Long-term ambient air pollutant exposure and risk of migraine and recurrent headache in children: A 12-year cohort study

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Abstract

Background

Although research has suggested environmental factors to be triggers of headache, the contribution of long-term air pollution exposure to migraine and recurrent headaches (migraine/headaches) is poorly understood. Hence, we executed this nationwide cohort study to investigate the association of levels of ambient air pollution with the incidence and the risk of migraine/headaches in Taiwan children from 2000 to 2012.

Methods

We collected data from the Taiwan National Health Insurance Research Database and linked them to the Taiwan Air Quality Monitoring Database. Overall 218,008 children aged <18 (0-17) years old were identified from January 1, 2000 and then followed until they were diagnosed by a physician ≥ 3 times with migraine/headaches or until December 31, 2012. We categorized the annual average concentration of each air pollutant (fine particulate matter, total hydrocarbon, methane, sulfur dioxide, and nitrogen dioxide) into quartiles (Q1-Q4). We measured the incidence rate, hazard ratios (HRs), and the corresponding 95% confidence intervals for migraine/headaches stratified by the quartiles.

Results

A total of 28037 children (12.9%) were identified with migraine/headaches. The incidence rate and adjusted HR for migraine/headaches increased with higher-level exposure of air pollutants, except sulfur dioxide.

Conclusions

We herein demonstrate that long-term ambient air pollutant exposure might be a risk factor for childhood migraine/headaches.

Introduction

Migraine, characterized by recurrent headaches, are among the most common childhood headaches [1,2]. Children with recurrent headaches result in great impact on their life but also on their families. Furthermore, childhood migraine may persist into adulthood [3]. The influence of environmental factors on the attacks of migraine and recurrent headaches (migraine/headache) leads to extensive debate over the past decades [4]. Determining the triggering factors of migraine/headaches is crucial to prevent the illness. Chemical exposure and specific environmental irritants are well-known triggers of migraine/headaches [4]. Air pollution is the most widespread and inevitable form of pollution, and it may contribute to serious short-term and long-term health effects [5], involving a large variety of ailments and conditions that include chronic obstructive pulmonary disease, neurobehavioral disorders, lung cancer, birth defects, leukemia, premature death, asthma, immune system defects, and cardiovascular diseases

[6–8]. Patients with migraine/headaches often complain that poor air quality aggravates or triggers their headaches [9]. Indeed, environmental factors, such as air pollutants and weather, may produce neurogenic inflammation and trigger migraine/headaches onset [10,11]. To date, several studies have suggested an association between some outdoor air pollutants and frequency, severity, or medical consultation rates for migraine/headaches [12–14]; nevertheless, among the mentioned studies, the majority have accentuated adult patients and short-term influences induced by air pollution on migraine/headaches [12–14]. Most of our current knowledge about migraine/headaches in children is based on extrapolations from studies conducted on adults. Children and adolescents are notably different from adults in terms of their rapid growth, significant neurological development, and psychological changes. Thus, the long-term influences engendered by air pollution on migraine/headaches should be examined for the pediatric age group specifically.

This nationwide cohort study entailed employing the Taiwan National Health Insurance Research Database (NHIRD) and the Taiwan Air Quality Monitoring Database (TAQMD) for probing the long-term influences induced by outdoor air pollution on the incidence rates and risk of childhood migraine/headaches. The findings may promote informed practical clinical perspectives and advance public awareness of the negative influences that are induced by air pollution on children's health.

Methods And Materials

Data Source

The Taiwan National Health Insurance (NHI) program is known to offer coverage to 99% of Taiwan's 25 million residents and to contains information regarding contracts with over 90% of the country's national health care facilities (<https://nhird.nhri.org.tw/en/index.html>) [15,16]. The corresponding electronic database of this program, namely the NHIRD, comprises the claims data of insurants. Published studies have validated the high reliability of NHIRD diagnostic data [15,16]. The NHIRD includes detailed information, such as outpatient visits, hospital admissions, prescriptions, procedures, and disease diagnoses executed on the basis of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) [17]. An exclusive personal identification number (PIN) is assigned to every individual in Taiwan. In the NHIRD, for patient privacy protection, data concerning patient identities are scrambled cryptographically [15,17]. The entirety of NHI data sets can also be cross-referenced with each individual's PIN. This study utilized an NHIRD-derived data file, namely the Children file, that comprises information from half (chosen at random) of all insured children in Taiwan [18]. The data set was determined to afford an adequate sample for pursuing the study objectives. This study was ratified by China Medical University Hospital's Institute Review Board (CMUH104-REC2-115), and it complied with the principles outlined in the Declaration of Helsinki.

