Air pollutants and attention deficit hyperactivity disorder medication administration in elementary schools

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Abstract. Air pollution is considered a risk factor for several diseases, particularly respiratory and cardiovascular diseases. However, the effects of air pollution on neurobehavioral disorders have not been confirmed as of yet. Thus, the aim of this study was to determine whether there was an association between seven air pollutants and ADHD medication administration (ADHD-MA) in Pennsylvania-located elementary schools over a 3-year period. An ecological study design involving records of 168,825 children from elementary schools in 49 Pennsylvania counties was used. The number of children with ADHD-MA was extracted from an online software specifically designed for allowing nurses to record health conditions in schools. Daily measurements of air pollutants were obtained from the U.S Environmental Protection Agency. The differences in the number of ADHD-MA among the four seasons, for all years, were statistically significant ($P<0.001$). Three air pollutants (SO_2, CO, and PM2.5) were significantly associated with ADHD-MA; no interactions among air pollutants were significant. Air pollution was thus likely associated with ADHD-MA. Prospective epidemiological and biomedical studies should next examine the molecular relationship between air pollution and ADHD symptoms.

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Introduction

Attention Deficit Disorder with Hyperactivity, also known as Attention Deficit Hyperactivity Disorder (ADHD), is a developmental, neuropsychiatric manifestation of inattention, hyperactivity, and impulsivity presenting in most affected children (1). ADHD is the most commonly diagnosed neurobehavioral childhood disorder, and its prevalence reaches 8-12% worldwide (2). In the U.S., 9.4% (6.1 million) children aged 2-17 years have at some point been diagnosed with ADHD, and 89.4% of these (5.4 million) currently have ADHD. Furthermore, 62.0% of children with ADHD are taking ADHD medication, and 46.7% have received behavioral treatment; 23.0% have not received any treatment. Thus, 5.2% of all U.S. children are taking ADHD medication (3).

The magnitude of symptoms in individuals with ADHD varies substantially, ranging from mild to severe. Despite this variation, diagnosis relies primarily on a child's inability to focus and their activity levels (4). A definitive ADHD diagnosis is only confirmed when primary symptoms are persistent and/or accompanied by additional symptoms (5). The persistence of ADHD into adolescence and adulthood is not uncommon (4). The altered behavior of children with ADHD distinguishes them from normal, similarly aged children. Those with ADHD tend to become distracted easily, move continuously, dream during the day, not accomplish tasks at school or in the community, and have lower educational achievement. When older, they may engage in risky behaviors, including substance abuse and delinquency. Moreover, other conditions such as conduct disorder, anxiety, depression, oppositional defiant disorder, and obsessive disorder can accompany ADHD (1,5-7).

ADHD is hypothesized to have hereditary origins; however, numerous studies have identified several environmental variables as risk factors or contributors (8), including food additives, lead contamination, cigarette and alcohol exposure, and maternal smoking during pregnancy (9). Another important

environmental risk factor hypothesized and explored in several recent studies is air pollution (10-16). Due to increasing human activity, enormous amounts of pollutants are being emitted into the atmosphere with industrial discharges and automobile emissions constituting the primary main sources (17-19). Indoor air can also be polluted by sources such as second-hand smoke, mold, and cleaning product vapors (20). Air pollution exposure is linked to several childhood health problems including neurodevelopmental effects. For example, cognitive functions are adversely affected amongst children in New York City prenatally exposed to Polycyclic Aromatic Hydrocarbons (PAH). These children exhibited lower IQ scores at the age of 5 compared with children with lower levels of PAH exposure (21). Investigations of the same children through to age 8 identified additional neurobehavioral changes; higher levels of anxiety and depression from the age of 4.8 years upwards, and higher levels of attention problems at 4.8 and 7 years old (22).

Furthermore, several studies have found an association between ADHD in children and air pollution from outdoor sources, such as traffic air pollution (23), total PAHs and benzo[a]pyrene exposure, and basal ganglia functioning as well as ADHD symptoms in primary school children (11). Both pre- and postnatal exposure to particulate matter with a diameter of <10 μm (PM_{10}), current exposure to nitrogen dioxide (NO_2), and decreased Normalized Difference Vegetation Index were associated with a higher relative risk of ADHD incidence (6,13,14).

