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Effects of short-term exposure to air pollution on hospital admissions for autism spectrum disorder in Korean school-aged children: a nationwide time-series study

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ABSTRACT

Objectives This study explored the effects of short-term exposure to air pollution on hospital admissions for autism spectrum disorder (ASD), a proxy for symptom aggravation, among Korean children aged 5–14 years.

Design Time-series study.

Setting, participants and outcome measures We used data from the National Health Insurance Service (2011–2015). Daily concentrations of fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2) and ozone (O_3) levels in each region were used as exposures. ASD cases were defined based on a principal admission diagnosis of the claims data. We applied distributed lag non-linear models and a generalised difference-in-differences method to the quasi-Poisson models to estimate the causal effects of air pollution for up to 6 days. We also performed weighted quantile sum regression analyses to assess the combined effects of air pollution mixtures.

Results $PM_{2.5}$ levels at lag day 1, NO_2 levels at lag day 5 and O_3 levels at lag day 4 increased the risks of hospital admissions for ASD (relative risk (RR)=1.17, 95% CI 1.10 to 1.25 for $PM_{2.5}$; RR=1.09, 95% CI 1.01 to 1.18 for NO_2 and RR=1.03, 95% CI 1.00 to 1.06 for O_3). The mean daily count of hospital admissions for ASD was 8.5, and it would be 7.3, 7.8 and 8.3 when the $PM_{2.5}$ levels would be decreased by 10.0 μg/m^3, NO_2 by 10 ppb and O_3 by 10 ppb, respectively. The weighted quantile sum index, constructed from $PM_{2.5}$, NO_2 and O_3 levels, was associated with a higher risk of hospital admissions for ASD (RR 1.29, 95% CI 1.14 to 1.46), where NO_2 was found to contribute to the effects most (the weight of 0.80).

Conclusions These results emphasise that reduction of air pollution exposure should be considered for ASD symptom management, with important implications for the quality of life and economic costs.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first study to directly investigate the effects of short-term exposure to air pollution on autism spectrum disorder (ASD)-related outcomes.
⇒ All cases of hospital admissions for ASD in Korean children aged 5–14 years were considered.
⇒ We estimated causal effects rather than observational associations by applying a causal inference method (ie, a difference-in-differences method).
⇒ We used regional air pollution levels not individual levels as exposures, leading to measurement error.
⇒ Due to the remaining social stigma, patients with ASD with mild symptoms might be less likely to receive psychiatric treatments and not be included in the analyses.

INTRODUCTION

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disease with a wide range of symptoms and severity, characterised by deficits in social communication and interaction, restricted interests, and repetitive behaviours.[1] Due to its high prevalence (1.5% in the USA and 2.2% in the Republic of Korea)[2 3] and the high lifelong cost to support an individual with ASD (US$2.2 million in the USA and US$2.4 million in the UK),[4] ASD is considered a major public health problem.

Neuroinflammation and systemic inflammation are often accompanied by ASD.[5] Recent studies have also reported that ongoing inflammatory responses, represented by serum inflammatory cytokine levels, are associated with the severity of ASD symptoms,[6] and the core symptoms of ASD can be improved by modulating the inflammatory status (eg, with drugs, supplements and dietary formulations), especially among patients with ASD with high serum proinflammatory cytokine levels.[7 8] Collectively, these results suggest an association between the immune system and ASD symptoms and the presence of an immune subtype of ASD, which can potentially benefit from immune modulatory treatment and prevention strategies.[9]

Given the potential side effects from chronic application of immune modulatory agents, identification of risk factors for ASD symptom aggravation (which may lead to hospital admissions due to reasons, such as hyperactivity, aggression and self-injurious problems) is important with regard to the quality of life of patients and their family and economic costs due to treatment and care. Short-term exposure to air pollution (ie, days to weeks) can induce systemic inflammation and neuroinflammation (possibly due to the penetration of particulate air pollutants through the lungs and olfactory epithelium, changes in blood–brain barrier and activation of microglia) and may aggravate ASD symptoms.[10–12] However, previous air pollution studies have only focused on the association between long-term exposure to air pollution (ie, months to years) during pregnancy (and early postnatal period in a few studies) and ASD development among children and have provided incomplete evidence for the association.[13] To the best of our knowledge, no study has directly investigated the association between short-term exposure to air pollution and ASD symptom aggravation.

