Association between short-term exposure to environmental air pollution and atopic dermatitis flare in patients treated with dupilumab

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Background: The magnitude of short/medium-term air pollution exposure on atopic dermatitis (AD) flare has not been fully investigated. The aim of the study was to investigate the association of short/medium-term exposure to airborne pollution on AD flares in patients treated with dupilumab.

Methods: Observational case-crossover study. Patients with moderate-to-severe AD under treatment with dupilumab were included. The exposure of interest was the mean concentrations of coarse and fine particulate matter (PM_{10}, $PM_{2.5}$), nitrogen dioxide, and oxides (NO_2, NO_x). Different intervals were considered at 1 to 60 days before the AD flare and control visit, defined as the visit with the highest *Eczema Area and Severity Index* scores >8 and ≤7, respectively. A conditional logistic regression analysis adjusted for systemic treatments was employed to estimate the incremental odds (%) of flare every 10 $\mu g/m^3$ pollutant concentration.

Results: Data on 169 of 528 patients with AD having 1130 follow-up visits and 5840 air pollutant concentration measurements were retrieved. The mean age was 41.4 ± 20.3 years; 94 (55%) men. The incremental odds curve indicated a significant positive trend of AD flare for all pollutants in all time windows. At 60 days, every 10 $\mu g/m^3$ PM_{10}, $PM_{2.5}$, NO_x, and NO_2 increase concentration was associated with 82%, 67%, 28%, and 113% odds of flare, respectively.

Conclusions: In patients treated with dupilumab**,** acute air pollution exposure is associated with an increased risk for AD flare with a dose-response relationship. (JAAD Int 2023;11:72-7.)

Key words: Air pollution; atopic dermatitis; dupilumab; flare; particulate matter.

INTRODUCTION

The issue of climate change has been raising concern in the recent years, including its harmful impact on human health.[1] Anthropic activities as fossil fuel combustion and industry emissions have increased the atmospheric concentrations of environmental air pollutants.[2] Environmental air pollution comprises a mixture of toxic volatile compounds including coarse (2.5−10 μm diameter) and fine (<2.5 μm diameter) particulate matter (PM) and gaseous products, i.e., carbon monoxide (CO) and oxides of nitrogen (NO_x), such as nitrogen monoxide (NO) and nitrogen dioxide (NO_2).[3] An increasing mole of literature supports that exposure to air pollutants, in particular ambient PMs, is associated with adverse health outcomes. PMs directly

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overcome the cutaneous barrier but also penetrate deep from the respiratory system to the blood stream indirectly reaching different distant targets.[4]

Acne, psoriasis, photoaging, and atopic dermatitis (AD) are inflammatory cutaneous diseases aggravated by exposure to air pollution.[3-5] AD is a chronic inflammatory disease characterized by relapsing-remitting course and exaggerated cutaneous hyperreactivity to environmental triggers. Evidence from animal models, in vitro experiments, case-control, and cohort studies suggests that indoor and outdoor air pollution exposure may worsen the symptoms of AD, but the magnitude of the short/medium-term air pollution exposure on AD disease activity using a case-crossover design has not been fully investigated.[6,7] To our knowledge, most of the existing studies assessed the association between airborne pollution and visit counts because of AD symptoms without validated clinical assessment, and data on patients receiving biologics are missing. The aim of this study was to investigate the association of short/medium-term exposure to environmental air pollution on AD flares in patients receiving treatment with dupilumab.

CAPSULE SUMMARY

How does this article integrate into what is already known?

- The prevalence of atopic dermatitis is on the rise in emerging countries in parallel with urbanization and industrial development.

How do the findings change practice?

- Acute air pollution exposure is associated with an increased risk for atopic dermatitis flare with a dose-response relationship in patients with moderate-to-severe atopic dermatitis treated with dupilumab.

