Article

Harmful Effects of Ambient Nitrogen Dioxide on Atopic Dermatitis: Comparison of Exposure Assessment Based on Monitored Concentrations and Modeled Estimates

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Abstract: Precise exposure assessment of air pollutants is crucial in epidemiologic studies to ensure valid estimates of health effects. We conducted a longitudinal study to evaluate the role of air quality monitoring (AQM) measurements and high-resolution modeling outcomes focusing on nitrogen dioxide (NO₂) exposure and atopic dermatitis (AD). A total of 128 young children with AD in Seoul Metropolitan Area, Korea, were recruited as a panel. We estimated the participants' exposure to NO₂ for four months, from 1 April through 31 July 2014 based on (1) monitored levels from 60 AQM stations located at varying distances from residential areas (AQM station-based NO₂, AQM-NO₂) and (2) estimates from a community multi-scale air quality (CMAQ) modeling system with a high-resolution (1 × 1 km) (CMAQ-NO₂). We then compared the effect of AQM-NO₂ on AD symptoms with that of CMAQ-NO₂. The average distance between the participants' residences and the nearest AQM station was 2.03 ± 1.06 km, ranging from 0.28 km to 5.73 km. Based on AQM-NO₂, the AD symptoms increased by 10.28% (95% confidence interval (CI): 3.24, 17.79) with an increase of 10 ppb of NO₂. The effect estimates of CMAQ-NO₂ were similar to those of AQM-NO₂ when assessed in patients living within 3 km from the nearest AQM station. Even within 1 km, the CI estimate obtained from the CMAQ was much narrower than from AQM (44.18–49.54 vs. 7.02–64.75). However, the association of AQM-NO₂ with AD symptoms of patients living beyond 3 km was not positive, whereas that of CMAQ-NO₂ maintained positive. In conclusion, exposure to ambient NO₂ is significantly associated with aggravation of AD symptoms in young children. In addition, our study suggests that exposure assessment of NO₂ using measurement data obtained from monitoring stations far from residential locations can lead to misclassification bias.

Keywords: atopic dermatitis; nitrogen dioxide; air pollution; air pollutants; risk assessment; environmental exposure; child

1. Introduction

Exposure assessment is an important component of epidemiologic studies investigating the impact of air pollution on human health. Many investigators have conducted measurements at air quality

monitoring (AQM) stations to characterize exposure to ambient air pollutants at a population level [1]. However, such monitoring stations offer limited spatial resolution and may only be useful when estimating exposure close to the AQM stations [2]. The characteristics of air pollutants (e.g., chemical components and particle properties) vary spatially [3], and their concentrations may differ depending on the distance from the AQM stations. Therefore, monitoring data obtained from stations located at a large distance from residential places may lead to misclassification bias [4,5].

Air quality modeling with high spatial and temporal resolution can be used to improve exposure assessment, especially for study populations that are located far from the AQM stations [4]. The community multiscale air quality (CMAQ) modeling system is a sophisticated, regional air quality model capable of estimating the concentrations of air pollutants on a local, regional, or continental scale [6]. The CMAQ combines inputs obtained from meteorological and emissions models. Based on this information, the CMAQ system simulates chemical and physical events to analyze pollutant transformation, transport, and fate. Compared to approaches that rely exclusively on monitoring data, the CMAQ data offer improved spatial coverage, and greater spatial and temporal resolution [4]. Based on the perceived advantages, the modeled data obtained from CMAQ system can be used in epidemiologic studies and compared to evaluate the results based on the AQM measurements.

