Early-Life, Long-Term Exposure to Ambient Particulate Matter in Infants with Atopic Dermatitis Decreases Remission and Increases Sensitization

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Abstract

Background: Studies that examine a link between long-term exposure to ambient particulate matter (PM) and atopic dermatitis (AD) in children are lacking. This longitudinal study aimed to investigate the effect of long-term exposure to PM on AD in infants. **Methods:** A total of 150 infants diagnosed with AD before age 2 were enrolled and followed until age 3 in Seoul, Korea. Long-term exposures to ambient PM with an aerodynamic diameter [?]10 μm (PM_{10}) from birth to age 3 were assessed at an individual level. Effects of long-term exposure to PM_{10} on AD persistence and sensitization to aeroallergens were evaluated using Cox proportional hazard regression models after adjusting for potential confounders. **Results:** Out of 150 infants, 54 (36.0%) showed remission of AD at age 3. The risk of AD persistence at age 3 significantly increased with an increase in long-term exposure to PM_{10} [Hazard Ratio (HR) = 1.07, 95% Confidence Interval (CI): 1.01-1.12, $p = .017$ per 1 $\mu g/m^3$]. Moderate-to-severe AD at enrollment was more likely to persist at age 3 with increased exposure to PM_{10} ($p < .05$), whereas the persistence of mild AD was not influenced by PM_{10} exposure. Long-term exposure to PM_{10} increased the risk of sensitization to pollen (HR = 1.14, 95% CI: 1.02-1.27, $p = .021$). However, it did not affect sensitization to house dust mites or pet allergens. **Conclusions:** An early-life long-term exposure to ambient PM_{10} in infants with AD decreases remission and increases sensitization to pollen at age 3.

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The authors have no conflicts to disclose.

Ethical APPROVAL

We obtained ethical approval from the Institutional Review Board at Samsung Medical Center (IRB No: 2014-07-064).

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Methods: A total of 150 infants diagnosed with AD before age 2 were enrolled and followed until age 3 in Seoul, Korea. Long-term exposures to ambient PM with an aerodynamic diameter [?]10 μm (PM_{10}) from birth to age 3 were assessed at an individual level. Effects of long-term exposure to PM_{10}on AD persistence and sensitization to aeroallergens were evaluated using Cox proportional hazard regression models after adjusting for potential confounders.

Results: Out of 150 infants, 54 (36.0%) showed remission of AD at age 3. The risk of AD persistence at age 3 significantly increased with an increase in long-term exposure to PM_{10} [Hazard Ratio (HR) = 1.07, 95% Confidence Interval (CI): 1.01-1.12, $p = .017$ per 1 $\mu g/m^3$]. Moderate-to-severe AD at enrollment was more likely to persist at age 3 with increased exposure to PM_{10} ($p < .05$), whereas the persistence of mild AD was not influenced by PM_{10}exposure. Long-term exposure to PM_{10} increased the risk of sensitization to pollen (HR = 1.14, 95% CI: 1.02-1.27, $p = .021$). However, it did not affect sensitization to house dust mites or pet allergens.

Conclusions: An early-life long-term exposure to ambient PM_{10} in infants with AD decreases remission and increases sensitization to pollen at age 3.

Keywords

Atopic dermatitis; particulate matter; young children; remission; long-term exposure; pollen

Key Message

This study provides an evidence that an early-life long-term exposure to ambient particulate matters in infants with atopic dermatitis decreases remission and increases sensitization to pollen.

Abbreviation

AD: atopic dermatitis

AQMS: air quality monitoring system

BMI: body mass index

CI: confidence intervals

CMAQ: Community Multiscale Air Quality

HDM: house dust mite

HR: hazard ratio

$PM_{2.5}$: particulate matter with a diameter less than 2.5 μm

PM_{10}: particulate matter with a diameter less than 10 μm

RH: relative humidity

SCORAD: SCORing Atopic Dermatitis (SCORAD)

SD: standard deviation

TCS: topical corticosteroid

1 | Introduction

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disorder mostly found in childhood.[1] It has become a growing health issue as its prevalence is increased worldwide including Korea.[2,3] Besides its grave influence on quality of life, AD also affects the entire family socially and economically.[4] Moreover, as an initial manifestation of atopic march, more than 30% of AD patients has been reported to develop allergic rhinitis or asthma in their later lives, with the risk being higher in early-onset, severe, and persistent AD.[5,6] AD is also associated with sensitization to inhalant allergens.[7,8] Identifying risk factors for severe or persistent phenotype, sensitization, and allergic comorbidities might help establish a better management plan for AD patients.