Study population, outcome of interest, endpoints, and confounding factors

This was a retrospective cohort study. From the Children file, we formed a child cohort by selecting individuals aged <18 (0-17) years on of January 1, 2000 (baseline). The study period was from January 1,

2000, to December 31, 2012. The follow-up period of each participant began from baseline until migraine/headaches, end of the follow-up, termination of insurance, or death. Individuals who were missing information such as their address, sex, and air pollution data and individuals that had ever been diagnosed with migraine/headaches before the baseline were excluded. Migraine/headaches were defined as ≥ 3 times diagnoses of ICD-9-CM code 346 and/or 784.0 in any diagnosis field during any inpatient or ambulatory claim process during study period. By the end of the study period, some participants would be entering adulthood. The final study population contained 218,008 participants. Our mean (standard deviation) follow-up years for patients with migraine was 10.7 (2.6). Urbanization level of residence, age, number of consultations/visits with a physician per year, monthly income, sex, and allergic diseases constituted the confounding factors. On the basis of the method realized by Liu et al [19], we classified the study patients' residential areas, encompassing 365 townships of Taiwan, into seven urbanization levels, with Levels 1 and 7 representing the "most urbanized" and "least urbanized," respectively. We stratified the townships for defining urbanization levels by using several variables, including the following: population ratio of people with an educational level of college or higher, population density (people/km²), population ratio of agricultural workers, number of physicians per 100,000 people, and population ratio of elderly people aged older than 65 years [19]. Because Levels 4-7 were determined to have low sample size, we combined these four levels into a single group (Level 4). Thus, we stratified the factor urbanization level into four levels, with Levels 1 and 4 representing the highest density and lowest density, respectively. We also classified monthly income into the following three groups: >NT\$20,000, NT\$15,000-19,999, and <NT\$15,000.

Exposure assessment

Ambient air monitoring of monthly average data for SO₂, NO₂, THC, CH₄, and PM_{2.5} are available for 74 Taiwan Environmental Protection Administration (EPA) monitoring stations on Taiwan's main island since 1994. Concentrations of each pollutant are measured hourly—CO by nondispersive infrared absorption, NO₂ by chemiluminescence, SO₂ by ultraviolet fluorescence, THC and CH₄ by flame ionization detector, and PM_{2.5} by beta-gauge—and are reported hourly.

We identified the map coordinates of the monitoring stations and air pollution sources. The ultraviolet fluorescence in these recording stations were automatically monitoring and recording readings of PM_{2.5}, THC, CH₄, SO₂, and, NO₂. The daily air pollution data were averaged based on these recording stations. Yearly average concentrations of pollutants were calculated from the baseline to the date of migraine and recurrent headaches occurrence, the withdrawal of patients, or the end of the study period, and the data were categorized into quartiles. The participants were assigned to residential districts based on the clinic where they most frequently sought treatment for acute upper respiratory infection (ICD-9-CM code 460). We divided the annual average air pollutant concentrations into quartiles: Q1, Q2, Q3, and Q4. We categorized annual average PM_{2.5} into Q1 (<11120 µg/m³), Q2 (11120-12652 µg/m³), Q3 (12652-15056 µg/m³), and Q4 (>15056 µg/m³); THC into Q1 (<835 ppm), Q2 (835-877 ppm), Q3 (877-949 ppm), and Q4 (>949 ppm); CH₄ into Q1 (<735 ppm), Q2 (735-754 ppm), Q3 (754-770 ppm), and Q4 (>770 ppm); SO₂ into Q1 (<1346 ppb), Q2 (1346-1914 ppb), Q3 (1914-2338 ppb), and Q4 (>2338 ppb); NO₂ into Q1 (<7896

ppb), Q2 (7896-8894 ppb), Q3 (8894-10214 ppb), and Q4 (>10214 ppb). The air pollutant measurements from Taiwan EPA monitoring stations were integrated into monthly point data and interpolated to pollutant surfaces using inverse distance weighting (IDW). For the IDW approach, we used inverse squared distance (1/squared distance) weighted average of the three nearest monitors to compute monthly mean concentration. IDW predicts values of unknown points based on the similarity of two objects by its distance. When the unknown point to be estimated is closer to the known measuring point, the weighted value of the unknown point will be higher. We used the air pollution exposure in 2-year before and current year of diagnosis headaches to predict the monthly air pollution. And used IDW method to estimate the air pollution concentrations between the measured values of the air monitoring stations around the household registered by each patient according to the distance. Then explore the association between air pollutant and headaches (All data were managed by a geographic information system (ArcGIS version 10.3; ESRI, Redlands, CA, USA)).