Two concerns emerged from the limited literature regarding the effects of air pollution on ADHD among children: i) The effect of some chemicals present in adulterated air on ADHD incidence has not been investigated, and ii) the relationship between air pollution and ADHD symptoms remains largely unexplored. Therefore, the research question of this ecological study was: 'Does an association exist between seven selected air pollutants and school-time ADHD medication administration, used as a proxy for ADHD symptoms, among elementary school children'.

Materials and methods

Study population. For this study, electronic health record (EHR) data from 168,825 students attending elementary schools in 42 of 67 Pennsylvania counties, excluding Philadelphia and the surrounding counties, were analyzed. Data were extracted from an EHR embedded in 'Health eTools for Schools' (hereafter referred to as eTools), a web-based information system, used in over 1,100 Pre-K-12 Pennsylvania schools (24). Annual fluctuations in school involvement created somewhat inconsistent participation rates (25-27).

Via online access to eTools, school nurses made daily EHR entries for all students who were administered at least one medication. From these entries, daily numbers of students administered an ADHD medication were calculated for every school over 3 consecutive years, 2008-2010. Incomplete records for which medication entry could not be identified were excluded. ADHD-MA could not be recorded if a child for whom ADHD medications were prescribed was absent from school on a given day or if medication was accessed outside of school. Similarly, children with undiagnosed ADHD or misdiagnosis, and who therefore were not prescribed ADHD medication, were not included in the study population. Records only included student sex and age; race or socioeconomic status data were unavailable at the individual level. Since school attendance is compulsory, Pennsylvania public schools are open to all children regardless of race, ethnicity, family income, sex, or religion, and several parochial schools participated in eTools, thus data were assumed to be representative of Pennsylvania elementary school students diagnosed with ADHD (28).

Study design. This study used an ecological design, involving daily cross-sectional measurements of seven air pollutants and daily ADHD-MA data from an EHR system. This design provides a gross image of the relationship between variables of interest and responses at a population level, analyzing groups' responses rather than individual responses, thus eliminating inter-individual variability. Analysis of variables and responses at a group level reflect the association of two or more factors related to a population living in a geographical area. Ecological relations are global indicators usually used to establish hypotheses for causality to be tested by further research. Initial assumptions derived from ecological studies are further tested through additional cohort epidemiological and biomedical studies. Follow-up investigation helps revise hypotheses from previous studies. Group-level analysis is assumed to be representative of the whole population; in this case, elementary school children living within a state. Almost 170,000 elementary students with EHR lived within the Commonwealth of Pennsylvania.

Data collection. As previously indicated, data from daily EHR entries by school nurses were accessed and summed to establish the total daily number of children receiving ADHD medication during 2008, 2009, and 2010, excluding school breaks and holidays. Typically, data were unavailable for summer breaks that generally encompassed the first week of June through the third week of August. Data were also not available for four school breaks, i.e., fall, Thanksgiving, winter, and spring.

Records for seven air pollutants, NO_2, NOx, SO_2, CO, O_3, $PM_{2.5}$, and PM_{10} were obtained from the United States Environmental Protection Agency (USEPA) website (29). Records originated from 48 EPA monitoring stations across Pennsylvania. Daily and hourly readings for all air pollutants were available; however, only data from regular school days were analyzed. Additionally, only records spanning 1 am-3 pm were included as these covered mornings before school started onward throughout the school day. Data for PM_{10} were unavailable from 1 am-3 am, and 1 pm-3 pm. SO_2 and NO_2 units of measurements were parts per billion (ppb), CO, O_3, and NOx were parts per million (ppm), and, for $PM_{2.5}$ and PM_{10}, μg per cubic meter ($\mu g/m^{-3}$).

Statistical analysis. A Poisson repeated measure procedure was used to analyze 3 years of exposure for each air pollutant, assuming measures were correlated. In general, regression analysis methods of this type have long been used to link air pollution and health outcomes, as variables such as weather changes, seasonal variations, metrological factors, and other confounders can be accounted for in the analysis (9,12,21,30-33). Long-term trends and predicting models

can be developed, while controlling for confounders, to estimate the magnitude of effect in the short- and long-term (30).

Poisson repeated measure analysis uses generalized equation estimate (GEE) for repeated measures. GEE is advantageous for analyzing correlated measures even if normality cannot be assumed; a correct specification of the correlation matrix is not required to have a consistent estimator of the regression parameters. Having the predicted correlation matrix closer to the true correlation is preferred to achieve greater statistical accuracy for the regression parameter (34). For this study, the assumption of normality was accepted for correlations among measures. Repeated measures were taken for the same day over the study period, and each day measure was represented by its mean. A one-way ANOVA was used for differences in the number of ADHD-MA numbers amongst the different seasons. SPSS version 23 (IBM Corp) was used for all analyses. $P<0.05$ was considered to indicate a statistically significant difference.