Atopic dermatitis (AD) is a chronic inflammatory skin disease that is most prevalent in early childhood. During the past few decades, the prevalence of AD in children has increased in both developing and developed countries. AD negatively affects quality of life in both patients and their families [7–9]. Because of its increasing prevalence and the risk of progression to respiratory allergies, the management of AD is an important public health issue. Many environmental factors, including air pollution, have been reported to induce or aggravate AD [7,10,11]. In previous studies, elevated outdoor concentrations of particulate matter with a diameter $\leq 10 \mu\text{m}$ (PM_{10}) were significantly associated with increased symptoms of AD [12,13]. Ambient nitrogen dioxide (NO_2) is another potential risk factor. Nitrogen dioxide generates free radicals, which lead to oxidation of amino acids and peroxidation of polyunsaturated fatty acids [14,15]. An epidemiologic study of 4907 French children residing at their current address for 3 years or longer reported a significant association between lifetime eczema and NO_2 exposure [16]. A multivariate logistic regression model revealed that the higher mean annual level of NO_2 was significantly associated with the prevalence of eczema in US children [17].

We, therefore, investigated the reliability of NO_2 measurements from the AQM stations with low spatial resolution in epidemiologic studies focusing on the acute effects of short-term exposure to ambient NO_2 on AD symptoms in young children. Towards this end, we stratified the AQM measurements based on distance from the residential places to the monitoring stations, and estimated the effects of ambient NO_2 on AD symptoms. We also compared the effect sizes based on AQM data with those based on CMAQ modeling estimates.

2. Methods

2.1. Study Design

A longitudinal study was designed to assess exposure to NO_2 and to evaluate the association between the exposure to NO_2 and AD symptoms in children. A total of 128 young children (78 males and 50 females < 6 years old) with AD living in Seoul Metropolitan Area, Korea were recruited as a panel. These patients were followed between April and July 2014. This study period included spring and summer, during which the highest and the lowest symptom scores of the year were observed, respectively [18]. Exposure to NO_2 was assessed by two methods: (1) collection of measurements at AQM stations selecting the nearest stations to the residential locations, and (2) CMAQ modeling with high spatial resolution. We then evaluated the effects of NO_2 on AD symptoms and compared the effects of subgroups stratified by distance from the residential location to the monitoring stations.

Written informed consent was obtained from each participant and his/her parents or guardians. Study protocols were reviewed and approved by the Institutional Review Board (IRB) at Samsung Medical Center (IRB No: 2013-05-009).

2.2. Exposure Assessment of NO₂

To estimate NO₂ exposure based on AQM station (AQM-NO₂), we obtained hourly NO₂ concentrations from 60 national AQM stations in the Seoul Metropolitan Area. NO₂ is routinely monitored at hourly intervals using the chemiluminescence method (detection limit of 0.1 ppb) by the Korean Ministry of the Environment. Based on the hourly data, the daily 24 h average concentrations of NO₂ were calculated for each AQM station. The NO₂ values from the station nearest to each subject's home address were used to measure the daily exposure for each subject. The average distance between the participants' residences and the nearest AQM station was 2.03 ± 1.06 km, ranging from 0.28 km to 5.73 km.

To obtain a high-resolution concentration of NO₂, we used the CMAQ modeling system (ver.5.0.2) (CMAQ-NO₂), which was developed by the United States Environmental Protection Agency (USEPA) [19]. The CMAQ model was run between April and July 2014 in a nested mode under 27, 9, 3, and 1 km horizontal grid dimensions (D1: 118×125 , D2: 67×79 ; D3: 55×49 ; and D4: 49×49). The fine-scale innermost domain (D4) was applied to the target area covering the Seoul Metropolitan Area. The study area, residences of the AD patients, and the four modeling domains are shown in Figure 1.

The Advanced Research Weather Research and Forecasting model (WRF) ver. 3.6 [20] was used as the meteorological driver of the CMAQ modeling system. The WRF model was configured with 43 vertical layers, with up to 100 hPa and an approximate thickness of 30 m at the lowest level (sigma layer = 0.996). The simulations were conducted using the initial/lateral boundary conditions generated by interpolating the National Center for Environmental Prediction (NCEP) Final (FNL) Operational data (1° , 6 h interval) (NCEP, 2000). We considered the detailed topography and land use in Korea for the WRF model using high-resolution data obtained from the Korean Environmental Geographic Information System (EGIS, 2019). Appropriate physical parameterization schemes were employed to simulate the meteorological fields over the Korean peninsula [21]. The 27 and 9 km grid scales were adjusted for nudging of winds.