Among air pollutants, exposure to particulate matter (PM) is associated with adverse health outcomes, especially allergic diseases.[9-11] Several studies have already reported that AD symptoms are aggravated by short-term exposure to PM. A longitudinal study involving children aged 1 to 5 years with AD has revealed a significant association between a 10 $\mu g/m^3$increase in ambient $PM_{2.5}$ exposure and AD symptoms (adjusted OR [aOR] = 1.399, 95% confidence interval [CI]: 1.216-1.610).[12] In another panel study involving 125 AD children aged 0-6 years, the overall risk of AD symptoms significantly increased with higher levels of ambient $PM_{2.5}$ and PM_{10}exposure.[13] In that study, the risk of AD symptoms resulting from exposure to ambient PM was significantly higher during dry, moderate weather as determined by spatial synoptic classification. That study also found a lagged effect of $PM_{2.5}$ up to 4 days on days with dry, moderate weather. To observe short-term effect of exposure to indoor $PM_{2.5}$ on AD symptoms, a longitudinal study was conducted on 64 Korean children with moderate-to-severe AD.[14] In that study, a 10 $\mu g/m^3$increase in indoor $PM_{2.5}$ concentration led to a 16.5% increase in AD symptom scores in spring (95% CI: 6.5-27.5) and a 12.6% increase in winter (95% CI: 4.3-21.5).

Compared to the short-term effect of PM on AD symptoms, studies on the impact of long-term exposure to PM on AD are lacking. A previous study has evaluated the relationship between air pollution and the incidence of AD using the National Health Insurance Service-National Sample Cohort database, including 1,030,324 person-years and 3,203 incident cases. It found that long-term exposure to air pollutants significantly increased the development of AD.[15] However, there is very limited evidence of whether long-term exposure to ambient PM affects AD remission or allergic march, particularly in young children.

Thus, this longitudinal study aimed to investigate whether long-term exposure to PM could affect remission of AD at age 3 after the development of AD during infancy. Effect of long-term exposure to PM on aeroallergen sensitization in infants with AD was also evaluated.

2 | Materials and Methods

2.1 | Study population and clinical data

We enrolled 150 infants and young children (88 boys, 62 girls) aged under 2 years with AD visiting our hospital, Samsung Medical Center, who were living in the Seoul Metropolitan Area of Korea. Locations of their residences are shown in Figure 1. AD was diagnosed according to the Hanifin and Rajka criteria.[16] They were followed up until they were 3 or 4 years old.

At enrollment, demographic data were obtained, including date of birth, age of AD onset, and body mass index (BMI). AD severity was assessed using the SCORing Atopic Dermatitis (SCORAD) index, developed by the European Task Force Group on AD in 1993.[17] Subjects were classified into three groups, 'mild (< 25)', 'moderate (25-49)', and 'severe ([?] 50)', according to SCORAD at enrollment. Levels of total IgE and specific IgE against egg white, cow's milk, soybean, wheat and peanut in the peripheral blood were measured using ImmunoCAP (ThermoFisher Scientific Inc., Waltham, MA, USA) and considered positive when levels were 0.69 kU/L or above.

To evaluate the status of AD, AD children were brought to the hospital at least once a year until the age of 3 years. AD remission was defined as absence of AD symptoms in the past 6 months without needing medical treatments including topical corticosteroid (TCS).

When they visited the hospital at age 3, skin prick tests were performed to detect specific IgE against common inhalant allergens including*Dermatophagoides pteronyssinus* , *D. farinae* , tree pollen mixture, grass pollen mixture, weed pollen mixture, and cat and dog dander (Lofarma, Milan, Italy). Histamine was used as a positive control, and normal saline was used as a negative control. A positive response to allergens in the skin prick test was determined when wheal size was [?] 3 mm with adequate reactions to controls.