MATERIALS AND METHODS

A case-crossover analysis was designed to investigate the association of short/medium-term exposure to environmental air pollution to AD flares (Fig. 1).[8] In the case-crossover analysis, each patient serves as his own control; the exposure of interest is compared at different time periods in the same patient group, which is followed longitudinally. We retrospectively extracted and analyzed data on patients with moderate-to-severe AD in treatment with dupilumab from the electronic medical records of the Dermatology Unit of the University Hospital of Verona, Italy from between December 2018 and December 2021. Inclusion criteria were: (1) patients with ≥3 consecutive measurements of Eczema Area and Severity Index (EASI) score at 3 months intervals, (2) patients with residency (assessed by *Zoning Improvement Plan* code) within 10 km from the air pollutants collection (3) patients with at least one disease flare, defined as the highest EASI score ≥ 7 between 2 dermatological visits separated by a timeframe of 3 months within the same time frame. Exclusion criteria were treatment with methotrexate, cyclosporine, tralokinumab, upadacitinib, and phototherapy. At baseline, the following data on clinical features were collected: age, sex, disease duration, body mass index, blood total levels of IgE, history of asthma, and rhino-conjunctivitis. Air pollutant data were collected from the local fixed monitoring station, which records daily measurements of pollutant concentration. The official, open-source, bulletin of the *Italian Institute for Environmental Protection and Research* was consulted to retrieve air pollutants daily concentrations ($\mu g/m^3$) of the area and time of interest.[9] In particular, the following air pollutants were available: PM_{10}, $PM_{2.5}$, NO_2, and NO_x. Patients' records and air pollution exposure were associated through *Zoning Improvement Plan* code centroids.

Short/medium-term exposure was investigated at different time intervals (i.e., at 1, 7, 14, 30, 45, and 60 days) before the dermatological visits with the EASI assessment in patients followed longitudinally. Flare was defined as the visit with the highest EASI score >8, and control was defined as the visits with EASI ≤7.[10,11] Each time interval was anchored to an EASI measurement. We defined hazard period as the time interval before flare and control periods as the time interval period before a control. Each patient contributed to a hazard period and multiple non-overlapping control periods.

Statistical analysis

- Mean and area under the curve (i.e. the definite integral of the concentration as a function of time) air pollutants concentrations of the flare and control visits were first tested compared with t-student and Mann−Whitney U tests (for normally and non-normally distributed, respectively) at 30, 45, and 60 days. Then, multivariate conditional logistic regression matched within a patient and adjusted for dupilumab treatment assessing the association between the risk of AD flare and incremental exposure to air pollutants was run at incremental time intervals. The incremental odds (%) of AD flare every 10 $\mu g/m^3$ concentration of pollutants were calculated. To illustrate the

Abbreviations used:

AD: atopic dermatitis
CO: carbon monoxide
EASI: Eczema Area and Severity Index
IQR: interquartile range
NO_x: oxides of nitrogen
NO: nitrogen monoxide
NO_2: nitrogen dioxide
PM: particulate matter
SO_2: sulfur dioxide

temporal dose-response trend for the risk of AD flares, restricted cubic splines were used to generate a smoothed time incremental odds curve.

- Assuming a confidence interval of 95%, with a control-cases ratio of 5 sample size, and a power of 80%, 508 visits were estimated as a satisfactory sample size. All statistical analyses were performed independently using SPSS Version 26 (SPSS, Inc., Chicago, IL, USA) and Stata version 13 (Stata Corp, Texas, USA).

The study was conducted according to the protocol BIOREVE 534CESC, reviewed and approved by the *University of Verona local Ethic Committee*, in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The exemption of informed consent of study participants was granted by the local Ethics Committee.