The emission estimates for the CMAQ in the model-ready grid scale were developed using the Sparse Matrix Operator Kernel Emissions system (SMOKE; <https://www.cmascenter.org/smoke>). The anthropogenic emission inventory consists of the Intercontinental Chemical Transport Experiment-Phase B (INTEX-B) [22] for Asia (i.e., China, Japan, and North Korea) and the 2012 Clean Air Policy Support System (CAPSS) national emission inventory [23] for South Korea. Biogenic emissions over South Korea were calculated using the Biogenic Emission Inventory System model (ver. 3.14) with the Environmental Geographical Information System (<http://egis.me.go.kr/egis/>) land-use data and the Forest Geographical Information System (<http://fgis.forest.go.kr/fgis/>) vegetation data provided by the Korea Ministry of Environment and the Korea Forest Service.

The CMAQ chemical transport model (CCTM) was run with 23 vertical layers compressed from the WRF's 43 layers; however, the first 12 layers up to approximately 1 km were maintained. The CCTM simulation employs the SAPRC99 gas-phase chemical mechanism [24] and AERO5 aerosol module [25]. The initial and boundary conditions of ozone (O₃) and its precursors for the coarse domain (18 km grid) were derived based on the default profile distributed with Models-3/CMAQ by the USEPA. The spatiotemporal variations in NO₂ concentrations were simulated using the CMAQ modeling system configured with the aforementioned options. Using the simulated NO₂ concentrations in the study area with a 1 km grid scale (domain D4 in Figure 1), we calculated the daily average values for the first model layer. The values at the nearest grid points to the AD patients' residential locations were then selected as the levels of ambient NO₂ exposure.

Figure 1. A map of the study area (D4), the residences of the atopic dermatitis patients (red dots), and modeling domains (D1–D4). Black dashed lines indicate the domains for the weather research and forecasting (WRF) model. The solid red line reflects the community multiscale air quality (CMAQ) modeling. The study area (D4) includes Seoul (A) and parts of Incheon (B) and Gyeonggi provinces (C).

2.3. AD Symptoms

The diagnosis of AD was determined according to the Hanifin and Rajka criteria [26]. The AD severity was assessed using the Scoring Atopic Dermatitis (SCORAD) scale, ranging from 0–103 [27]. Patients with a SCORAD score >15 were enrolled. In children with AD, the total Immunoglobulin E (IgE) and specific IgE levels against egg white, cow’s milk, soybean, wheat and peanut were measured in the peripheral blood using ImmunoCAP (ThermoFisher Scientific Inc., Waltham, MA, USA). Immunoglobulin levels >0.35 kU/L were considered positive.

Parents used the Atopic Dermatitis Symptom Score (ADSS), a smartphone-based symptom diary designed to record their daily levels of itching, sleep disturbances, erythema, dryness, oozing, and edema on a scale of 0 to 4 [28]. Patients were considered to manifest AD symptoms when the symptom score was ≥ 2 for the sum of itching and sleep disturbance scores, plus at least two of the following on the same day: erythema, dryness, edema, or oozing [29]. We matched the daily AD symptoms with AQM-NO₂ and CMAQ-NO₂.

2.4. Association Analysis

Repeated measurement of allergic symptoms provides longitudinal data with a binomial distribution. Therefore, a generalized linear mixed model (GLMM) was adopted to estimate the effects of NO₂ on AD symptoms. The GLMM is an extension of the generalized linear model containing

random effects in addition to the usual fixed effects [30]. In the GLMM model, we treated the NO_2 exposure as a fixed effect and each subject as a random effect. We controlled for age, sex, SCORAD at enrollment, the presence of fever (0 or 1, as a proxy of infection), use of topical corticosteroids (TCSs), day of the week, ambient temperature, and relative humidity. The model specifications are as follows:

$$\ln(Y_{ij}) = \beta_0 + \beta_1(\text{NO}_2) + \sum CF_{ij} + \gamma_j(\text{subject}) + \varepsilon_{ij},$$

where Y_{ij} denotes the expected expression of AD symptoms; NO_2 is nitrogen dioxide; and CF_{ij} indicates the confounding factors including ambient temperature and relative humidity, age, sex, day of the week, SCORAD at enrollment, the presence of fever, and use of topical corticosteroids. The random effect for each subject is represented by γ_j .