Therefore, we investigated the effects of short-term exposure to air pollution on hospital admissions for ASD as a proxy for ASD symptom aggravation.[14] Because the developing nervous system is more susceptible to environmental exposures than the adult nervous system[15] and because ASD cannot be reliably diagnosed until 3 years of age,[16] we performed analyses using data on all hospitalisations for ASD in Korean children aged 5–14 years.

METHODS

Study design and hospital admission data

We conducted a time-series study using data on daily counts of hospital admissions for ASD among children aged 5–14 years between 1 January 2011 and 31 December 2015. The data, which were provided by the National Health Insurance Service, the sole health insurance provider of the universal coverage system, were aggregated according to the 16 regions of the Republic of Korea (online supplemental table 1) and sex. The National Health Insurance Service had medical information on all the residents of the Republic of Korea, including the data of those covered by either the National Health Insurance (97%) or the Medical Aid programme (3%).[17] Because the National Health Insurance Service data used in this study did not disaggregate according to emergency visit or follow-up visit, we considered hospital admissions regardless of the route of admission (eg, emergency visit, follow-up visit) and could not perform analyses excluding follow-up visits. We constructed a sex-combined time-series daily count dataset from sex-aggregated raw data and used the sex-combined dataset for further analyses, except for sex-stratified analyses.

Air pollution and meteorological factors

Previous studies have reported associations between long-term exposure to particulate matter with an aerodynamic diameter ≤2.5 µm ($PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3) and ASD development.[18 19] Thus, we selected $PM_{2.5}$, NO_2 (daily mean concentrations) and O_3 (daily 8-hour maximum concentrations) as exposures of interest in this study.

Due to the lack of national monitoring data during the study period (2011–2015), $PM_{2.5}$ levels were estimated using the Integrated Multi-Scale Air Quality System for Korea, as described in detail elsewhere.[20] Briefly, we combined meteorological and chemical data and simulated hourly $PM_{2.5}$ for each 3×3 km grid cell using the Community Multi-Scale Air Quality model (V.4.7.1). Region-specific daily mean $PM_{2.5}$ levels were then estimated by averaging daily gridded $PM_{2.5}$, calculated from predicted 24 hours $PM_{2.5}$.

Meanwhile, data on NO_2 and O_3 levels in each region were obtained from 318 fixed-site monitoring stations of the National Ambient Air Monitoring Information System, which collects 24 hours air pollution monitoring data with stringent quality control.[21] After excluding missing values of raw data from monitoring stations (<5%), we estimated region-specific daily mean NO_2 levels and daily 8-hour maximum O_3 levels by averaging daily mean NO_2 levels and daily 8-hour maximum O_3 levels of all monitoring stations in each region.

Additionally, data on temperature (°C) and relative humidity (%) in each region were obtained from the Korea National Meteorological Administration. The region-specific daily mean temperature and relative humidity were calculated by averaging the respective temperature and relative humidity levels from all weather stations in each region.

Autism spectrum disorder

ASD was defined as a principal admission diagnosis based on the International Statistical Classification of Diseases and Related Health Problems, 10th revision codes F84.0, 84.1, 84.5, 84.8 and F84.9. The accuracy of the diagnosis in the National Health Insurance Service data was assessed to be high, especially in inpatient settings.[22]

Statistical analysis

To evaluate the associations between short-term exposure to air pollution and hospital admissions for ASD considering delayed effects for up to 6 days, we constructed quasi-Poisson generalised linear regression models, which applied distributed lag non-linear models[23] for air pollution exposures with lag structures (polynomial functions) and concentration-response curves (natural cubic splines) with 3 df, respectively. Although the df was determined according to a previous study,[24] the consistency of the results was also assessed using different df as a sensitivity analysis.