Results

EHR entry records indicated equal student distribution based on sex, with 75% of individuals included racially white. Based on school-level data regarding the percentage of students in each school eligible for free or reduced-price lunch and school zip code, one in four students were considered low Socio-Economic Status (SES), and most lived in urban and suburban areas of high population densities (Table I) (35).

Accounting for 42% of visits, ADHD-MA was the most common reason for students to visit the school nurse. There was a difference in ADHD-MA rates amongst the seasons over the 3-year period; apart from summer break months (June-August), ADHD-MA events generally increased from January to December each year. For 2008, 2009, and 2010, the lowest events were observed in January (n=124), January (n=281), and February (n=419), respectively, whereas the highest events were reported in December (n=276), December (n=431), and May (n=519), respectively. Differences in ADHD-MA visit rates amongst the seasons were also statistically significant ($P<0.001$); post-hoc multiple comparison analysis found statistically significant differences between all seasons, except for spring and winter. Means by season, excluding summer, for all years revealed that fall had the highest ADHD-MA rate with 367.81±96.783 events, followed by 319.65±153.548 in spring, and 297.17±144.635 in winter.

The levels of O_3, SO_2, CO, NO_2, NOx, $PM_{2.5}$, and PM_{10}, varied across seasons (Table II). Summer had the lowest concentrations of SO_2, CO, NO_2, and NOx over the 3-years. Air pollutants, except for O_3 and PM_{10}, were highest in winter.

Poisson regression showed significant associations between SO_2, CO, and $PM_{2.5}$ concentrations and ADHD-MA (Table III). The association was strongest for CO, which was positively associated with ADHD-MA with a factor of 2 [95% CI, 0.303-3.75, P=0.021], followed by SO_2, which was negatively associated with ADHD-MA [B=-0.092, 95% CI, -0.160- -0.024, P=0.008]. $PM_{2.5}$ associations were the weakest; a positive factor of 0.007 [95% CI, 0.011-11.91, P=0.001]. Conversely, O_3, PM_{10}, NO_2, and NOx were not statistically significantly associated with ADHD-MA. Further, the interaction effect among the seven air pollutants was also not statistically significant (B=$7.5835x10^{-10}$; 95% CI, $-5.0063x10^{-9}$-$6.523x10^{-9}$; P=0.797).

Table I. Demographic characteristics of students at schools enrolled in the eTools system.

Demographic variable	Percentage (%)
Sex[a]	
Male	50.8
Female	49.2
Race[b]	
White	74.78
African American	8.3
Hispanic	7.91
Asian	1.41
American Indian and Alaska native	0.2
Native Hawaiian and other pacific islanders	0.3
Other	3.1
Multi-race	4.27
Socio-economic Status[b]	
Free or reduced-price lunch eligible students	38.36
Free or reduced-price lunch ineligible students	61.64
Urban Rural Distribution[b]	
Rural school students	39.22
Suburban school students	42.65
Urban school students	18.13

[a]Highmark Foundation eTools Schools-Demographic Characteristics (Dataset). In: InnerLink I, ed. Lancaster, PA: eTools, 2011. [b]National Center for Education Statistics, Institute of Education Sciences. School District Demographic System-Map Viewer. 2012. Available at: http://nces.ed.gov/surveys/sdds/ed/index.asp?st¼PA.

Discussion

Based on the aggregate data, the results showed the cyclical changes in ADHD-MA, reflected by seasonal changes in ADHD-MA rates and increased levels of certain upper air pollutants compared with others. Although receiving medication is not necessarily restricted to school grounds, there is considerable administration of ADHD medicines at schools. The noticeable administration of medications on school grounds could be attributed to the strict laws of Pennsylvania which mandate drug-free school zones and full control of school administration and authorities over any medication administration or use (36).

Weekly measurements for air pollutants provided a credible prediction for the number of ADHD-MA-related student/school nurse visits. Interestingly, significant predictors of ADHD-MA visits had a positive estimate (B) value, except for SO_2, which indicated an inverse relationship. Therefore, no clear explanation of the link between ADHD-MA with air

Table II. Means of the upper air indicators and pollutants in all four seasons over a 3-year period.