We stratified the dataset into 5 subgroups based on distance between AQM stations and residential places: 0–1 km, 1–2 km, 2–3 km, 0–3 km and >3 km. We then fitted the GLMM models for both AQM and CMAQ by each subgroup to estimate the effects of NO_2 on AD symptoms.

We also examined the lag effects on AD symptoms for up to 5 days after NO_2 exposure. LAG1, LAG2, LAG3, LAG4 and LAG5 represent the effects of NO_2 on days 1, 2, 3, 4 and 5 post-exposure, respectively. LAG0 indicates the effects on the same day of exposure. Additionally, the effects of AQM- NO_2 on itching, sleep disturbances, erythema, dryness, oozing, and edema were examined. The percent change in risk and 95% confidence interval (CI) were calculated using regression coefficients and standard errors according to 10 ppb increases of NO_2 .

All procedures were conducted using the R version 3.6.3 (The Comprehensive R Archive Network: <http://cran.r-project.org>) with the “lme4” package (version 3.1-2) for GLMM model fitting. All tests were two-sided. An alpha level <0.05 was considered statistically significant.

3. Results

3.1. Subject Characteristics and AD Symptoms

A total of 8392 person-days of AD symptoms in 128 children diagnosed with AD were recorded during the four-month study period. Among them, 5300 (63.2%) and 3092 (36.8%) person-days were recorded for males and females, respectively. The average age of the study subjects was 1.9 ± 1.6 years. Among 8392 person-days of records, the disease symptoms were observed in 44.0%. The presence of AD symptoms was higher in males (48.7%) than in females (36.0%) ($p \leq 0.0001$) (Table 1). Based on distance to the nearest AQM station, patients in the subgroups were: 22, 50, 33, and 23 every 0–1 km, 1–2 km, 2–3 km and > 3 km, respectively.

Table 1. The characteristics of the study population.

Characteristics	Total	Males	Females	p-Value ^a
No. of subjects	128	78 (60.9%)	50 (39.1%)	
Age (year) ^b	1.9 ± 1.6	1.8 ± 1.5	2.1 ± 1.7	0.230
SCORAD at enrollment ^{b,c}	30.0 ± 11.0	30.6 ± 11.6	29.2 ± 10.8	0.502
Presence of fever (%)	3.8	3.4	4.6	0.010
Use of TCS (%) ^d	54.1	56.6	49.9	<0.0001
Presence of AD symptoms (%) ^e	44.0	48.7	36.0	<0.0001
No. of records (person-days)	8392	5300 (63.2%)	3092 (36.8%)	

^a Test for differences between males and females: *t*-test for means of age and SCORAD and Mann–Whitney *U* test for the presence of fever, use of TCS, and the presence of symptoms; ^b Data are expressed as means $\pm$ standard deviations; ^c SCORAD, Scoring Atopic Dermatitis index; ^d TCS, topical corticosteroid; ^e AD, atopic dermatitis.

3.2. Exposure to NO_2

Based on the values obtained from nearest AQM stations, the participants' levels of NO_2 were assessed during the study period. The average level of AQM- NO_2 was 31.5 ± 13.3 ppb and the

concentrations for each subgroup by distance are shown in Table 2. There was no significant difference between subgroups.

Table 2. Comparison of NO₂ exposure levels by AQM measurements and CMAQ predictions.