To estimate the causal effects of short-term exposure to air pollution on hospital admissions for ASD that strictly controlled for potential confounders, including seasonality,[19] we applied a generalised difference-in-differences method.[25] By adjusting for spatial units (regions) and

temporal units (days) as indicator variables, measured and unmeasured confounding factors related to these spatial and temporal units can be effectively controlled. This method can provide estimators for causal effects in the potential outcome framework, although it is time-intensive and resource-intensive and computationally exhaustive.[25] Additionally, we adjusted the analyses for temperature and relative humidity, both of which were modelled with lag structures up to 6 days (3 df) and concentration-response curves (3 df), similar to air pollution. Finally, terms for the population of regions at each year were included as offsets. Therefore, main analytical models can be described as follows: $\log[E(Y_{s,t})] = \beta_0 + \beta_1 \text{Air Pollut}_{s,t} + \beta_2 I_s + \beta_3 I_t + \beta_4 \text{Temp}_{s,t} + \beta_5 \text{Humi}_{s,t} + \log(\text{Pop}_{s,t})$.

In this equation, $Y_{s,t}$ is the number of hospital admissions for ASD in region *s* at day *t*. Air $\text{Pollut}_{s,t}$, $\text{Temp}_{s,t}$ and $\text{Humi}_{s,t}$ are the cross-basis matrices of air pollutant levels, temperature and relative humidity in region '*s*' at day '*t*' with lag structures up to 6 days (3 df) and concentration-response curve (3 df), respectively. I_s and I_t are indicator variables for regions and days, respectively. $\text{Pop}_{s,t}$ is the population of region '*s*' in the year of day '*t*'.

Previous animal and epidemiological studies have suggested stronger effects of air pollution exposure on ASD-related outcomes among men than among women.[15] Therefore, to investigate the potential heterogeneity of the associations by sex, we evaluated the interactions between air pollution exposure and sex. We tested the interaction terms between a natural cubic spline of each air pollution exposure (3 df) and sex, added to the above-mentioned main models with the main effect term of sex by performing F-tests comparing models with and without the interaction terms.[26] Analytical models for interaction analyses can be described as follows: $\log[E(Y_{s,t})] = \beta_0 + \beta_1 \text{Air Pollut}_{s,t} + \beta_2 I_s + \beta_3 I_t + \beta_4 \text{Temp}_{s,t} + \beta_5 \text{Humi}_{s,t} + \beta_6 \text{Sex} + \beta_7 \text{Ns Air Pollut}_{s,t} : \text{Sex} + \log(\text{Pop}_{s,t})$.

In this equation, Sex is the indicator variable coded as 1 if the data are for boys and 0 if the data are for girls. Ns Air $\text{Pollut}_{s,t}$ is a natural cubic spline of air pollution exposure in region '*s*' at day '*t*' (3 df). We also performed stratified analyses according to sex and region characteristics (seven metropolitan cities (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon and Ulsan) versus nine non-metropolitan regions (Gyeonggi-do, Gangwon-do, Chungcheongbuk-do, Chungcheongnam-do, Jeollabuk-do, Jeollanam-do, Gyeongsangbuk-do, Gyeongsangnam-do and Jeju-do) (online supplemental table 1). We conducted the regional stratified analyses assuming that hospital visits due to ASD symptom aggravation might differ by region characteristics.

Because there may be confounding by other air pollutants due to substantial correlations among them, we constructed a multiple pollutant model that incorporated all three air pollution exposures ($PM_{2.5}$, NO_2 and O_3) into the main model. Furthermore, to estimate the combined effect considering potential interactions among air pollutants and to identify the relative importance of individual exposure with respect to the effects on the outcome,[18 19] we performed a weighted quantile sum regression analysis.[27] In this analysis, we multiplied the quartiles of air pollution exposures identified to be associated with hospital admissions for ASD in the main model (ie, $PM_{2.5}$ at lag day 1, NO_2 at lag day 5 and O_3 at lag day 4) by the magnitude of each effect of individual exposure (constrained between 0 and 1 and summed to 1) as weights, resulting in the weighted quantile sum index, which represents pollutant mixtures considered of relative importance. We then constructed an analytical model facilitating the weighted quantile sum index as an exposure and hospital admissions for ASD (modelled as a quasi-Poisson distribution) as an outcome. The model was adjusted for region, temperature (a natural cubic spline of 3 df) and relative humidity (a natural cubic spline of 3 df). The weighted quantile sum regression weights were estimated from 40% of 1000 bootstrap sample data, and the association between the weighted quantile sum index and hospital admissions for ASD was evaluated using the remaining 60% of the data. We did not constrain the parameter estimates as positive or negative.