RESULTS

From a total of 528 potentially eligible patients with moderate-to-severe AD receiving treatment with dupilumab identified in the database, 29 were excluded because of insufficient consecutive EASI score measurements, 243 were excluded because their residence was farther than 10 km from the centroid, and 87 because of lack of disease flare (Supplementary Fig 1, available via Mendeley at https://doi.org/10.17632/42kwtm4b6w.1). A total of 169 of 528 patients with moderate-to-severe AD treated with dupilumab were included in the case-crossover analysis (Table I). Data on 1130 follow-up visits and >5800 measurements of air pollutant concentrations were retrieved. The patients were visited every 3 months for a median follow-up of 5 (interquartile range [IQR], 4–7) visits. During this follow-up period, patients were exposed to a mean concentration of PM_{10}, 30.64 $\mu g/m^3$; $PM_{2.5}$, 20.45 $\mu g/m^3$; NO_x, 41.16 $\mu g/m^3$; NO_2, 22.94 $\mu g/m^3$. According to the EU's ambient air quality standards, the set limits are PM_{10}, 40 $\mu g/m^3$; $PM_{2.5}$, 25 $\mu g/m^3$; and NO_2, 40 $\mu g/m^3$.[12] The median EASI at flare was significantly higher than the EASI at the control, 18 (IQR, 6.25–26) vs 1 (IQR, 0–2), $P < 0.001$, respectively. Mean and area under the curve air pollutant concentrations were higher in 60 days before the flare compared with the control visits. We conducted further sensitivity analysis restricting the lag of exposures to 30 and 45 days that confirmed similar results (Supplementary Tables II–IV, available via Mendeley at https://doi.org/10.17632/42kwtm4b6w.1). In the conditional logistic regression, a total of 117 case periods were compared with 592 control periods. Notably, PM_{10}, $PM_{2.5}$, NO_x, and NO_2 exposure in all the considered time intervals, were associated with higher odds of AD flare (Supplementary Table I, available via Mendeley at https://doi.org/10.17632/42kwtm4b6w.1). As an example, at 1 day, every 10 $\mu g/m^3$ PM_{10}, $PM_{2.5}$, NO_x, and NO_2 increase concentration was associated with 9%, 23%, 9%, and 41% incremental odds of AD flare, respectively. At 14 days, with 31%, 31%, 19%, and 63%, respectively. At 60 days, with 82%, 67%, 28%, and 113%, respectively. A clear dose-response relationship was exhibited in the smoothed incremental odds curves, indicating significant positive trend of AD flare for all pollutants in all time windows (Fig. 2). Duration to significant improvement from the flare varied case by case because it depended on the magnitude of the flare, treatments combined to dupilumab, either topical or systemic, patients' characteristics and ranged from 1 to 4 weeks.

DISCUSSION

We found that acute air pollution exposure is associated with an increased risk for AD flare in patients living in an industrialized area of the Po valley (Verona), with a dose-response relationship, independently from treatment with dupilumab. Such findings have relevant clinical implications, suggesting that environmental air pollutants can be considered as triggers of AD in the same way as respiratory allergens, contact irritants, and/or bacterial pathogens.[13]

The patients included in our study were all residents in Verona, which is an industrialized city in Northeast Italy with a population of approximately 260,000 inhabitants. Interestingly, the average levels of environmental pollutants were found to be below the limits set by the EU that define air quality standards.[10] Our results are consistent with the results of previous studies.[14-19] Most of them assessed the association between airborne pollution and the number of visits for dermatologic consultation because of AD symptoms. For example, Wang et al. demonstrated that short-term exposure to air

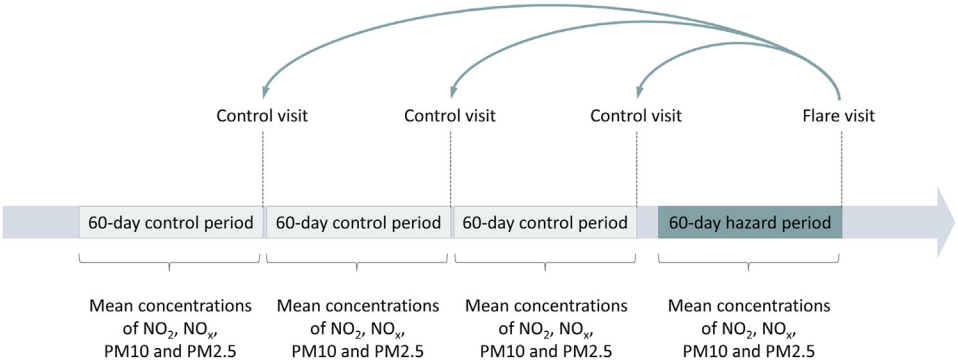

Fig. 1. Case-crossover study design. In the case-crossover analysis each patient serves as its own control; the exposure of interest is compared in multiple different periods in the same group of patients followed longitudinally.

Table I. Descriptive characteristics of the patients with atopic dermatitis

Characteristic	
No. of patients	169
Sex, *n* (% males)	94 (55)
Age, mean (± SD), y	41.4 ± 20.3
Body mass index (Kg/m^2), mean (± SD)	24.8 ± 6.1
Disease duration (± SD), y	28.6 ± 20.3
Asthma, *n* (%)	64 (38)
Rhino-conjunctivitis, *n* (%)	67 (39)
IgE (IU/mL), mean ± standard deviation)	1,394 ± 2,887