Season	Statistic	O_3, ppm	SO_2, ppb	CO, ppm	NO_2, ppb	NOx, ppm	$PM_{2.5}$, $\mu g/m^3$	PM_{10}, $\mu g/m^3$
Winter	Mean	9.51	6.28	0.32	15.42	23.95	14.82	19.74
	SD	4.59	2.35	0.10	5.43	13.22	8.40	10.02
Spring	Mean	29.58	3.97	0.24	10.94	14.70	11.88	21.07
	SD	8.97	1.25	0.05	3.28	6.26	4.70	9.93
Summer	Mean	25.87	3.01	0.20	9.72	13.16	12.01	22.55
	SD	7.21	1.09	0.05	2.20	3.91	6.02	10.88
Fall	Mean	14.06	3.69	0.22	12.00	19.80	10.61	17.96
	SD	6.65	1.36	0.09	4.07	11.11	5.30	9.64

ppm, parts per million; ppb, parts per billion.

Table III. Significant predictors used to estimate ADHD medication administrations in GEE poison regression modeling.

Parameter	Estimate	Standard error	Wald 95% confidence limits		P-value
CO, ppm	2.02	0.8783	0.303	3.75	0.021[a]
SO_2, ppb	-0.092	0.0347	-0.160	-0.024	0.008[b]
$PM_{2.5}$, $\mu g/m^3$	0.007	0.0021	0.003	0.011	0.001[c]
O_3	-0.002	0.0015	-0.005	0.0005	0.100
NO_2	-0.010	0.0124	-0.034	0.015	0.440
NOx	-0.005	0.0076	-0.020	0.010	0.516
PM_{10}	-4.585×10^{-5}	0.0076	-0.015	0.015	0.995

[a]P<0.05, [b]P<0.01, [c]P<0.001. ppm, parts per million; ppb, parts per billion.

pollution was found, except for seasonal fluctuations. This is contradictory to a study by Yorifuji *et al* (2017) that found a positive association between SO_2 and unfavorable behavioral problems related to attention (12). However, the association reported by Yorifuji *et al* was for prenatal rather than postnatal exposures. Moreover, only $PM_{2.5}$, but not PM_{10}, for upper air pollutants measured, was significantly associated with ADHD-MA in the current study. The relationship between PM_{10} and ADHD is not consistent across studies. While some studies have found a positive and even strong association between PM_{10} with ADHD (6,10), other studies concluded insignificant or inconsistent associations (33,37). Nevertheless, upper air pollutants that were positively associated with ADHD-MA visit rates (i.e., CO and $PM_{2.5}$) are well known for their adverse health effects, including ADHD (14,19,38).

Upper air pollutants used in the model to predict ADHD-MA were similarly used in other studies to predict the prevalence or incidence of ADHD (13-16). In addition, pollutants that were found to be significantly associated with ADHD-MA in the current study, were likewise significantly associated with ADHD in other studies. For example, the positive association of ADHD with $PM_{2.5}$ was reported by Newman *et al* (23) and Fuertes *et al* (33). Moreover, a study by Markevych *et al* (13) and another by Min and Min (10) found that higher levels of NO_2 were associated with higher relative ADHD risk. Furthermore, prenatal exposure to air pollutants, including PM, NO_2, and SO_2, during gestation was associated with a higher risk of behavioral problems related to attention and delinquency or aggressive behavior in Japanese children (12). Nevertheless, other studies found no association of ADHD with traffic-related air pollution (32,37). Traffic-related air pollution includes the six criterion air pollutants stated by the USEPA, which includes the Ozone, Particulate Matter, Carbon Monoxide, Lead, Sulfur Dioxide, and Nitrogen Dioxide (39). The six criterion air pollutants were all included in the analysis of this study, except for lead.

Whether the association between upper-air pollution and ADHD is considered valid or not, other factors, such as epigenetics, inevitably play a role in ADHD etiology. For instance, interactions of genes with environmental stressors are known to predispose the occurrence of ADHD in children. Studies supported the contention that genetic factors can intervene and moderate the relationship between environmental stressors and behavioral deficit outcomes (14,40,41). Other factors related to ADHD include SES and the familial environment (13,14,42-45). Such factors vary among regions and communities in Pennsylvania, making the cause-effect relationship between air pollution and ADHD more complex. Unfortunately, due to the nature of the study design and data availability, neither genetic background, SES, nor familial environments could be measured. Nonetheless, the large sample size and the availability of measurements over a 3-year

period are supportive of a potential relationship between ADHD-MA and air pollution.

