J Korean Med Sci. 2024 Aug 5;39(30):e218
https://doi.org/10.3346/jkms.2024.39.e218
eISSN 1598-6357·pISSN 1011-8934

JKMS

Original Article
Public Health & Preventive Medicine

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Estimation of Attributable Risk and Direct Medical and Non-Medical Costs of Major Mental Disorders Associated With Air Pollution Exposures Among Children and Adolescents in the Republic of Korea, 2011–2019

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Received: Apr 3, 2024
Accepted: Jun 21, 2024
Published online: Jul 8, 2024

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ABSTRACT

Background: Recent studies have reported the burden of attention deficit hyperactivity disorder [ADHD], autism spectrum disorder [ASD], and depressive disorder. Also, there is mounting evidence on the effects of environmental factors, such as ambient air pollution, on these disorders among children and adolescents. However, few studies have evaluated the burden of mental disorders attributable to air pollution exposure in children and adolescents.
Methods: We estimated the risk ratios of major mental disorders (ADHD, ASD, and depressive disorder) associated with air pollutants among children and adolescents using time-series data (2011–2019) obtained from a nationwide air pollution monitoring network and healthcare utilization claims data in the Republic of Korea. Based on the estimated risk ratios, we determined the population attributable fraction (PAF) and calculated the medical costs of major mental disorders attributable to air pollution.
Results: A total of 33,598 patients were diagnosed with major mental disorders during 9 years. The PAFs for all the major mental disorders were estimated at 6.9% (particulate matter < 10 μm [PM_{10}]), 3.7% ($PM_{2.5}$), and 2.2% (sulfur dioxide [SO_2]). The PAF of PM_{10} was highest for depressive disorder (9.2%), followed by ASD (8.4%) and ADHD (5.2%). The direct medical costs of all major mental disorders attributable to PM_{10} and SO_2 decreased during the study period.
Conclusion: This study assessed the burden of major mental disorders attributable to air pollution exposure in children and adolescents. We found that $PM_{10,}$ $PM_{2.5}$, and SO_2 attributed 7%, 4%, and 2% respectively, to the risk of major mental disorders among children and adolescents.

Keywords: Air Pollution; PM_{10}; $PM_{2.5}$; SO_2; Mental Disorders; Burden; Children; Adolescents

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Funding
This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean Ministry of Science and ICT and the Ministry of Education (No. 2019M3E7A1035155). This study was also supported by a faculty research grant from Yonsei University College of Medicine (grant No. 6-2021-0245).

Disclosure
The authors have no potential conflicts of interest to disclose.

Author Contributions
Conceptualization: Cho J, Kim C. Formal analysis: Ha YW. Investigation: Kim TH, Kang DR, Park KS, Shin DC. Writing - original draft: Ha YW. Writing - review & editing: Cho J, Kim C.

INTRODUCTION

Mental health problems are one of the main causes of the social and economic burden of diseases worldwide. Globally, it was estimated that 655 million and 970 million people suffered from mental illnesses in 1990 and 2020, respectively.[1] The burden and cost of disorders, such as attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and depressive disorder, are significant among children and adolescents. It is known that about 10% of people aged 3 to 17 years are diagnosed with ADHD in their lifetime in the United States.[2] A study showed that the burden of ADHD contributed 39% to all mental illnesses among people aged 10 years or younger in the Republic of Korea.[3] With ADHD, ASD is one of the neurodevelopmental diseases that also develops in early period. In 2019, the disease burden caused by ASD was estimated 43.07×10^5 DALYs worldwide, and it was found to increase every year.[4] One study examined prevalence and economic burden of ASD in Korea.[5] The prevalence of ASD showed a trend of increasing from about 5.0 to 11.0 per 100,000 people over 8 years, and consistently total costs of ASD were rising. Depressive disorder is considered the second leading cause of disability worldwide.[1] The prevalence of depressive disorder doubled over 10 years from 2.8% in 2002 to 5.3% in 2013.[6] In the United States, the prevalence of depressive disorder tripled from 1.8% in 2012 to 3.1% in 2018 among people aged 4 to 17 years.[7]

Environmental factors such as air pollution are known to contribute to the development of mental illnesses among children and adolescents. A cohort study demonstrated that a 5 $\mu g/m^3$ increase in particulate matter < 2.5 μm [$PM_{2.5}$] was associated with a 1.5-fold increased risk of ADHD.[8] In a cohort study conducted in Taiwan over 10 years, it was found that the incidence of ASD significantly increased with the increase of sulfur dioxide (SO_2), nitrogen dioxide (NO_2), ozone (O_3), and carbon monoxide (CO) and a 10 ppb increase in NO_2 was associated with a 340% increased risk of ASD.[9] Furthermore, in two time-series studies conducted in Korea, they reported associations between short-term exposure to air pollutants and ADHD and ASD among adolescents.[10,11] A few studies have calculated the risk and inpatient visits costs of mental disorders due to air pollution at all ages and identified more sensitive age groups by dividing the ages into 0–44, 45–64, and 65 years or older.[12-15] However, there is little evidence regarding the burden of mental disorders attributable to air pollution exposure among children and adolescents. Additionally, there is a lack of evidence regarding the medical costs of mental disorders attributable to exposure to air pollution among children and adolescents.

This study aimed to assess the PAF and medical costs of three major disorders (ADHD, ASD, and depressive disorder) associated with air pollution exposure among children and adolescents using nationwide healthcare utilization data.

METHODS

Data sources

Medical utility data and definition of major mental disorders

Using customized National Health Insurance Service data, we used a time-series data to assess the risk of exposure to air pollution and outpatient and inpatient visits in patients with major mental disorders under the age of 19 years of age. This database included information on medical use and demographic variables such as birth, sex, date of visits, and address. Using addresses, we divided the administrative areas into 16 regions: 7 metro cities (Seoul, Incheon, Busan, Daegu, Daejeon, Gwangju, and Ulsan), and 9 provinces (Gangwon-do, Gyeonggi-do, Chungcheongbuk-do, Chungcheongnam-do, Gyeongsangbuk-do, Gyeongsangnam-do, Jeollabuk-do, Jeollanam-do, and Jeju). Outpatient and inpatient visits for major mental disorders were defined as the earliest outpatient and inpatient visits records of children and adolescents aged < 19 years between January 2011 and December 2019. Each mental disorder was identified using the International Classification of Diseases, 10th edition (ICD-10): ADHD (code F90.0), ASD (codes F84.0, F84.1, F84.5, F84.8, and F84.9), and depressive disorder (major depressive disorder) (code: F32–F33).[10,11,16] In addition, to select only the subjects that developed major mental health disorders during the study period (new cases), we excluded counts of the visit if there were medical records before 2011 due to the availability of the data. Defining the outcome as the earliest visit to clinic may cause another problem. The visit to clinic may be scheduled and may not reflect the time of occurrence of the disease correctly. We then aggregated daily counts of major mental disorders in total, following the above regions.