We presented the results of all analyses, except for the weighted quantile sum regression analyses, by 10.0 $\mu g/m^3$ increase for $PM_{2.5}$ (reference of 10.0 $\mu g/m^3$) and 10.0 ppb increase for NO_2 (10.0 ppb) and O_3 (30.0 ppb). In the weighted quantile sum regression analysis, we presented the result of a one-unit increase in the weighted quantile sum index, which is approximately interpreted as a one-quartile increase in pollutant mixtures. We also approximately calculated a daily mean count of outcomes in a hypothetical case when the $PM_{2.5}$ levels would be decreased by 10.0 $\mu g/m^3$, or NO_2 or O_3 levels would be decreased by 10.0 ppb, respectively, using the following equation: the daily mean counts of outcomes × 1/relative risk (RR).

All analyses were performed using R (V.4.0.5; R Foundation for Statistical Computing, Vienna, Austria).

Patient and public involvement

This time-series study using secondary claims data was designed and conducted without patient and public involvement. Our results will be disseminated to the public through publication in this journal.

RESULTS

The mean (SD) of the daily counts of hospital admissions for ASD during the study period (2011–2015) was 8.5 (8.2) for the total study population. The daily counts of hospital admissions for ASD were substantially higher among boys (7.0) than among girls (1.6). The means (SD) of daily mean $PM_{2.5}$ and NO_2 levels and daily 8 hours maximum O_3 levels during the study period (2011–2015) were 19.3 (14.7) $\mu g/m^3$, 20.7 (10.7) ppb and 37.2 (16.4) ppb, respectively, among which the daily mean $PM_{2.5}$ and NO_2 levels were higher than the levels of the USA but lower than the levels of China, and the daily 8 hours

Table 1 Means and SD of daily counts of hospital admissions for autism spectrum disorder, air pollution levels and meteorological factors during the study period (2011–2015)

	Total	Warm seasons*	Cool seasons†
Daily counts of hospital admissions			
Autism spectrum disorder			
Total	8.5 (8.2)	8.3 (7.9)	8.8 (8.4)
Boys	7.0 (6.9)	6.8 (6.8)	7.1 (7.0)
Girls	1.6 (1.5)	1.5 (1.4)	1.7 (1.7)
Air pollution levels‡			
$PM_{2.5}$ (μg/m^3)	19.3 (14.7)	15.1 (11.1)	23.6 (16.6)
NO_2 (ppb)	20.7 (10.7)	17.6 (9.1)	23.8 (11.3)
O_3 (ppb)	37.2 (16.4)	43.0 (16.6)	31.4 (13.9)
Meteorological factors			
Temperature (℃)	13.2 (9.8)	21.3 (4.5)	5.0 (6.3)
Relative humidity (%)	67.0 (15.2)	72.7 (12.5)	61.3 (15.4)

Values are presented as mean (SD).
*May–October.
†November–April.
‡Daily mean concentrations of $PM_{2.5}$ and NO_2 and daily 8 hours maximum concentrations of O_3.
NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter.

maximum O_3 levels were lower than the levels of both the USA and China.[28–30] The mean temperature was 13.2°C (21.3°C during warm seasons and 5.0°C during cool seasons) (table 1).

In the Pearson's correlation analysis for air pollution levels and meteorological factors, we found a moderate positive correlation between $PM_{2.5}$ and NO_2 levels (r=0.52, p<0.01), weak positive correlations between O_3 levels and temperature (r=0.43, p<0.01) and between temperature and humidity (r=0.43, p<0.01), and a weak negative correlation between NO_2 levels and temperature (r=−0.30, p<0.01). For other pairs, absolute values for correlation coefficients were smaller than 0.30, although correlations of all assessed pairs were statistically significant (p<0.05) (online supplemental figure 1).