Distance ^a	No. (Person-Days)	AQM (ppb) ^b	CMAQ (ppb) ^c
All	8392	31.5 ± 13.3	22.5 ± 8.7
≤1 km	1252	30.2 ± 12.9	20.5 ± 7.8
1–2 km	3507	31.9 ± 12.7	22.5 ± 8.7
2–3 km	2127	31.4 ± 13.3	24.0 ± 8.8
0–3 km	1506	31.5 ± 13.0	22.6 ± 8.7
>3 km	6886	31.5 ± 14.7	22.0 ± 8.6

^a Distance between residential place and nearest AQM site; ^b AQM, air quality monitoring; ^c CMAQ, community multiscale air quality.

The reproducibility of the NO₂ concentrations simulated in the CMAQ model was confirmed by comparing data of 60 points in the CMAQ grids locating 60 AQM stations within the study area with measurements collected at the AQM stations. Figure 2 shows that the multi-day evolution of NO₂ in the study area was significantly correlated ($r = 0.66$), with acceptable bias (normalized mean bias = −20.1%) and error (root mean squared error = 12.4 ppb).

Figure 2. Time series of daily averaged NO₂ concentrations by measurements (gray line) and by CMAQ estimates (black line) at the 60 AQM stations.

Based on the results of the CMAQ model, the daily grid-averaged NO₂ concentrations were generated during the entire study period, and used to estimate each participant's ambient NO₂ exposure. Figure 3a presents a horizontal distribution of the grid-averaged NO₂ concentrations from the CMAQ model of the study area between April and July 2014. Large spatial variations in concentration were observed. The high concentrations were particularly distributed in the southwestern and southeastern area of Seoul, reflecting the impact of high traffic density on ambient NO₂ concentration. Figure 3b shows a representative example of the estimated daily NO₂ exposure level of each study subject on 28 July 2014. It addresses the spatial variation in NO₂ levels at each patient's home address according to the results of high-resolution CMAQ modeling.

The average daily CMAQ-NO₂ at the patients' residential location during the study period was 22.5 ± 8.7 ppb, which was a lower estimate compared with AQM-NO₂ ($p < 0.0001$). When the AQM-NO₂ was compared with the CMAQ-NO₂ for the whole study area and period, the correlation coefficient was 0.51 ($p < 0.0001$), which was lower than that for the AQM- and CMAQ-NO₂ based on 60 points of CMAQ grids located in the 60 AQM stations (0.66, $p < 0.0001$), indicating the discrepancy in the location of residence with AQM stations in the whole data.

Figure 3. Spatial distribution of CMAQ-NO₂ concentrations. Average CMAQ-modeled NO₂ concentrations during the study period (a) and NO₂ levels on July 28, 2014 (b). Black triangles indicate 60 AQM stations. Colored circles represent the residential areas of each atopic dermatitis patient.

3.3. Effect of NO₂ on AD Symptoms

The effects of ambient NO₂ exposure on AD symptoms by subgroup stratified by distance between residential places and the nearest AQM stations are shown in Table 3. Based on AQM-NO₂, the overall AD symptoms increased by 10.28% (95% CI: 3.24, 17.79) with a 10 ppb increase in NO₂, while AD symptoms increased by 13.78% (95% CI: 3.49, 25.09) with a 10 ppb increase in CMAQ-NO₂. The effect estimates of AQM- and CMAQ-NO₂ were very similar when assessed using subgroups within 3 km from the nearest AQM station (Table 3). However, the effect estimate of AQM-NO₂ on AD symptoms of patients living beyond 3 km from the monitoring stations was −3.76% (95% CI: −5.66, −1.83). In contrast, a 10 ppb increase in CMAQ-NO₂ led to a 13.65% increase in AD symptom flares (95% CI: 11.29, 16.06).

Table 3. Comparison of the effects of AQM- and CMAQ-NO₂ on atopic dermatitis symptoms according to the distance from the residences to the nearest air quality monitoring sites.