Air pollutants and meteorological variables

Air pollutants, including PM_{10}, $PM_{2.5}$ NO_2, SO_2, O_3, and CO, were collected from the Air Korea website (http://m.airkorea.or.kr/main). These air pollutants (PM_{10}, $PM_{2.5}$, NO_2, SO_2, CO) were recorded hourly and O_3 were recorded the 8-hour maximum average from automatic nationwide monitoring stations. Therefore, we calculated the hourly data as daily mean data and recalculated them as regional daily mean data by averaging except O_3. For O_3, we used the 8-hour maximum average concentration. If there was more than one monitoring station in a region, the arithmetic mean was used. For $PM_{2.5}$, data were obtained and calculated from 2015 to 2019 because it was monitored nationwide from 2015. To control the effect of temperature (°C), and relative humidity (%), we obtained these variables, which were measured daily, from the Korea National Meteorological Administration (https://data.kma.go.kr/cmmn/main.do). We also calculated the daily mean by region using the same methods as for the air pollution data.

Census data

To adjust the region as the offset in the statistical model, the mid-year population was obtained from Statistics Korea and calculated by region, age group (< 5 years, 5–9 years, 10–14 years, and 15–19 years), and sex from 2011 to 2019.[17]

Korea Health Panel data (Version 1.7.3)

The average transportation costs were collected from the Korea Health Panel Survey of 2011, provided by the Korea Institute for Health and Social Affairs and the National Health Insurance Service. We calculated the average transportation costs of outpatients and inpatients for all mental disorders (ICD-10 codes: F00–F99) because there were no transportation costs for each disease (average outpatient transportation cost = 1,248 KRW and inpatient transportation cost = 10,358 KRW). Transportation costs during outpatient and inpatient visits were calculated under the assumption that parents were accompanying the patient when visiting the hospital, considering patients' age, and that outpatient and inpatient visits were round-trips. Given that we could only collect data from 2011, we calculated the values after 2011 by multiplying the 2011 values by the annual consumer price index (CPI).

$$\text{Transportation costs}\_(y+1) = \text{Average outpatient transportation cost}\_y \times \text{Number of outpatient visits (or inpatient)} \times CPI\_(y+1) \times 4$$

where CPI_y is the consumer price index in year y+1.

Statistical analysis

Risk ratio

We used a time-series data to estimate the risk ratio between exposure to air pollution and outpatient and inpatient visits for each of the 16 regions, using an over-dispersed generalized additive model (GAM).[18] From the calculated beta (exp (β) = risk ratio), we estimated risk ratio. Covariates were added to the model, and the degrees of freedom and splines of each variable were obtained from previous studies. The data, consisting of a series of numbers, were adjusted to control unmeasured long-term trends and were inserted into the model as a function of the spline with a degree of freedom (*df*) of 7 per year.[12,19] Temperature and relative humidity were also inserted into the model as a function of the spline with 6 *df*, respectively.[12,19,20] In addition, the day of the week and holidays known to affect outpatient and inpatient visits were added to the model as parametric variables. The total population of each region was also added as an offset term. The primary model is as follows:

$$Log[E(Ytiii)] = \alpha + \beta^{*} air\ pollutant\ level_i + ns\ (date,\ df = 7/year) + ns\ (temperaturei,\ df = 6 \times year) + ns\ (relative\ humidity_i,\ df = 3 \times year) + day\ of\ week + holiday + log(offset)$$

where $E(Y_i)$ is the number of major mental disorders on day i, ns represents the natural spline, df represents the degrees of freedom, and the offset is the total population of each region.

The lag effect, which is the effect of the concentration before exposure to air pollutants on health, was also considered. This was conducted using single-lag structure models (from lag 0 to lag 14) and cumulative-lag structure models (from cumulative lag 1 to cumulative lag 14). After estimating each region's risk ratio, we estimated the pooled risk ratios using random-effects meta-analyses, which reflect the heterogeneity between regions. Among the estimated pooled risk ratios, we selected those in which all air pollutants were statistically significant (cumulative lag 3), and subsequent analyses were performed in cumulative lag models.[13,21] Additionally, to identify group that are particularly vulnerable to air pollution exposure, we performed a subgroup analysis stratified by age group, sex, and specific mental disorders.

Attributable number (AN) and population-attributable fraction (PAF)

The PAF (%) was calculated from the AN and the total number of medical care visits during the study period.[21,22]

$$AN = \sum_{i}^{n} (Baseline\ risk) \times [\exp\ (\beta 0 \times \Delta C_i) - 1]$$

$$PAF\ (\%) = \frac{Attributable\ number}{Total\ number} \times\ 100$$

- *AN*: total attributable number due to exposure to air pollutants above the reference concentration
- *Baseline risk*: average counts at days with reference concentration
- *i*: days when air pollutant concentration is higher than the reference concentration
- *β*: coefficients extracted from GAM
- ΔC_i: difference between the air pollutant and reference concentrations
- *PAF*: population attributable fraction of major mental disorders
- *Total number*: total counts of major mental disorders during the study period

We applied the 2005 World Health Organization (WHO) air quality standards (24-hour average PM_{10}: 50 μg/m^3, $PM_{2.5}$: 25 μg/m^3, and SO_2:20 μg/m^3) as reference concentrations.[23]

Additionally, we applied the 2021 WHO air quality standards (24-hour average PM_{10}: 45 μg/m^3, $PM_{2.5}$: 15 μg/m^3, SO_2: 40 μg/m^3, and NO_2: 25 μg/m^3) as reference concentrations.[24] The unit of SO_2 and NO_2 concentration (ppm) was converted to that of the WHO air quality standards (μg/m^3). AN and PAF were not calculated for CO (due to the lack of reference concentrations) or O_3 (due to the lack of significant associations).

Direct medical costs, direct non-medical cost and costs attributable to air pollutants
Total direct costs were calculated from direct medical and non-medical costs. First, the direct medical costs were calculated by summing the outpatient, inpatient, pharmacy, uninsured outpatient, and uninsured inpatient costs. Outpatient and inpatient medical costs were analyzed using NHIS data. Uninsured medical costs were estimated by applying the rate of uninsured costs to the outpatient and inpatient costs. The rate of uninsured F00–F99 presented in the 2019 report was used because of a lack of data. Pharmacy costs for each disease were calculated by multiplying the pharmacy cost per claim by the number of cases calculated. The pharmacy cost per claim (F00–F99 from ICD-10 codes) was obtained from the 2019 Medical Aid Statistics.[25] Next, direct non-medical costs were calculated by defining transportation costs for hospital visits, as mentioned above. Finally, we summed the direct medical, pharmacy, and transportation costs and calculated the direct costs due to exposure to air pollution.[20]

$$AC_{ytotal} = AN_y \times Cost_{ytotal}$$

where $Cost_{ytotal}$ is the total direct cost per case in year y, AN_y the total attributable number due to exposure to air pollutants above the reference concentration in year y, and AC_{ytotal} is the attributable direct cost due to exposure to air pollutants in year y.