$PM_{2.5}$ levels at lag day 1, NO_2 levels at lag day 5 and O_3 levels at lag day 4 were associated with a higher risk of hospital admissions for ASD (RR=1.17, 95% CI 1.10 to 1.25 for $PM_{2.5}$; RR=1.09, 95% CI 1.01 to 1.18 for NO_2 and RR=1.03, 95% CI 1.00 to 1.06 for O_3), whereas $PM_{2.5}$ and NO_2 levels at lag day 0 were associated with a lower risk (table 2). The observed mean daily count of hospital admissions for ASD was 8.5 in this study, and it would be 7.3, 7.8 and 8.3 when the $PM_{2.5}$ levels would be decreased by 10.0 μg/m^3, NO_2 by 10 ppb and O_3 by 10 ppb, respectively.

The associations between air pollution exposures and hospital admissions for ASD were different between boys and girls, especially for $PM_{2.5}$ and NO_2 (p-interactions: 0.03 for $PM_{2.5}$, <0.01 for NO_2 and 0.14 for O_3). When the study

Table 2 Lag-specific associations of $PM_{2.5}$, NO_2 and O_3 levels with hospital admissions for autism spectrum disorder†

	$PM_{2.5}$	NO_2	O_3
	RR (95% CI)	RR (95% CI)	RR (95% CI)
Lag day 0	0.87 (0.81 to 0.92)*	0.84 (0.77 to 0.97)*	0.99 (0.94 to 1.04)
Lag day 1	1.17 (1.10 to 1.25)*	1.03 (0.91 to 1.18)	1.02 (0.97 to 1.07)
Lag day 2	1.04 (1.00 to 1.08)	0.95 (0.90 to 1.03)	0.99 (0.95 to 1.02)
Lag day 3	0.97 (0.93 to 1.02)	0.97 (0.91 to 1.06)	1.00 (0.96 to 1.03)
Lag day 4	0.99 (0.96 to 1.02)	1.06 (1.00 to 1.14)	1.03 (1.00 to 1.06)*
Lag day 5	1.00 (0.96 to 1.04)	1.09 (1.01 to 1.18)*	1.03 (1.00 to 1.07)
Lag day 6	0.97 (0.94 to 1.00)	1.01 (0.96 to 1.07)	0.99 (0.96 to 1.01)

*P<0.05.
†The results are presented for a 10.0 μg/m^3 increase for $PM_{2.5}$ and 10.0 ppb for NO_2 and O_3 from models adjusted for region, day, temperature, relative humidity and population.
NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter; RR, relative risk.

Table 3 Associations between $PM_{2.5}$, NO_2 and O_3 levels and hospital admissions for autism spectrum disorder among boys and girls†

	Boys			Girls		
	$PM_{2.5}$	NO_2	O_3	$PM_{2.5}$	NO_2	O_3
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Lag day 0	0.85 (0.80 to 0.91)*	0.87 (0.75 to 1.02)	0.99 (0.94 to 1.04)	0.95 (0.80 to 1.14)	0.66 (0.49 to 0.90)*	1.01 (0.90 to 1.14)
Lag day 1	1.19 (1.11 to 1.27)*	1.03 (0.89 to 1.19)	1.04 (0.98 to 1.10)	1.05 (0.89 to 1.25)	1.07 (0.80 to 1.43)	0.92 (0.82 to 1.03)
Lag day 2	1.04 (0.99 to 1.08)	0.93 (0.86 to 1.02)	0.99 (0.95 to 1.02)	1.05 (0.94 to 1.18)	1.09 (0.91 to 1.30)	0.97 (0.90 to 1.05)
Lag day 3	0.97 (0.93 to 1.01)	0.97 (0.88 to 1.05)	0.99 (0.96 to 1.03)	1.01 (0.91 to 1.14)	1.03 (0.85 to 1.23)	1.01 (0.94 to 1.09)
Lag day 4	0.99 (0.95 to 1.03)	1.07 (1.00 to 1.15)*	1.04 (1.00 to 1.07)*	0.98 (0.89 to 1.08)	0.98 (0.85 to 1.13)	1.02 (0.96 to 1.09)
Lag day 5	1.00 (0.96 to 1.04)	1.10 (1.02 to 1.20)*	1.04 (1.00 to 1.07)*	0.98 (0.88 to 1.09)	0.95 (0.80 to 1.12)	1.01 (0.94 to 1.09)
Lag day 6	0.97 (0.94 to 1.00)*	1.02 (0.96 to 1.08)	0.98 (0.96 to 1.01)	1.00 (0.92 to 1.09)	0.93 (0.82 to 1.05)	1.00 (0.95 to 1.06)