Written informed consent was obtained from the parent or guardian of each participating child. Study protocols were reviewed and approved by the Institutional Review Board (IRB) of Samsung Medical Center (IRB No. 2014-07-064).

2.2 | Assessment of PM exposure and other environments

To assess the long-term exposure to ambient PM with an aerodynamic diameter [?] 10μm (PM_{10}) from birthday through the age of 3, we utilized a fusion model combining monitoring data from the air quality monitoring sites (AQMSs) and Community Multiscale Air Quality (CMAQ) modeling data. This fusion technique can improve air pollution exposure estimation in a large and complex urban area like the Seoul Metropolitan Area where spatial heterogeneity of air pollution is significant and monitoring data are limited in space.

The CMAQ model (version 5.0.2)[18,19] was run for one year in 2018 to capture local gradient of PM_{10}concentrations in the Seoul Metropolitan Area in a nested mode at 27, 9, and 3 km horizontal grid dimensions; The fine-scale innermost domain (D3 in Figure 1) is the target area of the study that covers the Seoul Metropolitan Area. Detailed CMAQ-ready meteorological and emission inputs, initial and boundary conditions, and physical and chemical options used in our CMAQ modeling were described previously by Oh et al.[20] Hourly gridded concentrations predicted by the CMAQ model were averaged on a monthly basis to blend ambient monitored data. Monitored concentrations of PM_{10} and other air pollutants were obtained from 141 AQMS (Figure 1b) in the study area. Neighbor AQMS surrounding each patient's residential locations (updated monthly for three years) within a 5 km radius were first identified. An inverse-distance weighted (IDW) average of observed values was obtained. Fused concentrations were then calculated by multiplying IDW average concentrations with the ratio of CMAQ modeling data for the destination grid-cell containing the patient's residence to those containing the neighbor monitor. These fused concentrations were

calculated on a monthly basis and averaged throughout the exposure assessment period of 3 years. Monthly exposure to PM was assessed by checking subjects' addresses whenever they moved during the study period from January 2007 to June 2020.

2.3 | Statistical analysis

To investigate whether exposure to ambient PM affects the remission of AD in young children, we evaluated the associations of long-term exposure (from birth to age 3) to ambient PM_{10} with the persistence of AD and the incidences of allergen sensitizations at age 3 using Cox proportional hazard regression models. Ambient nitric dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3), carbon monoxide (CO), relative humidity (RH), and temperature, sex, BMI, SCORAD at enrollment, and the presence of inhalant allergen sensitization were included in the Cox models as confounding factors.

All procedures were conducted using R version 4.0.2 (Comprehensive R Archive Network: http://cran.r-project.org). The "survival" package (version 3.1-12) was used for Cox proportional hazard regression model fitting. All tests were two-sided, and an alpha level of less than 0.05 was considered significant.

3 | Results

Table 1 shows characteristics of the 150 subjects at enrollment and the remission rate of AD at age 3. According to the SCORAD at enrollment, AD severity was 'mild' in 72 (48.0%), 'moderate' in 61 (41.0%), and 'severe' in 17 (11.0%) children. The remission rate of AD at age 3 was 36.0%. There was no significant difference in the remission rate between boys and girls ($p = .529$). Sensitization rates to HDM and pollen at age 3 were 52.7% and 35.3%, respectively.

The monthly average level of PM_{10} exposed to each subject was 47.8 ± 3.9 $\mu g/m^3$ for the whole study period (Table 2). Average values of ambient NO_2, SO_2, O_3, CO, temperature, and RH for the residential places of the young children were 32.1 ± 3.8 ppb, 5.4 ± 1.2 ppb, 22.8 ± 1.6 ppb, 564.5 ± 63.1 ppb, 12.9 ± 0.5°C, and 63.9 ± 5.1%, respectively.