Additionally, all expenses were expressed in dollars ($) according to the exchange rate for each year (1$ = 1,152 KRW in 2011, 1$ = 1,071 KRW in 2012, 1$ = 1,055 KRW in 2013, 1$ = 1,099 KRW in 2014, 1$ = 1,173 KRW in 2015, 1$ = 1,208 KRW in 2016, 1$ = 1,071 KRW in 2017, 1$ = 1,116 KRW in 2018, and 1$ = 1,156 KRW in 2019).

All descriptive statistics were analyzed using SAS version 9.4 (SAS Institute, Cary, NC, USA). All time-series analyses were conducted using R '*mgcv*' package (version 1.8-40), and meta-analyses were conducted using R '*metafor*' package (version 3.8-1). Statistical significance was set at P value < 0.05.

Ethics statement
This study was reviewed and approved by the Institutional Review Board (IRB) of the Yonsei University Health System (IRB number: 4-2022-1199) and adhered to the tenets of the Declaration of Helsinki. The IRB waived the requirement for informed consent due to the retrospective nature of the study.

RESULTS

Descriptive statistics
The total number of outpatient and inpatient visits for major mental disorders (%) was 309,656 during the study period, and those for ADHD, ASD, and depressive disorders were 166,668 (53.8), 80,928 (26.1), and 62,060 (20.0), respectively (**Table 1**). When comparing

Table 1. Characteristics of oupatient and inpatient visits for major mental disorders among children and adolescents between 2011 and 2019 in Korea

Characteristics	No. of events (%)
Total	309,656
Attention deficit hyperactivity disorder	166,668 (53.8)
Autism spectrum disorders	80,928 (26.1)
Depressive disorder	62,060 (20.0)
Age group, yr	
0–4	16,136 (5.2)
5–9	100,295 (32.4)
10–14	116,877 (37.7)
15–19	76,348 (24.7)
Gender	
Men	230,446 (74.4)
Women	79,210 (25.6)

number of total events across regions, the highest counts were observed in Seoul, Busan and Gyeonggi-do, although the lowest counts were observed in Jeju (**Supplementary Fig. 1**). The daily mean (standard deviation) count for major mental disorders was 5.9 (8.2). Specifically, the daily mean counts of children with ADHD were higher than those of children with ASD and depressive disorders (ADHD: 3.2 vs. ASD: 1.5 vs. depressive disorder: 1.2). During the study period, daily average concentration levels of PM_{10}, $PM_{2.5}$, O_3, NO_2, SO_2, and CO were 44.5 μg/m^3 (24.2), 24.5 μg/m^3 (13.8), 0.028 ppm (0.012), 0.02 ppm (0.01) and 0.5 ppm (0.1), respectively. Also, daily average concentration levels of relative humidity and temperature were 66.8% and 13.5°C and (data were not shown). Annual average concentration levels of PM_{10}, and $PM_{2.5}$ decreased from 2011 to 2019 (data were not shown), and the maximum concentration level of PM_{10} and $PM_{2.5}$ was 626.4 μg/m^3 and 140.6 μg/m^3, respectively. These maximum levels were much higher than the WHO 2005 air quality standards (24 hour-average PM_{10}: 50 μg/m^3 and $PM_{2.5}$: 25 μg/m^3).

Risk ratios of healthcare utilization for major mental disorders

Fig. 1 shows the association between air pollutant exposure and visits to outpatient and inpatient for major mental disorders on different lag days. The risk ratios of PM_{10} and CO were statistically significant in cumulative lag 1 to cumulative lag 10 although that of $PM_{2.5}$ showed only a significant association in cumulative lag 2 and 3. The risk ratios of NO_2 increased in most lags and were highest at a cumulative lag of 14 days. However, the effect of O_3 was not significant on any cumulative day. Among the major mental disorders, ADHD and depressive disorders were positively associated with exposure to air pollutants and outpatient and inpatient visits, except for SO_2 and O_3 levels (**Table 2**). In the ASD group, $PM_{2.5}$ and O_3 were not significant. In the case of PM_{10} and NO_2, the risk ratio increased in all disorders, with depressive disorder being higher in PM_{10} and $PM_{2.5}$, and ASD being higher in NO_2, SO_2, and CO compared to other disorders. Also, we displayed the risk ratios for each regions in a forest plot in **Supplementary Figs. 2-4**. and depicted the risk ratios of air pollutants for each disorders according to the cumulative lag days in **Supplementary Figs. 5-7**. We performed sensitivity analysis with different degrees of freedom for time trend, temperature, and relative humidity in **Supplementary Table 1**.

In the subgroup analysis, the risk ratios of $PM_{2.5}$, SO_2, and CO had the largest effect at ages 10 and 14 (**Supplementary Table 2**). Also, the risk in all pollutants was greater in women than in men, while there was no difference between gender (**Supplementary Table 3**).