pollution (including ambient $PM_{2.5}$, PM_{10}, sulfur dioxide [SO_2], NO_2 and O_3) was associated with a high risk of daily hospital visits for AD, and children were more sensitive to this effect.[14] Fadadu et al[15] in a cross-sectional study involving more than 4000 patients with AD found that short-term exposure to air pollution due to the wildfire was associated with increased health care use for patients with AD. A Korean time-series study Baek et al. found that high levels of PMs, O_3 and SO_2 were associated with increased risk of medical care visits for AD on the same days.[16] Few small size studies have investigated the association of airborne pollutants and AD symptoms, but never on biologics.[17] For example, a Korean study of 21 pre-school children living in an industrial urban area suggested that short-term exposure to PM can exacerbate AD symptoms and $PM_{2.5}$ had a stronger effect than PM_{10}.[18]

Moreover, recent evidence suggests that airborne pollutants are not only associated to high risk of AD flare but also to the onset of disease. In fact, the prevalence of AD is on the rise in parallel with urbanization and industrial development, particularly in the emerging countries of Southeast Asia, Africa, and Latin America.[19] A recent longitudinal cohort study found that long-term exposure to air pollutants, including SO_2, NO_2, CO, $PM_{2.5}$, and PM_{10} is independently associated with increased risk of developing AD.[20]

The harmful impact of airborne pollutants on AD might be derived from different patho-mechanisms including skin barrier dysfunction, oxidative damage, immune stimulation, and dysbiosis.[4] In pig models, PM has been demonstrated to disrupt the stratum corneum integrity by twofold, downregulating the expression of cytokeratin, filaggrin, and E-cadherin and increasing the expression of matrix metalloproteinases.[21] Pollutants can favor skin inflammation and pruritus by inducing expression of artemin and epidermal hyper-innervation through the activation of the transcription factor aryl hydrocarbon receptor.[22] Cigarette smoking, which is a complex combination of reactive oxygen species, CO, reactive nitrogen species, and aldehydes closely resembling outdoor air pollutants has been associated with increased trans epidermal water loss, a marker of skin barrier dysfunction.[23] Airborne pollutant exposure increases oxidative damage occurrence through increased reactive oxygen species production and depletion of skin antioxidant buffer resources.[6,24] Nuclear factor kappa-light-chain-enhancer of activated B cells is a redox sensitive transcription factor that once activated, translocates to the nucleus where it can trigger the gene expression of different inflammatory mediators, such as TNF-α, IL-1α, IL-1β, IL-6, IL-8, and cyclooxygenase-1,2. Such cytokines in turn stimulate local inflammation, resulting in erythema, edema, and itch. Barrier dysfunction and irritation prompt scratching, further aggravates the skin barrier. The existing deficits in skin barrier function results in increased permeability to pollutants and an