*P<0.05.
†The results are presented for a 10.0 μg/m^3 increase for $PM_{2.5}$ and 10.0 ppb for NO_2 and O_3 from models adjusted for region, day, temperature, relative humidity and population.
NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter; RR, relative risk.

population was stratified by sex, the associations between air pollution exposures and hospital admissions for ASD were more prominent among boys (RR 1.19, 95% CI 1.11 to 1.27 for $PM_{2.5}$ levels at lag day 1; RR 1.07, 95% CI 1.00 to 1.15 for NO_2 at lag day 4 and RR 1.10, 95% CI 1.02 to 1.20 for NO_2 at lag day 5; and RR 1.04, 95% CI 1.00 to 1.07 for O_3 at lag day 4 and RR 1.04, 95% CI 1.00 to 1.07 for O_3 at lag day 5) than among girls (table 3). Among boys, the mean daily count of hospital admissions for ASD was 7.0 in this study, and it would be 5.9, 6.5 and 6.4 when the $PM_{2.5}$ levels would be decreased by 10.0 μg/m^3, NO_2 by 10 ppb and O_3 by 10 ppb, respectively. Among girls, the mean daily count of hospital admissions for ASD was 1.6, and it would be 1.5 when the $PM_{2.5}$ levels would be decrease by 10.0 μg/m^3 and O_3 by 10 ppb.

In the analyses stratified by region characteristics, the associations between air pollution exposures and hospital admissions for ASD were generally more prominent in the nine non-metropolitan regions than those in the seven metropolitan cities, although the CIs overlapped (online supplemental table 2).

We found consistent associations between $PM_{2.5}$, NO_2 and O_3 levels and hospital admissions for ASD in the multiple-pollutant model (online supplemental table 3) compared with the main analytical models. These results suggest that the concern for confounding by other air pollutants would be low. In the weighted quantile sum regression analysis, the weighted quantile sum index, constructed from $PM_{2.5}$ at lag day 1, NO_2 at lag day 5 and O_3 at lag day 4, was associated with a higher risk of hospital admissions for ASD (RR 1.29, 95% CI 1.14 to 1.46). The weights for $PM_{2.5}$ at lag day 1, NO_2 at lag day 5 and O_3 at lag day 4 were approximately 0.20, 0.80 and <0.01, respectively (online supplemental figure 2).

In the sensitivity analyses modelling air pollution exposures using df of 4–7 (instead of 3 df as in the main analytical models) for lag structures and concentration-response curves, the results did not change appreciably (data not shown).

DISCUSSION

Short-term exposure to $PM_{2.5}$, NO_2 and O_3 was associated with a higher risk of hospital admissions for ASD. The associations were demonstrated to be more prominent among boys than among girls in sex-stratified analyses. In the weighted quantile sum regression analysis, the weighted quantile sum index was associated with a higher risk of hospital admissions for ASD with weights of 0.20, 0.80 and <0.01 for $PM_{2.5}$, NO_2 and O_3, respectively.

A recent systematic review and meta-analysis concluded that there is evidence of an association between long-term exposure to air pollution (especially $PM_{2.5}$ and NO_2) during pregnancy and ASD development among children.[31] A limited number of studies have been conducted on postnatal exposures, which also suggests an association between long-term air pollution exposure during early life after birth and ASD development. A case–control study in China reported the association between air pollution ($PM_{2.5}$, particulate matter with an aerodynamic diameter ≤10.0 μm (PM_{10}) and particulate matter with an aerodynamic diameter ≤1.0 μm) levels in the second and third year after birth and ASD.[32] Another case–control study in Denmark reported an association between air

pollution ($PM_{2.5}$, PM_{10}, NO_2 and sulfur dioxide) levels for 9 months after birth and ASD.[33]

Short-term exposure to air pollution has been shown to be associated with a higher risk of hospital admission or emergency department visit for psychiatric disorders, such as mental disorder, depression, schizophrenia, suicide attempt, substance abuse disorder and panic attack.[34] However, to the best of our knowledge, no direct evidence, except this study, exists on the association between short-term exposure to air pollution and ASD symptom aggravation.