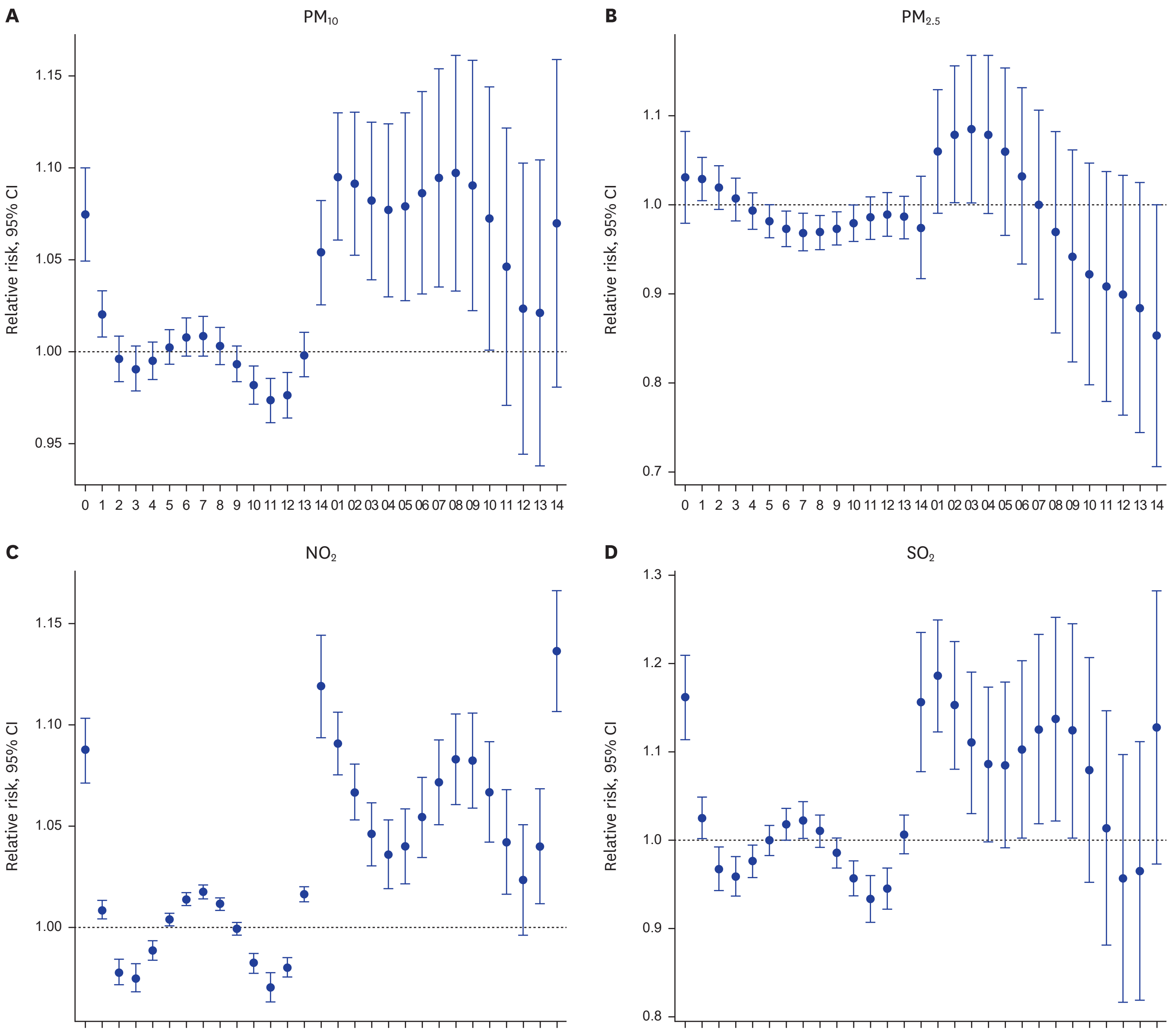

Fig. 1. Risk ratio (95% CI) of major mental disorders associated with air pollutants in different lag models. All models were adjusted for temperature, relative humidity, date, day of the week, holiday, and population of the region. (**A**) PM_{10} (per 10 μg/m³), (**B**) $PM_{2.5}$ (per 10 μg/m³), (**C**) NO_2 (per 1 ppb), (**D**) SO_2 (per 1 ppb), (**E**) O_3 (per 1 ppb), (**F**) CO (per 1 ppb).
CI = confidence interval, PM_{10} = particulate matter < 10 μm, $PM_{2.5}$ = particulate matter < 2.5 μm in aerodynamic diameter, NO_2 = nitrogen dioxide, SO_2 = sulfur dioxide, O_3 = ozone, CO = carbon monoxide.

(continued to the next page)

AN and PAF of outpatient and inpatient visits associated with major mental disorders due to exposure to air pollution

Table 3 presents the AN and PAF (%) based on the WHO air quality standards. During the study period, 21,366 cases were found to be caused by exposure to PM_{10}, accounting for approximately 6.9% of major mental disorders. Likewise, 7,453 counts (3.7%) were found to be caused by exposure to $PM_{2.5}$ during 5 years and 6,645 counts were found to be caused by exposure to SO_2 (2.2%). Regarding specific mental disorders, the PAF (%) of ADHD, ASD, and depressive disorder due to PM_{10} was 5.2% (95% CI, 1.2–12.7), 8.4% (2.4–30.5),

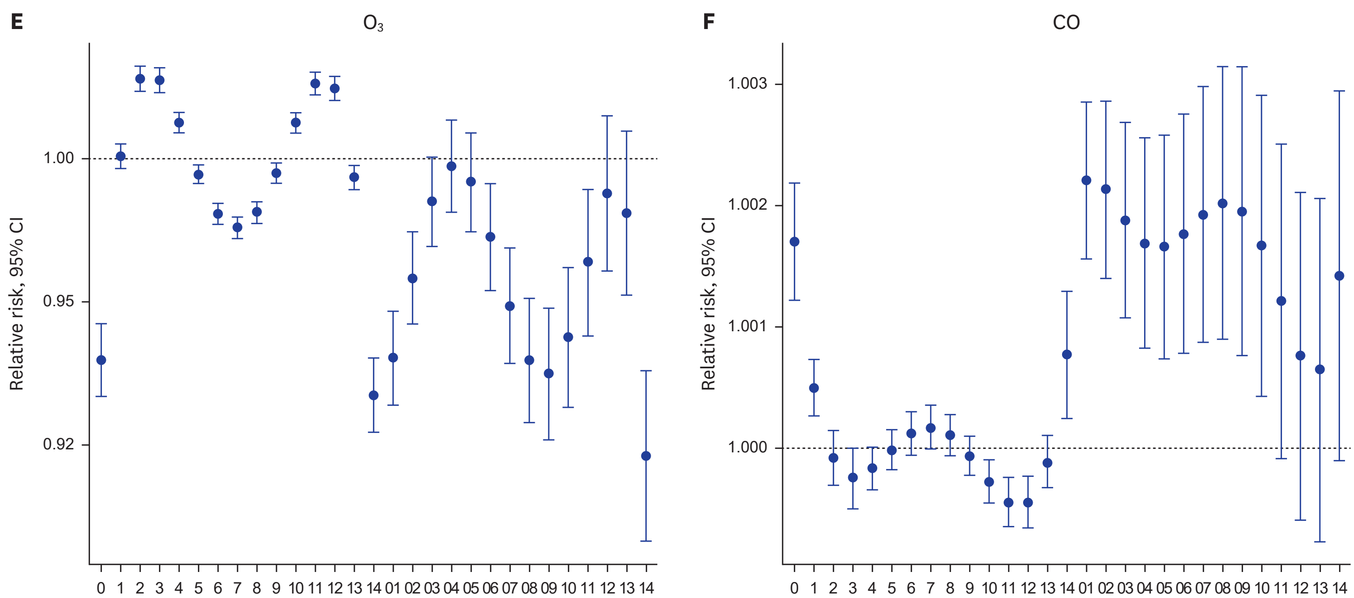

Fig. 1. (Continued) Risk ratio (95% CI) of major mental disorders associated with air pollutants in different lag models. All models were adjusted for temperature, relative humidity, date, day of the week, holiday, and population of the region. (**A**) PM_{10} (per 10 μg/m^3), (**B**) $PM_{2.5}$ (per 10 μg/m^3), (**C**) NO_2 (per 1 ppb), (**D**) SO_2 (per 1 ppb), (**E**) O3 (per 1 ppb), (**F**) CO (per 1 ppb).
CI = confidence interval; PM_{10} = particulate matter < 10 μm, $PM_{2.5}$ = particulate matter < 2.5 μm in aerodynamic diameter, NO_2 = nitrogen dioxide, SO_2 = sulfur dioxide, O_3 = ozone, CO = carbon monoxide.