If the prevalence of ADHD among Pennsylvania elementary school children mirrored that of the US, then 8,779 (5.2%) of the 168,825 subjects in this study would have ADHD (3). Therefore, the clear majority of students possibly received ADHD-MA outside of school hours. However, the frequency of ADHD-MA does not indicate ADHD diagnosis, which is based on the judgment of a qualified health care specialist and health determinants that influence access to healthcare. Furthermore, ADHD symptoms resemble some other behavioral diseases that are treated with similar medications, including stimulants such as amphetamine and methylphenidate, which are effective for some, but not all, ADHD patients (46). This further complicates the issue of the types of medications nurses use to manage symptoms, particularly for children who are not responsive to some medications. In addition, the frequent administration of medication for some children may be attributed to the clinical management strategy, especially when some children are switched between different medications, such as stimulants and non–stimulants, with adjusted doses based on symptoms, to decide which drug at which dose works best for the child (47).

All this notwithstanding, evidence of environmental influences on ADHD indicates that ADHD may be related to multiple environmental factors including chemical, physical, or social exposures that interact with ADHD-related genes and, thereby, contribute to ADHD incidence (9,48,49). The findings of this study indicated that monitoring overall air pollution could be a practical tool that can be used for predicting not only ADHD incidence, but also ADHD symptoms. However, ADHD medications could be used for a variety of symptoms; depression, anxiety, and bipolar disorder, and they could be given regularly to ADHD patients or at times of exacerbations (50). Therefore, it is not always known whether the symptoms noticed that mandated the administration of medication were directly related to ADHD, were given regularly, or given when symptoms increased. Moreover, students who experience more severe ADHD may stay at home for 1-2 days after and are thus not counted. Further prospective studies can help determine the strength of evidence for developing guidelines that recommend school nurses and parents of children with ADHD take precautions during specific days or periods of the year when levels of certain upper air pollutants tend to increase.

The present study has some limitations. One of the limitations is that the data presented is 10 years old, and recent data is not available, although requested. Nonetheless, a causal or correlational relationship, if statistically proven, should not be affected by the age of the data. Since both variables (ADHD-MA and air pollutants) could be quantitatively measured and a plausible biological relationship between both variables are possible regardless of when the data is collected, a statistical relationship is still valid. Another limitation is the availability of data for some schools that participated in the eTools and not all schools in PA, and the exclusion of some counties where data could not be obtained. Another limitation is the unavailability of data from June to August. These hot months are typically associated with more pollution. Furthermore, children are often given medication holidays in the summer, which could weaken any association with air pollution.

The barometric pressure was considered a covariate in several studies measuring air pollution. However, studies avoid controlling for it because the barometric reduction in winter is accompanied by increased air pollution from local sources, which complicates such considerations (51). Therefore, it was not considered in this study.

In conclusion, ADHD-MA among Pennsylvania elementary school children varied among seasons over 3 years (2008-2010), with fall having the highest rate of ADHD-MA. While causal mechanisms are unknown, upper air concentrations of SO_2, CO, and $PM_{2.5}$ were found to be significantly associated with ADHD-MA patterns. Nevertheless, this association suggests that ADHD is affected by the proximate environment and/or direct air pollutant exposures. Moreover, monitored and predicted levels of air pollutant concentrations can potentially be used as an indicator of the overall impact of ADHD on school children. Accordingly, preventative initiatives may be developed and implemented to minimize exposures of children with ADHD during days and/or periods of the year when high concentrations of air pollutants are predicted. Symptomatic management of ADHD, as a highly complex disorder, cannot be easily predicted by a single factor or even multiple factors and their interactions, making the development of a comprehensive model that includes all known factors affecting ADHD difficult. Therefore, familial, genetic, and environmental factors known to contribute to ADHD should be comprehensively and simultaneously examined in future research to obtain reasonable estimates of increases in ADHD symptoms of individuals within defined communities.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

RAS conceived and designed the study, performed the analysis, and wrote the first draft of manuscript. WPJ, DKL, and MZA assisted in data interpretation, manuscript writing, and critical editing. AHY designed the study and collected the data. WPJ, DKL, and AHY confirm the authenticity of all the raw data. ll authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Indiana University Bloomington, United.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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