Air pollution is known to impact the central nervous system by activating microglia and disrupting the blood–brain barrier through systemic inflammation, neuroinflammation, oxidative stress, cerebrovascular injury and neurodegenerative processes.[11] Short-term exposure to air pollution is known to activate microglia, the resident immune cells of the central nervous system involved in the production and secretion of proinflammatory cytokines, such as interleukin (IL)-6, IL-1β and tumour necrosis factor (TNF)-α.[12] Proinflammatory cytokine levels have been associated with the severity of communication impairment and aberrant behaviours among children with ASD,[6] emphasising the importance of ongoing inflammatory responses with regard to ASD symptoms. Immune modulatory treatment targeting microglia has, therefore, been suggested and assessed to be effective for symptomatic therapy for ASD (at least the immune subtype of ASD). By administering dietary formulation of luteolin, a natural flavonoid, to children with ASD, IL-6 and TNF levels were lowered, and ASD symptoms substantially improved in the communication, daily living skills and social domains among children with higher baseline IL-6 and TNF levels.[5 7] Risperidone and aripiprazole, second-generation antipsychotics approved for control of irritability symptoms among patients with ASD by the Food and Drug Administration, have also been suggested to affect ASD symptoms through anti-inflammatory properties, although their specific mechanisms remain unclear.[5 9]

This study unexpectedly found inverse associations between $PM_{2.5}$ and NO_2 levels at lag day 0 and hospital admissions for ASD. Because these inverse associations are clinically irrelevant (given that we considered hospital admissions as the outcome) and biologically implausible (considering the causal pathway via microglia activation and inflammatory status mentioned above), we assumed that the inverse associations between $PM_{2.5}$ and NO_2 levels at lag day 0 and hospital admissions for ASD may be explained by the harvesting effect (outcome displacement) induced by air pollution exposures at previous lag days (eg, $PM_{2.5}$ at lag day 1 and NO_2 levels at lag day 5).[35] The findings of this study are further supported by the clear paralleled and lagged distribution patterns of the daily $PM_{2.5}$ levels and counts of hospital admissions for ASD (online supplemental figure 3). Air pollution levels at previous lag days not only correlated with the air pollution levels at lag day 0 but also increased the risk of hospital admissions for ASD, leading to observed non-causal inverse associations.

Previous animal and epidemiological studies have shown male-specific and/or male-biased associations between air pollution exposure and ASD-related outcomes, consistent with the findings of this study. For example, male mice with perinatal exposures to $PM_{2.5}$ have reduced anogenital and body sniffing behaviours (indicators of reciprocal social interaction).[36] In epidemiological studies, $PM_{2.5}$ levels during pregnancy and the first year after birth have been associated with ASD development only among boys.[37] This sex difference may be explained by a larger number of microglia,[38] activation of microglia due to testosterone[39] and lower antioxidant (eg, glutathione and sulphate) levels among boys compared with that among girls.[40]

The association between O_3 levels and hospital admissions for ASD remained after adjustment for $PM_{2.5}$ and NO_2 levels. However, the weight of O_3 was estimated to be low (<0.01) in the weighted quantile sum regression analysis. It is notable that there is significantly less evidence for O_3 than for $PM_{2.5}$ and NO_2 in previous epidemiological studies exploring the effects of long-term exposure to air pollution on ASD development (OR 1.00, 95% CI 1.00 to 1.01 for O_3; OR 1.06, 95% CI 1.01 to 1.11 for $PM_{2.5}$ and OR 1.02, 95% CI 1.01 to 1.04 for NO_2 in random effects meta-analysis),[31] although several animal studies have reported the effects of O_3 exposure on neurobehavioral outcomes, such as social recognition memory.[41] Collectively, the results of this study may be interpreted as the effect of O_3 being independent, whereas the contribution of O_3 might be relatively small with regard to ASD symptom aggravation in air pollution mixtures. Because this study is the first to investigate the effects of short-term exposure to O_3 on ASD-related outcomes and it is not appropriate to determine the relative importance of exposures solely dependent on statistical models, further studies are warranted to confirm the results of this study regarding the contribution of O_3.