Table 2. Association between exposure to air pollutants and outpatient and inpatient visits by specific mental disorders

Disorders	Risk ratio and 95% confidence interval		
	ADHD	ASD	Depressive disorder
PM_{10} at cumulative lag 3	1.067 (1.017–1.116)	1.094 (1.034–1.154)	1.099 (1.032–1.166)
$PM_{2.5}$ at cumulative lag 3	1.094 (1.000–1.188)	1.018 (0.889–1.147)	1.127 (1.002–1.253)
NO_2 at cumulative lag 3	1.036 (1.019–1.053)	1.066 (1.044–1.087)	1.046 (1.023–1.069)
SO_2 at cumulative lag 3	1.089 (0.997–1.180)	1.149 (1.037–1.261)	1.132 (0.996–1.267)
O_3 at cumulative lag 3	0.991 (0.976–1.006)	0.967 (0.950–0.984)	1.001 (0.981–1.020)
CO at cumulative lag 3	1.002 (1.001–1.003)	1.003 (1.002–1.004)	1.002 (1.000–1.003)

All models were adjusted to temperature, relative humidity, date, day of the week, holiday, and population of the regions.
PM_{10} = particulate matter < 10 μm, $PM_{2.5}$ = particulate matter < 2.5 μm in aerodynamic diameter, NO_2 = nitrogen dioxide, SO_2 = sulfur dioxide, O_3 = ozone, CO = carbon monoxide, ADHD = attention deficit hypertensive disorder, ASD = autism spectrum disorder.

Table 3. AN and PAF (%) of major mental disorders, and specific mental disorders associated with air pollution using WHO 2005 guideline, 2011–2019

Disorder	Air pollution	Reference concentration	AN (95% CI)	PAF (%), 95% CI
Total	PM_{10}	50 μg/m^3	21,366 (8,609–47,139)	6.9 (2.8–15.2)
	$PM_{2.5}$[a]	25 μg/m^3	7,453 (191–15,786)	3.7 (0.1–7.8)
	SO_2	20 μg/m^3 (7.63 ppb)	6,645 (1,567–13,930)	2.2 (0.5–4.5)
ADHD	PM_{10}	50 μg/m^3	8,686 (1,954–21,120)	5.2 (1.2–12.7)
	$PM_{2.5}$[a]	25 μg/m^3	4,471 (2–9,708)	4.0 (0.002–8.7)
	SO_2	20 μg/m^3 (7.63 ppb)	N/E	N/E
ASD	PM_{10}	50 μg/m^3	6,828 (1,902–24,712)	8.4 (2.4–30.5)
	$PM_{2.5}$[a]	25 μg/m^3	N/E	N/E
	SO_2	20 μg/m^3 (7.63 ppb)	2,550 (503–6,141)	3.2 (0.6–7.6)
Depressive disorder	PM_{10}	50 μg/m^3	5,731 (1,361–27,446)	9.2 (2.2–44.2)
	$PM_{2.5}$[a]	25 μg/m^3	2,320 (32–5,178)	5.1 (0.1–11.5)
	SO_2	20 μg/m^3 (7.63 ppb)	N/E	N/E

AN = attributable number, PAF = population attributable fraction, CI = confidence interval, ADHD = attention deficit hyperactivity disorder, ASD = autism spectrum disorder, PM_{10} = particulate matter < 10 μm, $PM_{2.5}$ = particulate matter < 2.5 μm in aerodynamic diameter, SO_2 = sulfur dioxide, N/E = non-estimable.
[a]For $PM_{2.5}$, AN and PAF were for 2015–2019.