Table 3 shows the long-term effects of PM_{10} exposure on AD persistence and inhalant allergen sensitization in young children. The overall hazard ratio (HR) of AD persistence at age 3 was 1.06 [95% confidence interval (CI): 0.99-1.14] due to long-term exposure to PM_{10} by 1 $\mu g/m^3$. There was no significant association between PM_{10} exposure and the incidence of sensitization to HDM or pet allergens at age 3. However, a 1 $\mu g/m^3$ increase in PM_{10} exposure significantly increased pollen sensitization at age 3 (HR = 1.19; 95% CI: 1.06 - 1.33).

Effects of PM_{10} on AD persistence and inhalant allergen sensitizations stratified by severity were then evaluated, because the disease course over time was mostly affected by its severity (Table 4). In children with moderate or severe AD, there were significantly positive associations between AD persistence and long-term exposure to PM_{10}. Furthermore, the higher the SCORAD at enrollment, the greater the PM effect; HR of AD persistence was 1.23 (95% CI: 1.07-1.40) for the moderate group and 1.67 (95% CI: 1.16-2.41) for the severe group by 1 $\mu g/m^3$ increase of PM_{10} exposure. However, AD persistence in the mild group was not affected by long-term exposure to PM_{10}.

When effects of ambient PM_{10} exposure on incidence of HDM sensitization were stratified by severity, there were no statistically significant effects in any subgroups, although the P -value was close to 0.05 in the severe group (HR = 1.45; 95% CI: 0.98-2.13, $p = .058$). PM exposure was also not associated with sensitization to pet allergens either, regardless of AD severity. Of interest, the effect of ambient PM_{10} exposure on pollen sensitization was significant in the moderate group (HR = 1.33; 95% CI: 1.08-1.61). In the severe group, the association of ambient PM_{10} exposure with pollen sensitization could not be evaluated statistically because the number of patients was too small.

4 | Discussion

Skin damage attributed to PM primarily results from oxidative stress and subsequent inflammation.[21] Upon exposure to PM with polycyclic aromatic hydrocarbons (PAHs), human keratinocytes increase production

of reactive oxygen species (ROS).[22]$PM_{2.5}$ can also stimulated IL-6 production in human keratinocytes via ROS production and oxidative stress.[23] In addition, keratinocytes exposed to PM can upregulate cytokine expression, indirectly leading to diminished expression of skin barrier proteins and skin barrier dysfunction. $PM_{2.5}$ exposure can induce the expression of tumor necrosis factor (TNF)- α in human keratinocytes, which subsequently suppresses the expression of filaggrin (FLG) and loricrin (LOR) through an aryl hydrocarbon receptor (AhR)-dependent pathway.[24] PAHs as components of PM are known to penetrate the stratum corneum effectively due to their lipophilic properties, initiating skin inflammation through binding to the AhR, a ligand-dependent transcription factor.[25] PM can also triggers the release of alarmins such as thymic stromal lymphopoietin (TSLP) from keratinocytes, which can then promotes Th2-type immune response and reduce FLG expression.[26] These findings indicate that PM can alter the molecular structure and function of the epidermal barrier, thereby exacerbating AD.

The objective of this investigation was to elucidate the impact of chronic exposure to PM on the progression of AD in infants. A methodological challenge was how to accurately quantify individual patient exposure to ambient PM. To address this, we utilized an advanced exposure assessment approach, integrating data from AQMS with the CMAQ modeling outputs and updating the relocation of patients' residences for 3 years. This fusion technique of exposure assessment is more advantageous than AQMS only in urban environments with spatial variability and limited monitoring resources, making our results more reliable.

In this study, a significant association between AD persistence and prolonged exposure to PM in subjects with moderate or severe AD was observed. Conversely, this association was not evident in the mild AD group. This disparity might be attributed to increased susceptibility of the skin with moderate or severe AD to PM penetration and subsequent inflammatory response, as compared to the skin with mild AD.