Statistical analysis

The sociodemographic factors in the current study included residential area urbanization level, sex, monthly income, age, and daily average exposure to air pollutants. To test the differences in daily average concentration distributions for each air pollutant by quartile and urbanization, we executed χ^2 testing. Moreover, we calculated the incidence density rate of migraine/headaches (per 1000 person-years) according to each quartile of daily average concentrations for the five air pollutants. By employing Cox proportional hazard regression, we also derived estimates of the hazard ratios (HRs) as well as 95% confidence intervals (CIs) corresponding to migraine/headaches at the Q2-Q4 levels for air pollutant concentrations relative to the lowest level (Q1). To address the concern of constant proportionality, we examined the proportional hazard model assumption using a test of scaled Schoenfeld residuals. In the model evaluating the migraine and recurrent headaches risk throughout overall follow-up period, results of the test revealed a significant relationship between Schoenfeld residuals for PM_{2.5}, THC, CH₄, SO₂, and NO₂ and follow-up time (p-value<0.001, respectively), suggesting the proportionality assumption was violated. To deal with non-proportional hazards, we were used extended Cox models with time-dependent terms shows results. We adjusted the applied the multivariable model for allergic diseases, sex, number of consultations/visits with a physician per year, urbanization level, age, and monthly income. We also added the exposures as a continuous variable to estimate the risk of migraine and recurrent headaches as sensitivity testing. Further, we calculate the month average air concentration to estimate the month exposed air concentration for each patient by Inverse Distance Weighting Method (IDW methods). The IDW method is one of the most commonly used spatial interpolation methods in Geosciences, which calculates the prediction values of unknown points by weighting the average of the values of known points (This data were analyzed with ArcGIS version 10.3). We accessed the air pollution in 2-year before and current year the diagnosis of migraine and recurrent headaches and used IDW method to estimate the air pollution concentrations between the measured values of the air monitoring stations around the household registered by each patient according to the distance as sensitivity testing. The Statistical Package for the ArcGIS version 10.3 as well as SAS 9.3 (SAS Institute Inc, Cary, NC) constituted the

platforms for all the executed analyses in this study. Additionally, for all executed statistical analyses, we deemed 2-tailed P values of <0.05 to indicate statistically significant tests.

Results

During the study period, a total of 28,037 children (12.9%) were diagnosed with migraine/headaches in the cohort of 218,008 children. Table 1 presents the participants' sociodemographic factors. The mean age of participants was 6.01 years (standard deviation, 2.98). The mean follow-up period was 10.7 years (standard deviation, 2.6). The proportion of boys was slightly higher than that of girls (52% vs 48%), that is similar to national demographic data reported by the Taiwan Ministry of Internal Affairs (the ratio of male to female under 15 is about 1.09:1). In addition, most participants lived in densely populated areas (65.9%).

Table 1
Sociodemographic data of the study cohort

N = 218,008		n	%
Gender	Boys	113364	52.0
	Girls	104644	48.0
Age, years	mean, SD	6.01	2.98
Monthly income (NTD) [†]	< 15,000	187199	85.9
	15,000 – 19,999	23668	10.9
	≥ 20,000	7141	3.28
Urbanization level	1 (highest)	74591	34.2
	2	69003	31.7
	3	40924	18.8
	4 (lowest)	33490	15.4
Outcome			
Migraine and recurrent headaches	Yes	28037	12.9
Follow-up time, years	mean, SD	10.7	2.60
Monthly income, new Taiwan Dollar (NTD), 1 NTD is equal to 0.03 USD.			
The urbanization level was categorized by the population density of the residential area into 4 levels, with level 1 as the most urbanized and level 4 as the least urbanized.			