https://doi.org/10.3346/jkms.2024.39.e218

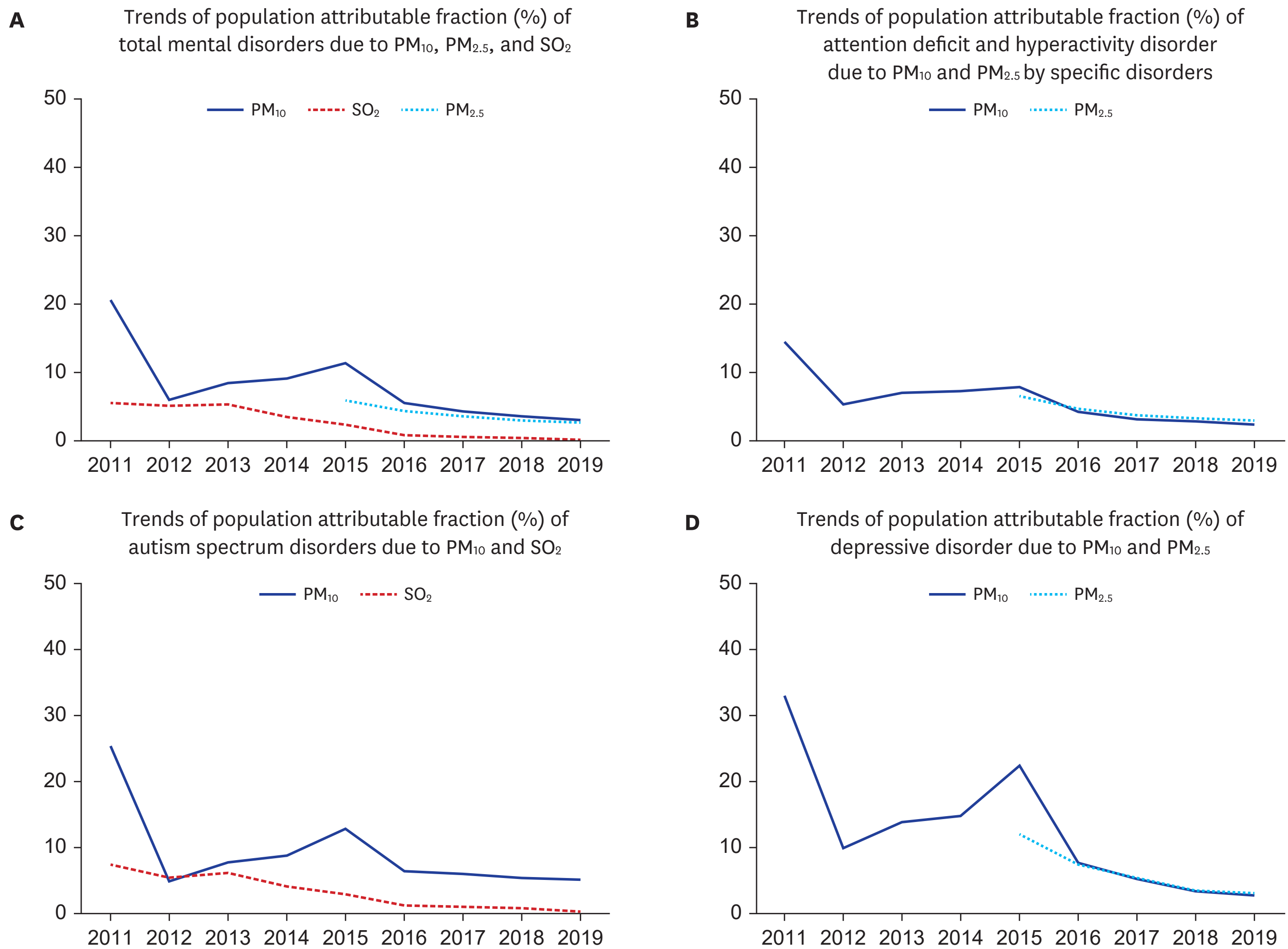

Fig. 2. Trends of population attributable fraction (%) of specific mental disorders due to PM_{10}, $PM_{2.5}$, and SO_2. (**A**) Trends of population attributable fraction (%) of total mental disorders due to PM_{10}, $PM_{2.5}$, and SO_2. (**B**) Trends of population attributable fraction (%) of attention deficit and hyperactivity disorder due to PM_{10} and $PM_{2.5}$ by specific disorders. (**C**) Trends of population attributable fraction (%) of autism spectrum disorders due to PM_{10} and SO_2. (**D**) Trends of population attributable fraction (%) of depressive desorder due to PM_{10} and $PM_{2.5}$.
PM_{10} = particulate matter < 10 µm, $PM_{2.5}$ = particulate matter < 2.5 µm in aerodynamic diameter, SO_2 = sulfur dioxide.

and 9.2% (2.2–44.2), respectively. In the case of $PM_{2.5}$, the PAF of ADHD and depressive disorder was 4.0% (95% CI, 0.002–8.7) and 5.1% (0.1–11.5) over 5 years. Additionally, for SO_2, it was estimated at approximately 3.2% (0.6–7.6) in ASD. The AN and PAFs of total mental disorders and specific disorders due to PM_{10} and $PM_{2.5}$ increased, while those of SO_2 decreased (**Supplementary Table 4**). Also, applying WHO 2021 guidelines, NO_2 resulted in PAFs of approximately 28% for total major mental disorders and 20% for ADHD, respectively. **Fig. 2** shows the PAF (%) during the study period. The PAF applying 2005 WHO standards decreased from 20.5%, 5.9%, and 5.5% in 2011 and 2015 to 3.0%, 2.7%, and 0.2% in 2019 for PM_{10}, $PM_{2.5}$, and SO_2, respectively.

Direct medical costs and non-medical costs of visits to outpatient and inpatient for mental disorders and the associated costs attributable to air pollutants

Among the three major mental disorders, the total direct medical cost and non-medical cost of outpatient and inpatient visits was the highest for ADHD from 2011 to 2019. In the case of ADHD and depressive disorder, there was an increasing trend (**Supplementary Fig. 8A**).

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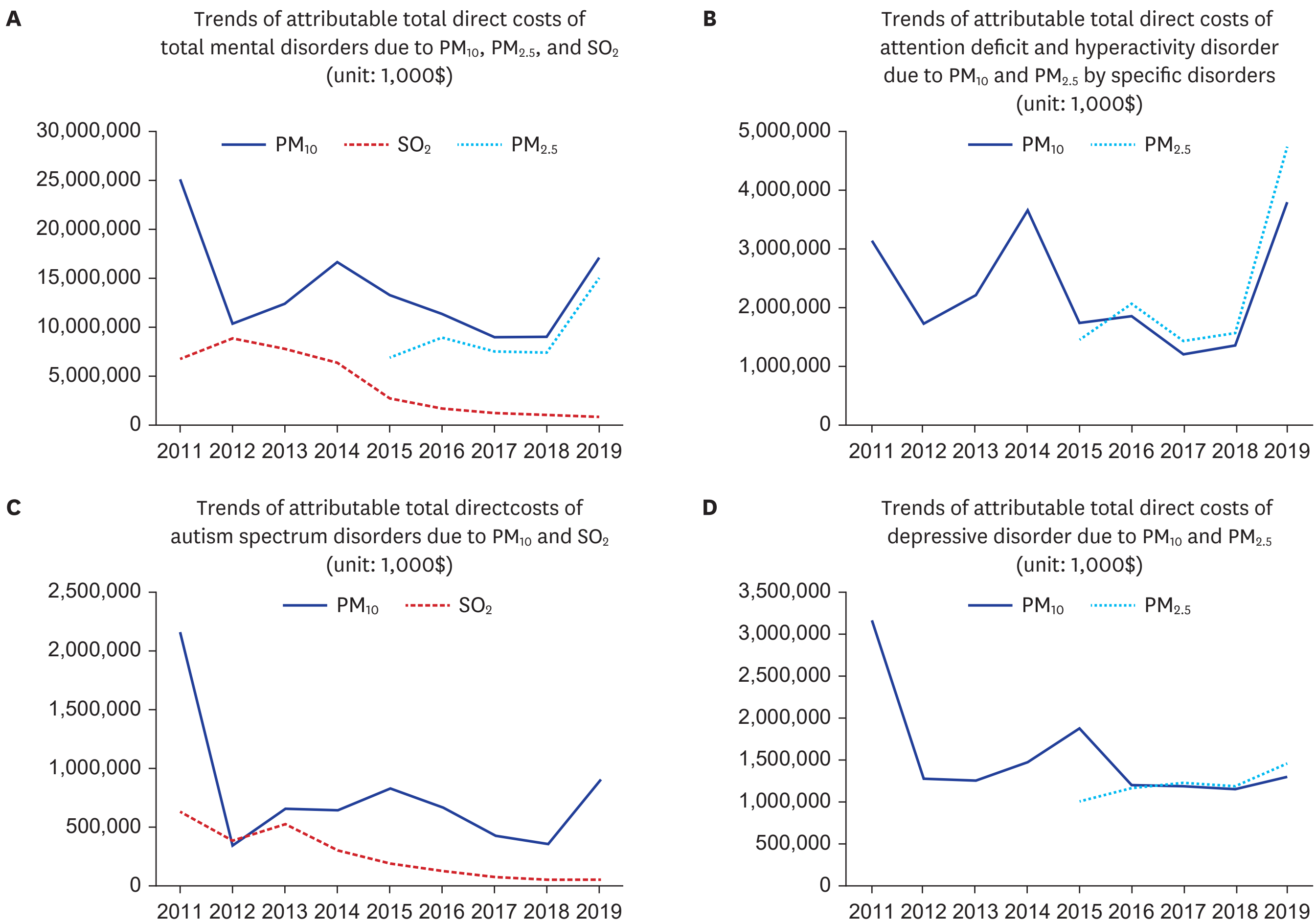

Fig. 3. Trends of attributable costs of specific mental disorders due to PM_{10}, $PM_{2.5}$, and SO_2. (**A**) Trends of attributable total direct costs of total mental disorders due to PM_{10}, $PM_{2.5}$, and SO_2 (unit: 1,000$). (**B**) Trends of attributable total direct costs of attention deficit and hyperactivity disorder due to PM_{10} and $PM_{2.5}$ by specific disorders (unit: 1,000$). (**C**) Trends of attributable total direct costs of autism spectrum disorders due to PM_{10} and SO_2 (unit: 1,000$). (**D**) Trends of attributable total direct costs of depressive disorder due to PM_{10} and $PM_{2.5}$ (unit: 1,000$).
PM_{10} = particulate matter < 10 μm, $PM_{2.5}$ = particulate matter < 2.5 μm in aerodynamic diameter, SO_2 = sulfur dioxide.