Distance ^a	AQM ^b (% Change (95% CI))	CMAQ ^c (% Change (95% CI))
All	10.28 (3.24, 17.79) *	13.78 (3.49, 25.09) *
≤1 km	32.79 (7.02, 64.75) *	46.84 (44.18, 49.54) *
1–2 km	6.60 (−2.87, 17.00)	4.80 (−7.88, 19.22)
2–3 km	29.15 (10.39, 51.11) *	29.67 (2.64, 63.81) *
0–3 km	14.21 (6.03, 23.03) *	13.88 (2.56, 26.46) *
>3 km	−3.76 (−5.66, −1.83) *	13.65 (11.29, 16.06) *

^a Distance between residential place and nearest AQM site; ^b AQM, air quality monitoring; ^c CMAQ, community multiscale air quality; * indicates statistically significant with an alpha level <0.05.

Figure 4 shows penalized regression curves controlling for age, sex, SCORAD at enrollment, the presence of fever, use of TCS, day of the week, ambient temperature and humidity. The curves describe the relationship between AQM- or CMAQ-NO₂ levels and AD symptoms on the same day (LAG0). The AD symptoms increased linearly as ambient NO₂ increased when based on whole CMAQ-NO₂ (Figure 4b) and AQM-NO₂ for patients living 0–3 km distant from the AQM stations (Figure 4c). However, the relationship between AQM-NO₂ and AD symptoms in all patients was not linear.

Figure 4. Associations between atopic dermatitis symptoms and the estimated exposure to NO_2 . Penalized regression curve (solid line) with a 95% confidence interval (two dashed lines) based on (a) AQM- NO_2 in all patients, (b) CMAQ- NO_2 in all patients, and (c) AQM- NO_2 from a subgroup residing within 3 km from AQM stations. Statistical analyses were performed after controlling for age, sex, SCORAD at enrollment, the presence of fever, use of topical corticosteroids, day of the week, and ambient temperature and humidity.

Table 4 shows the lag effect of NO_2 exposure on AD symptoms as a result of GLMM fitting using the dataset of patients living at a distance of 0–3 km from the nearest AQM stations. The AQM- and CMAQ- NO_2 showed a very similar pattern in the 0-, 1-, 2-, 3-, 4-, 5-day lag effect estimates. In both models, one-day lag was seen in the NO_2 effect on AD symptoms in children, while no significant lag effects of NO_2 occurred 2–5 days after exposure (LAG2–LAG5). An increase in AQM- NO_2 by 10 ppb on a single previous day (LAG1) was significantly associated with an increase in AD symptoms by 12.96% (95% CI: 5.28, 21.21). Interestingly, males appeared to be more sensitive to NO_2 exposure than females. The AD symptoms in males increased by 17.48% (95% CI: 6.55, 29.54) per 10 ppb of AQM- NO_2 increase, whereas the effect in females was not significant (9.56% (95% CI: −2.10, 22.61)). The effects in males were also statistically significant in LAG1 based on AQM- NO_2 , and in LAG0–LAG2 based on CMAQ- NO_2 . However, none of the results was statistically significant for females.

Table 4. The lag effects of AQM- and CMAQ-NO₂ on AD symptoms (0–3 km) ^a.

Lag Time ^b		AQM ^c (% Change (95% CI))	CMAQ ^d (% Change (95% CI))
Both	LAG0	14.21 (6.03, 23.03) *	13.88 (2.56, 26.46) *
	LAG1	12.96 (5.28, 21.21) *	13.06 (2.27, 24.99) *
	LAG2	5.92 (−1.29, 13.66)	8.51 (−2.03, 20.18)
	LAG3	3.14 (−4.08, 10.92)	0.42 (−9.80, 11.80)
	LAG4	4.67 (−2.62, 12.51)	0.45 (−9.58, 11.59)
	LAG5	2.22 (−4.79, 9.75)	2.43 (−7.58, 13.53)
Males	LAG0	17.48 (6.55, 29.54) *	18.92 (3.90, 36.11) *
	LAG1	20.17 (9.27, 32.15) *	20.68 (5.51, 38.03) *
	LAG2	8.43 (−1.36, 19.20)	16.41 (1.72, 33.20) *
	LAG3	4.07 (−5.58, 14.71)	1.33 (−12.10, 16.80)
	LAG4	5.38 (−4.42, 16.19)	4.34 (−9.18, 19.87)
	LAG5	4.49 (−5.10, 15.06)	8.56 (−5.59, 24.84)
Females	LAG0	9.56 (−2.10, 22.61)	7.44 (−8.78, 26.53)
	LAG1	4.59 (−5.91, 16.25)	5.33 (−9.97, 23.23)
	LAG2	2.81 (−7.58, 14.37)	0.44 (−14.33, 17.77)
	LAG3	2.09 (−8.52, 13.93)	0.52 (−14.77, 18.55)
	LAG4	3.65 (−6.92, 15.43)	−3.72 (−18.17, 13.28)
	LAG5	−0.71 (−10.64, 10.33)	−4.91 (−18.76, 11.30)