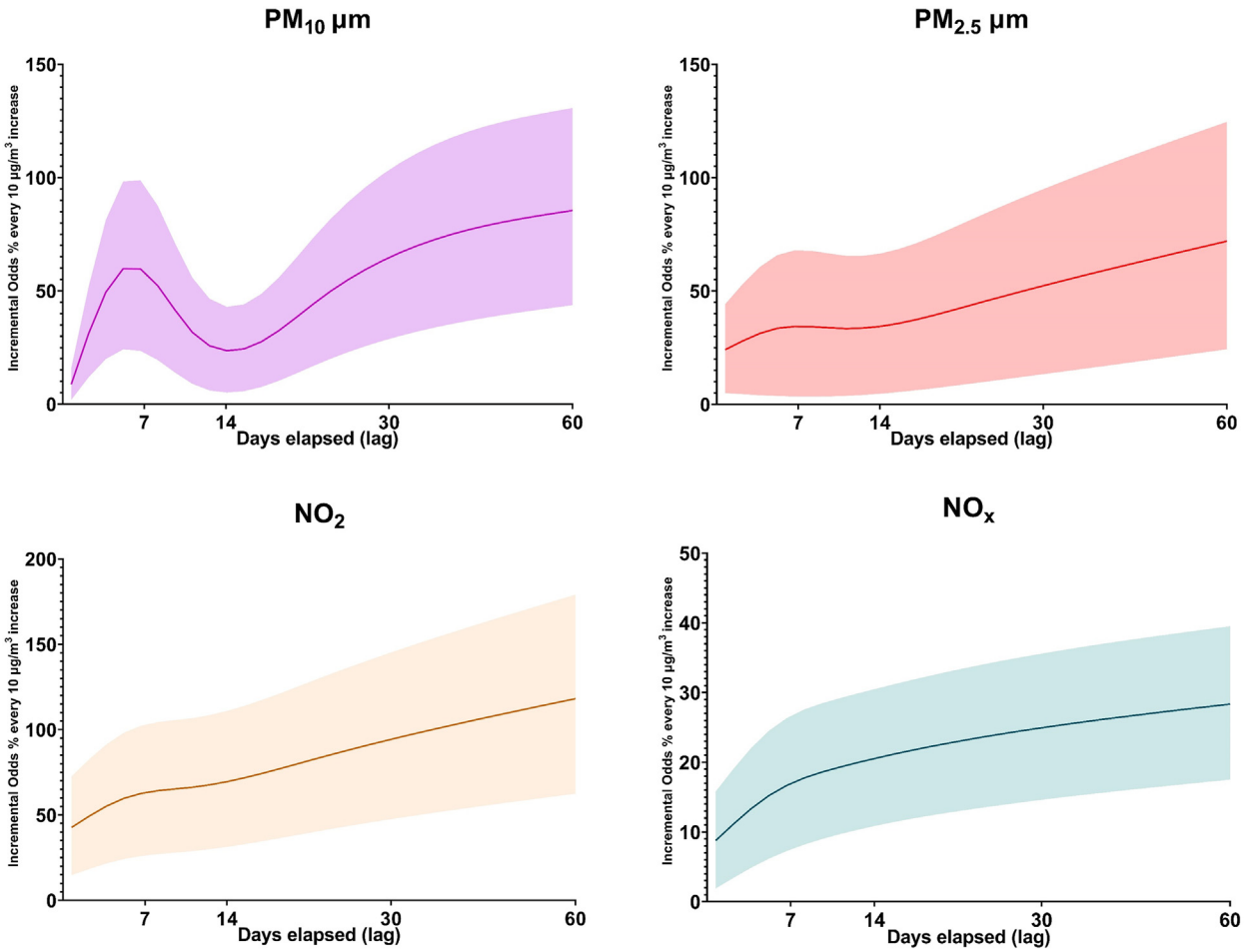

Fig. 2. Dose-response association between exposure to air pollutants and risk of atopic dermatitis flare showing incremental odds (%) of AD flare every 10 $\mu g/m^3$ concentration of pollutants. The curve was fitted using the conditional logistic regression model and smoothed with restricted cubic splines with knots at 1, 7, 14, 30, and 60 days.

exaggerated inflammatory response.[4] Finally, air pollutants, including PM, can induce changes in the normal skin microbiome decreasing resident flora and increasing *Staphylococcus aureus* colonization.[25]

This study has strength and limitations. We included a cohort of patients with moderate-to-severe AD in treatment with dupilumab observed longitudinally with regular clinical evaluations for 2 years. Moreover, we had access to a broad dataset of daily measurements of different toxic air compounds. The case-crossover is a proper study design to examine the association between transient exposure to potential risk factors and the risk of acute disease and/or flare of chronic diseases. We used such a design with a conditional logistic regression analysis where each case serves as their own controls, eliminating confounding by stable individual characteristics. This specific case-crossover design was able to document a clear dose response between air pollution and AD severity, according to EASI. A limitation of the study is that we did not consider the potential influence of the application of topical treatments (i.e., corticosteroids and emollients). Nonetheless, we assumed that our patients were well trained to apply topicals as needed and such possibility was randomly distributed in the whole period of interest. We also assumed that the matching hazard period with multiple control periods randomly distributed over the year adjusted for the confounding of seasonality. Socioeconomic status and smoking habits data, which may hide crucial information such as effect modification, were not collected. Finally, we cannot assume that air pollution can be a trigger factor for AD even in patients with mild disease because we included in the study only patients with moderate-to-severe disease.

Preventive strategies to face the effects of airborne on (skin) health are crucial. These include patients' behavior, physician strategies, and health care policies. The avoidance of pollutant exposure, regular cleansing to remove pollutants, and protection of skin barrier may prove helpful in improving skin barrier and irritation.[4]

In conclusion, air pollution could be considered as an environmental trigger factor that explains unexpected AD flares that are not necessarily due to a loss of response to targeted drug treatment. Further studies are needed to confirm our results.

None.

Conflicts of interest

None disclosed.

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