On the other hand, in ASD, there was a slight decrease. Similarly, total outpatient costs were higher for ADHD compared to the other two disorders (**Supplementary Fig. 8B**). The total costs attributable (AC_{total}) to PM_{10} for major mental disorders were the highest among all pollutants, although they fluctuated (**Fig. 3**). For $PM_{2.5}$, the total attributable costs increased gradually, whereas the total costs attributable to PM_{10} and SO_2 decreased. For ADHD, the total costs attributable to PM_{10} and $PM_{2.5}$ gradually increased, and the total costs attributable to $PM_{2.5}$, were greater than those of PM_{10} in 2019 (PM_{10}: $3,796,540 vs. $PM_{2.5}$: $4,740,357). In depressive disorders, costs gradually increased for $PM_{2.5}$ although costs attributable to PM_{10} and SO_2 in patients with ASD decreased.

DISCUSSION

Using nationwide air quality and healthcare utilization data from 2011 to 2019 in the Republic of Korea, this study assessed the burden of major mental disorders attributable to exposure to air pollution among children and adolescents. We estimated the PAF of major mental

https://doi.org/10.3346/jkms.2024.39.e218

disorders associated with air pollution exposures (6.9% for PM_{10}, 3.7% for $PM_{2.5}$, and 2.2% for SO_2). The PAF associated with PM_{10} was the highest for depressive disorder, followed by ADHD. Using these estimates, we quantified the direct medical costs attributable to air pollution exposure for major mental disorders. Mounting evidence suggests increased risks of mental disorders related to long-term exposure to PM.[26-28] Furthermore, some studies reported mental disorders due to short-term exposure to air pollutants,[29-31] and estimated the burden.[12-15] However, previous studies only investigated the burden of inpatient visits for mental disorders associated with air pollution exposure among all age groups or specifically for adults. Therefore, our study estimated the burden for children and adolescents including both outpatient and inpatient visits for the first time.

A multi-city study from China evaluated inpatient visits for any mental disorder associated with short-term exposure to PM_{10} and $PM_{2.5}$.[19] The attributable fractions of any mental disorder associated with PM_{10} and $PM_{2.5}$, were 9% and 10%, respectively, using WHO's 2005 air quality guidelines, and those of depressive disorder associated with $PM_{2.5}$ were 12%. Another study reported that attributable costs of $PM_{2.5}$ accounted for about 16% of overall inpatient visits costs for mental disorders.[12] Using WHO's guideline, other study also showed that the attributable fraction of any mental disorders associated with SO_2 was 0.3% and that of depressive disorder associated with SO_2 was 0.5%.[13] In another study evaluating all mental disorders with inpatient visits, the relative risks per 10 $\mu g/m^3$ increase in PM_{10} and $PM_{2.5}$ were 1.01 and 1.02, respectively. When applying the 2021 WHO guideline, the attributable fractions were 2.4% and 4.5%, respectively.[32] Although it could not be directly compared with previous studies that evaluated inpatient visits including all ages, our study including children and adolescents exhibited lower estimates associated with PM. We found that PM_{10} and $PM_{2.5}$ attributed 7% and 4%, respectively, to the risk of major mental disorders among children and adolescents. Also, the PAF of depressive disorder associated with PM_{10} and $PM_{2.5}$ were 9% and 5%, respectively, which was lower compared to that of previous study. Notably, the PAF of major mental disorders associated with PM_{10} was higher than that associated with $PM_{2.5}$ Another study showed that the attributable fraction of mental disorders associated with $PM_{2.5}$ (0.2%) was two-times higher than that of PM_{10} (0.1%).[14] This discrepancy may be due to differences in geographical characteristics and constituents of PM. In addition, our study estimated the PAF using time-series data, which is in line with previous studies.

It should be noted that the AN of air pollution exposure decreased during the 9-year study period except $PM_{2.5}$, and the contribution of air pollution exposure to the medical costs of major mental disorders decreased in this study. The AN decreased from 4,328 and 1,164 in 2011 and 1,581 and 77 in 2019 for PM_{10} and SO_2, respectively. The AN associated with $PM_{2.5}$, also relatively constant from 1,779 in 2015 to 1,388 in 2019. This decreasing trend in the AN may be due to the improvement in air quality over the study period in the Republic of Korea. We observed declines in the annual average concentrations of PM_{10}, $PM_{2.5}$, and SO_2 and the number of days with air quality that did not meet the WHO guidelines. Accordingly, we showed that the medical costs of mental disorders attributable to PM_{10} and SO_2 decreased during the study period. The attributable medical costs decreased from $25,112,016 and $6,754,015 in 2011 to $17,124,166 and $839,496 in 2019 for PM_{10} and SO_2, respectively. Nonetheless, we showed that the medical costs of mental disorders attributable to $PM_{2.5}$ exposure increased during the study period. This trend may be consistent with the constant AN of mental disorders in children and adolescents. Stricter management of air quality may contribute to reducing AN and the attributable medical costs for major mental disorders in children and adolescents.

 https://doi.org/10.3346/jkms.2024.39.e218

Exposure to air pollution may increase the risk of ADHD, ASD, and depressive disorders via several biological pathways. In ADHD, PM exposure may promote the secretion of inflammatory molecules such as inteleukin-1, inteleukin-6, and tumor necrosis factor-α in the lungs.[33-37] These increased levels of inflammatory molecules enter the circulation, leading to systemic inflammation. Circulating cytokines and inflammatory molecules can damage the blood-brain barrier and indirectly induce neuroinflammation. These processes may increase the risk of ADHD. In ASD, similar to ADHD, PM exposure was reported to contribute to the development of ASD not only through the secretion of inflammatory molecules, the increased oxidative stress, the cause of neuroinflammation but also through microglial activation.[38,39] In depressive disorder, exposure to $PM_{2.5}$ may be involved in the secretion of inflammatory cytokines, and activation of the hypothalamic-pituitary-adrenal-axis.[40,41]