Pollen sensitization is associated with PM exposure,[27]and is increased in patients with AD.[28] Exposure to pollen, in turn, leads to an exacerbation of AD symptoms.[29] Indeed, bioaerosols from pollen adhere to PM and facilitate penetration into the human body, potentially exacerbating allergic responses.[30] Consequently, the identification and mitigation of risk factors contributing to pollen sensitization in infants with AD are important for favorable disease prognosis. This study demonstrated the effect of long-term exposure to PM on pollen sensitization among infants with moderate or severe AD. Our finding supports the implementation of proactive strategies aimed at reducing PM exposure in infants with AD to modify the disease course.

In contrast to pollen exposed outdoors, the present study demonstrated that sensitization to HDM, an indoor allergen, did not have an association with PM exposure. This result is not consistent with a previous report showing that epicutaneous sensitization to various allergens including HDM could occur.[8] Our observation might be attributed to the estimation of long-term PM exposure based on ambient PM concentrations. However, upon examining the relationship between PM exposure and HDM sensitization in patients with severe AD, the P value was close to 0.05. This suggests that an increase in the sample size of moderate or severe AD patients might yield statistically significant results.

One of the limitations of this study was that chronic exposure to PM was estimated from birth to age of 3 years rather than commencing from AD onset to age 3. The reason was that the exact time of AD onset could not be identified. Rather, pathophysiological changes of AD might have begun immediately after birth. Another limitation was that we did not include indoor environments in exposure assessments, including indoor PM, temperature, relative humidity, volatile organic compounds, and so on. However, it is impossible to monitor indoor environmental factors at each patient's residence for a long period covering over 3 years. Since indoor PM originates partly from the outside, assessing indoor PM exposure was not completely excluded. Selection bias was also possible in the present study.

In conclusion, chronic exposure to ambient PM_{10} in infants with AD might affect the disease course by decreasing remission and increasing sensitization to pollen at age 3. In infants with AD, efforts are needed to reduce short-term and long-term exposure to PM in early life to prevent acute exacerbation and improve disease prognosis.

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Table 1 Characteristics of the study population.

Characteristics	Total
No. of subjects, *n* (%)	150 (100.0)
BMI (kg/m^2) [a]	15.7 ± 1.2
SCORAD at enrollment [b]	27.8 ± 16.4
Family history of allergic diseases, *n* (%)	88 (58.7)
Severity at enrollment, *n* (%)[c]	Severity at enrollment, *n* (%)[c]
Mild	72 (48.0)
Moderate	61 (41.0)
Severe	17 (11.0)
Total IgE at enrollment (U/L)	332.5 ± 610.0
Atopic dermatitis status at age 3, *n* (%)	Atopic dermatitis status at age 3, *n* (%)
Persistence	96 (64.0)
Remission	54 (36.0)
Sensitization at age 3, *n* (%)	Sensitization at age 3, *n* (%)
Food allergens[d]	77 (51.3)
Inhalant allergens	Inhalant allergens

Characteristics	Total
House dust mite[e]	79 (52.7)
Pollen[f]	53 (35.3)
Pet[g]	35 (23.3)

[a]Data are expressed as mean ± standard deviation.

[b]SCORing Atopic Dermatitis (SCORAD) index at enrollment.

[c]Severity is categorized according to SCORAD at enrollment; 'Mild' indicates infants with SCORAD <25, 'Moderate' with 25[?] SCORAD <50), and 'Severe' with 50[?] SCORAD.

[d]Sensitized to at least one of 5 common food allergens, including egg white, cow's milk, soybean, wheat, and peanut.

[e]Sensitized to house dust mite (*Dermatophagoides pteronyssinus* or *D. farinae*).

[f]Sensitized to pollen (at least one of pollen mixture allergens, including tree, grass, and weed)

[g]Sensitized to pet (cat or dog allergens).

Table 2 Monthly PM_{10} levels exposed to the infants with atopic dermatitis during the study period from January 2007 to June 2020.

Group	Monthly level of PM_{10} (μg/m^3)	p-Value[a]
All	47.8 ± 3.9	
Mild[a]	47.1 ± 3.3	-
Moderate	48.3 ± 4.1	.057
Severe	48.5 ± 5.0	.264

Data are expressed as mean ± standard deviation.