^a Values are percent changes in the presence of AD symptoms caused by 10 ppb increases in NO₂ and all effect estimates were results from patients living under 3 km distant from nearest AQM sites; ^b LAG0, effect of NO₂ exposure on AD symptoms on the same day; LAG1, LAG2, LAG3, LAG4 and LAG5, symptoms lagged by 1, 2, 3, 4 and 5 days after exposure, respectively; ^c CMAQ: community multiscale air quality; ^d AQM: air quality monitoring; * statistically significant with an alpha level <0.05.

Table 5 shows the effect of AQM-NO₂ on each AD symptom in results of fitting Poisson regression model with random effect using the dataset of patients living at a distance of 0–3 km from the nearest AQM stations. Itching and sleep disturbance were significantly increased according to an increase in NO₂.

Table 5. Effects of AQM-NO₂ on each AD symptom (0–3 km) ^a.

Symptom	% Change (95% CI)
Itching	2.53 (0.50, 4.60) *
Sleep disturbance	3.62 (1.05, 6.26) *
Erythema	0.45 (−1.62, 2.56)
Dryness	1.84 (−0.37, 4.09)
Edema	1.96 (−1.67, 5.72)
Oozing	−9.11 (−15.29, −2.47)

^a Values are percent changes in the presence of AD symptoms caused by 10 ppb increases in NO₂; * statistically significant with an alpha level <0.05.

4. Discussion

In our longitudinal study using AQM measurements and high-resolution CMAQ predictions, we found that AQM data with low spatial resolution obtained from stations distant from residential areas resulted in misclassification of exposure and misunderstanding of the health effect. For example, when we compared the results of AQM- and CMAQ-NO₂ estimates in the GLMM models after selecting 23 subjects residing more than 3 km away from the nearest AQM stations, the AQM-NO₂ showed a negative relationship with AD symptoms. The effect of the CMAQ-modeled NO₂ on AD symptoms from the dataset was, however, positive (Table 3). The AQM data of residents living far from the AQM stations may not be reliable for use in epidemiologic studies. Conversely, the AQM-NO₂ measurements can be used for exposure assessment in epidemiologic studies if study participants

lived within 3 km from the nearest AQM stations in this study area. Therefore, the use of AQM measurements in the evaluation of health effects of NO₂ on AD should be attended with caution. Indeed, the concentrations of CMAQ-NO₂ match well with those of AQM-NO₂ in areas within 3 km of the study stations, and CMAQ-NO₂ consistently showed an adverse effect on AD symptoms even in subgroups residing beyond 3 km of distance from the monitoring stations. Considering that CMAQ modeled NO₂ estimates were based on grid points less than 0.7 km from residential places, they are reliable and useful in epidemiologic studies particularly for residents with no measurement.