This study has some limitations. First, there is the possibility of misclassifying exposure when using measured monitoring data as a proxy for exposure to air pollution. Contrary to the classical error, which makes the point estimate to shift towards null, Berkson type error does not shift the point estimate but makes the 95% CI wider. In the present study, both errors occur. Classical error occurs when the study participants move to other place than the monitored place, which is possible in the present setting. Berkson error occurs when the assigned exposure is different from the actual exposure (i.e., when the large area is covered with single monitoring station, or the averaging unit is large). Second, we did not take into account the non-medical costs of mental disorders (e.g., special education costs). This approach may have underestimated the economic burden of mental health disorders in children and adolescents. Few studies have assessed costs such as cognitive behavioral therapy and learning therapy, which may also occur due to ADHD and ASD. These additional costs have also been found in recent studies.[42] As a result of examining households of ASD and non-ASD patients, education costs are significantly higher in patients with ASD than in non-ASD patients. However, only direct medical costs were calculated in this study. Third, caregiver costs were not considered. Previous studies have shown that children and adolescents with mental disorders may incur additional costs in addition to medical expenses. Hong et al.[43] examined direct medical costs and direct non-medical costs for ADHD in 2012. This study showed that the caregiver's costs accounted for more than 80% of the direct non-medical expenses ($US 9,091,483 in 2012). Fourth, we could not calculate productivity loss due to the lack of sufficient survey data.

In summary, this study assessed the burden of major mental disorders attributable to air pollution exposure among children and adolescents. We found that PM_{10} and $PM_{2.5}$ attributed 7% and 4%, respectively, to the risk of major mental disorders among children and adolescents. Our study adds to evidence highlighting the importance of lowering air quality standards to curb the burden of mental disorders associated with air pollution exposure.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Association between exposure to air pollutants and outpatient and inpatient visits on cumulative lag 3 day in sensitivity analyses

Supplementary Table 2

Association between exposure to air pollutants and medical institutions visits by age group

 https://doi.org/10.3346/jkms.2024.39.e218

Supplementary Table 3

Association between exposure to air pollutants and medical institutions visits by gender

Supplementary Table 4

AN and PAF (%) of major mental disorders, and specific mental disorders associated with air pollution using 2021 air quality guideline, 2011–2019

Supplementary Fig. 1

Number of total events by regions.

Supplementary Fig. 2

Risk ratio in outpatient and inpatient visits with air pollutants in ADHD by regions. (**A**) Risk ratio in outpatient and inpatient visits with PM_{10} in ADHD by regions. (**B**) Risk ratio in outpatient and inpatient visits with $PM_{2.5}$ in ADHD by regions. (**C**) Risk ratio in outpatient and inpatient visits with NO_2 in ADHD by regions. (**D**) Risk ratio in outpatient and inpatient visits with SO_2 in ADHD by regions. (**E**) Risk ratio in outpatient and inpatient visits with O_3 in ADHD by regions. (**F**) Risk ratio in outpatient and inpatient visits with CO in ADHD by regions.

Supplementary Fig. 3

Risk ratio in outpatient and inpatient visits with air pollutants in ASD by regions. (**A**) Risk ratio in outpatient and inpatient visits with PM_{10} in ASD by regions. (**B**) Risk ratio in outpatient and inpatient visits with $PM_{2.5}$ in ASD by regions. (**C**) Risk ratio in outpatient and inpatient visits with NO_2 in ASD by regions. (**D**) Risk ratio in outpatient and inpatient visits with SO_2 in ASD by regions. (**E**) Risk ratio in outpatient and inpatient visits with O_3 in ASD by regions. (**F**) Risk ratio in outpatient and inpatient visits with CO in ASD by regions.

Supplementary Fig. 4

Risk ratio in outpatient and inpatient visits with air pollutants in depressive disorder by regions. (**A**) Risk ratio in outpatient and inpatient visits with PM_{10} in depressive disorder by regions. (**B**) Risk ratio in outpatient and inpatient visits with $PM_{2.5}$ in depressive disorder by regions. (**C**) Risk ratio in outpatient and inpatient visits with NO_2 in depressive disorder by regions. (**D**) Risk ratio in outpatient and inpatient visits with SO_2 in depressive disorder by regions. (**E**) Risk ratio in outpatient and inpatient visits with O_3 in depressive disorder by regions. (**F**) Risk ratio in outpatient and inpatient visits with CO in depressive disorder by regions.

Supplementary Fig. 5

Risk ratio in outpatient and inpatient visits with air pollutants along different cumulative lag days in ADHD. (**A**) Risk ratio in outpatient and inpatient visits with PM_{10} along different cumulative lag days in ADHD. (**B**) Risk ratio in outpatient and inpatient visits with $PM_{2.5}$ along different cumulative lag days in ADHD. (**C**) Risk ratio in outpatient and inpatient visits with NO_2 along different cumulative lag days in ADHD. (**D**) Risk ratio in outpatient and inpatient visits with SO_2 along different cumulative lag days in ADHD. (**E**) Risk ratio in outpatient and inpatient visits with O_3 along different cumulative lag days in ADHD. (**F**) Risk ratio in outpatient and inpatient visits with CO along different cumulative lag days in ADHD.

Supplementary Fig. 6

Risk ratio in outpatient and inpatient visits with air pollutants along different cumulative lag days in ASD. (**A**) Risk ratio in oupatient and inpatient visits with PM_{10} along different cumulative lag days in ASD. (**B**) Risk ratio in oupatient and inpatient visits with $PM_{2.5}$ along different cumulative lag days in ASD. (**C**) Risk ratio in oupatient and inpatient visits with NO_2 along different cumulative lag days in ASD. (**D**) Risk ratio in oupatient and inpatient visits with SO_2 along different cumulative lag days in ASD. (**E**) Risk ratio in oupatient and inpatient visits with O_3 along different cumulative lag days in ASD. (**F**) Risk ratio in oupatient and inpatient visits with CO along different cumulative lag days in ASD.

Supplementary Fig. 7

Risk ratio in outpatient and inpatient visits with air pollutants along different cumulative lag days in depressive disorder. (**A**) Risk ratio in outpatient and inpatient visits with PM_{10} along different cumulative lag days in depressive disorder. (**B**) Risk ratio in outpatient and inpatient visits with $PM_{2.5}$ along different cumulative lag days in depressive disorder. (**C**) Risk ratio in outpatient and inpatient visits with NO_2 along different cumulative lag days in depressive disorder. (**D**) Risk ratio in outpatient and inpatient visits with SO_2 along different cumulative lag days in depressive disorder. (**E**) Risk ratio in outpatient and inpatient visits with O_3 along different cumulative lag days in depressive disorder. (**F**) Risk ratio in outpatient and inpatient visits with CO along different cumulative lag days in depressive disorder.

Supplementary Fig. 8

Trends of total, outpatient, and inpatient costs by specific disorders. (**A**) Trends of total direct costs by specific disorders (unit: $). (**B**) Trends of total outpatient costs by specific disorders (unit: $). (**C**) Trends of total inpatient costs by specific disorders (unit: $).

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