The severity of atopic dermatitis (AD) was assessed using SCORing of AD (SCORAD) and classified into 'Mild (<25)', 'Moderate (25-49)', and 'Severe [?]50'.

PM_{10}, particulate matter with an aerodiameter <10 μm.

[a]t -test for means of PM_{10}concentration compared to that of the mild group.

Table 3 Effects of long-term exposure to ambient PM_{10} on atopic dermatitis persistence and allergen sensitization at age 3.

Outcome	HR[d] (95% CI)	p-Value
AD persistence	1.06 (0.99 - 1.14)	0.102
Sensitization to inhalant allergens	Sensitization to inhalant allergens	Sensitization to inhalant allergens
HDM[a] (79/150)	1.05 (0.97 - 1.14)	0.255
Pollen[b] (53/150)	**1.19 (1.06 - 1.33)**	**0.003**
Pet[c] (35/150)	1.00 (0.88 - 1.13)	0.970

Abbreviations: AD, atopic dermatitis; HDM, house dust mite; PM_{10}, particulate matter with an aerodiameter <10 μm.

[a]Sensitized to *Dermatophagoides pteronyssinus*or *D. farina.*

[b]Sensitized to at least one of pollen mixture allergens, including tree, grass, and weed.

[c]Sensitized to pet (cat or dog allergens).

[d]HR: hazard ratio due to PM_{10} exposure by 1 μg/m^3.

Table 4 Effects of long-term exposure to ambient PM_{10} on atopic dermatitis persistence and allergen sensitizations at age 3 by severity.

Outcome	Severity at enrollment[d]	Positive at age 3 N (%)	HR[e] (95% CI)	*p*-Value
AD persistence	AD persistence	AD persistence	AD persistence	AD persistence
	Mild	39/72 (54.2)	0.96 (0.84 - 1.09)	0.495
	Moderate	41/61 (67.1)	**1.23 (1.07 - 1.40)**	**0.003**
	Severe	16/17 (94.1)	**1.67 (1.16 - 2.41)**	**0.006**
Allergen sensitization	Allergen sensitization	Allergen sensitization	Allergen sensitization	Allergen sensitization
HDM[a]	Mild	37/72 (51.4)	0.99 (0.86 - 1.14)	0.914
	Moderate	29/61 (47.5)	1.13 (0.97 - 1.30)	0.107
	Severe	13/17 (76.5)	1.45 (0.98 - 2.13)	0.058
Pollen[b]	Mild	23/72 (31.9)	1.07 (0.88 - 1.31)	0.511
	Moderate	23/61 (37.7)	**1.33 (1.10 - 1.61)**	**0.003**
	Severe	7/17 (41.2)	NA	NA
Pet[c]	Mild	17/72 (23.6)	0.94 (0.76 - 1.16)	0.561
	Moderate	13/61 (21.3)	1.06 (0.82 - 1.37)	0.660
	Severe	5/17 (29.4)	NA	NA

Abbreviations: AD, atopic dermatitis; HDM, house dust mite; PM_{10}, particulate matter with an aerodiameter < 10 μm.

[a]Sensitized to *Dermatophagoides pteronyssinus*or *D. farinae* .

[b]Sensitized to at least one of pollen mixture allergens, including tree, grass, and weed

[c]Sensitized to pet (cat or dog allergens).

[d]The severity of atopic dermatitis (AD) was assessed using SCORing of AD (SCORAD) and classified into 'Mild (<25)', 'Moderate (25-49), and 'Severe [?]50'.

[e]HR: hazard ratio due to PM_{10} exposure by 1 μg/m^3.

FIGURE LEGENDS

Figure. 1. (a) Locations of the Seoul metropolitan Area (green area) and the 9-km (D2) and 3-km (D3) domains for CMAQ modeling. (b) Locations of AD patients' residences (circles) and AQMS (blue triangles) in the study area. The color tiles indicate one month-averaged PM_{10} concentrations predicted by the CMAQ model in May 2018. CMAQ, Community Multiscale Air Quality; AQMS, air quality monitoring system; PM10, particulate matter with a diameter <10 μm.