressions should be applied in the future to estimate spatiotemporal variations in air pollution across a city, so that daily information linking to both residential locations and activity spaces of individuals could be estimated.

5 CONCLUSIONS

Our study indicates that short-term exposure to ambient NO₂ might increase outpatient visits for psoriasis in Guangzhou, China. In particular, NO₂ exposure had a prolonged effect on the number of outpatient visits, especially in older individuals and individuals with medical insurance. These results highlight the importance of enhancing environmental and health policies and measures for mitigating air pollution to minimize the risk of psoriasis. Our results also highlight that a moderate level of air pollution may still increase the risk of psoriasis. Further emission reduction, as well as the KAP program and health surveillance, should be conducted to target vulnerable subpopulations in rapidly developing areas with high population densities.

ADDITIONAL INFORMATION AND DECLARATIONS

Availability of Data and Material

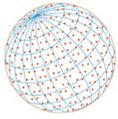
The air pollution data that support the findings of this study are available on request from the corresponding author, Bin Yang. The psoriasis outpatient visits data are not publicly available due to the privacy restriction.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

Conceptualization: Yu Wang, Bin Yang; **Data curation:** Yu Wang, Changchang Li, Zengliang Ruan; **Formal Analysis:** Changchang Li, Zengliang Ruan, Rouxuan Ye; **Investigation:** Yu Wang; **Methodology:** Changchang Li; **Supervision:** Hung Chak Ho; **Writing – original draft:** Yu Wang, Hung Chak Ho; **Writing – review & editing:** Bin Yang.

Supplementary Material

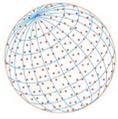
Supplementary material for this article can be found in the online version at <https://doi.org/10.4209/aaqr.220166>

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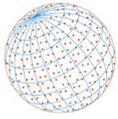
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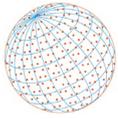
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