Our study demonstrated that high levels of ambient NO₂ were significantly associated with increased AD symptom flares in young children. The harmful effects of ambient NO₂ were acute on the same day, but were also delayed for up to one day. This finding is consistent with a previous study, in which transepidermal water loss was significantly increased in patients with AD after NO₂ exposure [14]. Interestingly, there was a distinct difference in the effects of NO₂ on AD symptoms between males and females. Although the mechanism is not clear, it may be attributed to physiological differences. It is well known that gender influences lung development and physiology, which play a major role in diseases from early life [31]. Males tend to have a greater inhalation capacity than females: The inhalation rate of males aged 1–2 years was 0.48 m³/kg/day on average, compared with 0.45 m³/kg/day in females [32]. This rate discrepancy implies that males also inhale more NO₂ than females. There may also be gender differences in dermal absorption and toxicity, according to physiological pharmacokinetic (PBPK) modeling [33,34]. Immune development, infection, and gut microbiota are known to affect males and females differently [35,36]. In general, males tend to be more physically active than females, which may also influence the harmful effects of NO₂ on AD symptoms. Ultimately, further detailed exposure assessments, including time–activity patterns and toxicological studies, with gender specific perspectives are required to elucidate these gender differences.

The strength of our study is that the usefulness of monitored NO₂ was investigated by stratifying by distance from stations and comparing the health effects of the monitored NO₂ with the CMAQ-NO₂ with high spatial resolution, along with a smartphone-based daily symptom diary. This method allowed us to assess individual NO₂ exposure and symptom changes on a daily basis, consequently reflecting the detrimental effects of NO₂ on AD at the population level. However, the CMAQ values are somewhat underestimated compared to the measurements from the AQM stations (Table 2). This discrepancy may be attributed to errors in NO₂ emission estimates, as well as uncertainty in NO₂ chemical loss rates [37,38].

This study has limitations. First, we did not consider the indoor NO₂ level, despite the fact that children spend most of their time indoors. However, traffic emissions are the major source of NO₂ in Seoul, and indoor NO₂ level is very dependent on outdoor conditions [39]. Therefore, presumably, it had no significant impact on the results, although our study did not evaluate the exposure to indoor NO₂. Second, we did not include ambient particulate matters (PMs) and O₃ in the GLMMs as confounders although ambient PMs and O₃ are associated with AD symptoms in children [29]. The GLMM results with PM₁₀ and O₃ could be biased if the measurements of exposure to PM₁₀ and O₃ were included. Indeed, when we included PM₁₀ and O₃ in the GLMM model to estimate the AQM-NO₂ effect on AD symptoms in participants living within 3 km from the nearest AQM stations, the result was very similar to that of a model without PM₁₀ and O₃. In the result of modeling with PM₁₀ and O₃, the AD symptoms increased by 12.39% (95% CI: 3.20, 22.40) due to 10 ppb of increase in AQM-NO₂, while those of the model without PM₁₀ and O₃ increased by 14.21% (95% CI: 6.03, 23.03), as shown in Table 3. Therefore, the results from the GLMMs for the whole groups in this study are not changed substantially assuming accurate exposure assessment of PM₁₀ and O₃. Finally, CMAQ predictions are of limited value. Uncertainties in CMAQ-ready inputs of meteorological and emission predictions and incomplete lateral boundary conditions for a nested modeling can lead to bias in the simulated NO₂ concentrations. These uncertainties and incomplete input data could especially increase the inaccuracy of NO₂ predictions when a long-range transport of air pollutants frequently occurs over the northeastern Asia in spring. The relatively large differences between CMAQ and monitored NO₂

concentrations in April and May shown in Figure 2 could be a result from this long-range transport contribution that CMAQ did not reproduce.

5. Conclusions

Exposure assessment of NO₂ using measurement data obtained from monitoring stations far from residential locations can lead to misclassification bias. Our results also suggest that exposure to ambient NO₂ is significantly associated with aggravation of AD symptoms in young children with lag effects, particularly in males. Efforts to reduce ambient NO₂ may be required to control disease flares in patients with pre-existing AD.

Author Contributions: K.A., Y.-M.K., and I.O. conceptualized the study. Y.-M.K. and I.O. designed the methods. J.K. and K.A. enrolled and followed the patients. Y.-M.K., I.O., and Y.-H.K. collected and analyzed data. J.K. and K.A. reviewed the clinical data. Y.-M.K., I.O., J.K., and K.A. interpreted the results. Y.-M.K. and I.O. wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

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