This study has some limitations. First, some results may be spurious, possibly occurring by chance due to extensive analyses. However, we did not adjust for multiple comparisons, because each analysis was not independent and all of the results were presented without selection. Second, although the results of this study may be driven by subgroups of the study population (eg, patients with immune subtype of ASD, who have high proinflammatory cytokine levels and are also a target for immune modulatory treatment; those with morbidities, such as gestational diabetes mellitus and infections; and those with lower socioeconomic status),[42] we could not evaluate this possibility due to a lack of essential information. Third, because this study was conducted in the Republic of Korea, a practically single-ethnic nation, caution should be exercised in generalising the results to other populations, given the potential heterogeneity of the results by race/ethnicity suggested by previous studies.[43] Fourth, there is a concern of exposure misclassification attributable to large spatial units, although several time-series studies

conducted in Korea used regional air pollution levels as exposures (instead of air pollution levels measured for a finer spatial unit).[44–46] This type of error (ie, Berkson error) is likely to lead to imprecision in the estimation of associations rather than bias. Fifth, we only considered three criteria air pollutants (ie, $PM_{2.5}$, NO_2 and O_3) as exposures according to previous studies.[18 19] The next step in future studies is to analyse the effects of other hazardous air pollutants, such as lead, mercury and arsenic, on ASD symptom aggravation. Sixth, although hospital admissions are commonly used as a proxy for symptom aggravation in epidemiological studies,[14] hospital admissions for ASD might disproportionately reflect aggravation of symptoms related to hyperactivity, aggression and self-injurious behaviour more than those related to deficits in social communication. In addition, private practice or community-based programmes are also potential options for providing care for ASD children with aggravated symptoms in Korea. This could have led to the underestimation of the effect of air pollution on ASD symptom aggravation observed in this study. We assume that the more prominent associations in the non-metropolitan regions than in metropolitan cities might also be explained at least in part by the fact that most resources for these treatment options other than those in hospitals were in metropolitan cities. Furthermore, predetermined scheduled hospital admissions can also be another source of outcome misclassification (in terms of ASD symptom aggravation) leading to imprecision in the estimation of associations. Therefore, further studies that directly evaluate ASD symptoms are necessary to address this issue. Seventh, due to the remaining social stigma for psychiatric treatments in the Republic of Korea,[47] patients with ASD with mild symptoms (and not accompanying intellectual disability) might be less likely to receive psychiatric treatments than patients with ASD with more severe symptoms. The possibility that the outcome of this study might reflect more severe ASD cases, rather than all ASD cases, needs to be considered to correctly interpret the results.

However, this study also has several strengths. First, this is the first study to directly explore the association between short-term exposure to air pollution and ASD symptom aggravation, which has relevant implications for immune modulatory prevention (regarding air pollution exposures) as a possible ASD management strategy. Second, because all cases of hospital admissions for ASD in Korean children aged 5–14 years were considered, we could perform various analyses, such as sex-stratified analyses, with sufficient power. Third, we estimated causal effects rather than observational associations. To do this, we applied a generalised difference-in-differences method, a causal inference method. Fourth, in contrast to most previous studies that considered only one exposure at a time, we analysed multiple air pollution exposures together and explored the combined effects using the weighted quantile sum regression model.

CONCLUSIONS

This study suggests that short-term exposure to air pollution affects ASD symptom aggravation, which is more prominent among boys than among girls. Air pollution mixtures were also found to be associated with ASD symptom aggravation, mostly driven by $PM_{2.5}$ and NO_2. These results emphasise that reduction of air pollution exposure needs to be considered for successful ASD symptom management, which is important with regard to quality of life and economic costs. Because this is the first study on this subject, further studies, especially studies directly investigating ASD symptoms in more detail, are warranted to confirm the results and draw policy implications.

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