The incidence rates for migraine/headaches increased with higher levels of PM_{2.5}, THC, CH₄, and NO₂ exposure (Table 2). The increasing incidence rates from Q1 to Q4 in PM_{2.5}, THC, CH₄, and NO₂ were from 8.62 to 15.0, from 8.06 to 16.3, and from 8.93 to 24.1, and from 11.8 to 12.9 per 1000 person-years, respectively (Table 2). The adjusted HR for migraine/headaches increased with higher levels of exposure in PM_{2.5}, THC, CH₄, and NO₂ (Table 2). We also analyzed incidence rate and adjusted HR stratified by quartiles and two age groups (≤ 6 years and > 6 years) in supplementary Table 1. The risk of migraine and recurrent headaches increased while exposed to higher level air pollutants in children older than 6. The Kaplan-Meier plots (Fig. 1A-E) with pollutant concentration stratified by quartiles showed that patients exposed to higher pollution concentrations had higher accumulative incidence of migraine/headaches than those exposed to lower pollution concentrations of fine PM_{2.5}, THC, CH₄, SO₂, and NO₂. Figure 2 showed the distribution of air pollution exposures during the follow up time. In the interaction analyses for the risk of migraine/headaches between ambient temperature and concentration of ambient air pollutants, we found that the highest incidence rate and the highest adjusted HR were in those exposed $\geq$ median temperature and $\geq$ median-level of pollutants (Table 3). We also used annual average concentrations as continuous variables and used extended Cox models with time-dependent terms to consider non-linear relations and interaction between air pollutants and time. Further analysis of the extended Cox models with time-dependent terms shows results, indicating that the strength of the association increased over time (HR [p value], for PM_{2.5}, 1.000072 [p < 0.001]; for interaction term of PM_{2.5} and time, 1.000016 [p < 0.001]; for SO₂, 1.0003 [p < 0.001]; for interaction term of SO₂ and time, 1.0001 [p < 0.001]), and reduced over time (HR [p value], for THC, 1.02 [p < 0.001]; for interaction term of THC and time, 0.99 [p < 0.001]; for CH₄, 1.045 [p < 0.001]; for interaction term of CH₄ and time, 0.99 [p < 0.001]; for NO₂, 1.0005 [p < 0.001]; for interaction term of NO₂ and time, 0.99 [p < 0.001]). Table 4 showed that the adjusted HR of migraine and recurrent headaches development was increased with five air pollutants concentration (PM_{2.5}, THC, CH₄, SO₂, and, NO₂). Supplement Table 1 showed that Inverse Distance Weighting (IDW) to speculate monthly average concentration of PM_{2.5}, THC, CH₄, SO₂, and, NO₂, and. Air pollutant concentrations were grouped into four levels based on quartile. After controlling for risk factors, patients exposed in higher air pollutant concentrations had a significant higher risk of migraine and recurrent headaches than patients exposed in lower air pollutant concentrations which including SO₂, and NO₂. For SO₂, relative to Q1 concentrations, the Q2 (adjusted HR = 2.14, 95%CI = 2.06–2.23 and adjusted HR = 1.39, 95%CI = 1.33–1.45), Q3 (adjusted HR = 3.59, 95%CI = 3.45–3.73 and adjusted HR = 1.67, 95%CI = 1.60–1.75), and Q4 (adjusted HR = 3.46, 95%CI = 3.33–3.60 and adjusted HR = 3.29, 95%CI = 3.15–3.44) concentrations were had a significant higher risk of migraine and recurrent headaches. Table 4 revealed the risks for migraine and recurrent headaches increased in participants exposed to various annual average concentrations as continuous variable of air pollutants.

Table 2

The risk of migraine and recurrent headaches in children exposed to air pollutants stratified by quartile of annual average concentration in Cox proportional hazard regression

	IR	cHR	(95%CI)	aHR†	(95%CI)
Fine particulate matter (PM2.5)					
Quartile 1, < 11120 µg/m ³	8.62	Reference group		Reference group	
Quartile 2, 11120–12652 µg/m ³	11.0	1.30	(1.26, 1.35)**	1.29	(1.25, 1.34)**
Quartile 3, 12652–15056 µg/m ³	13.5	1.59	(1.54, 1.65)**	1.57	(1.51, 1.62)**
Quartile 4, > 15056 µg/m ³	15.0	1.78	(1.72, 1.84)**	1.75	(1.69, 1.81)**
Total hydrocarbons (THC)					
Quartile 1, < 835 ppm	8.06	Reference group		Reference group	
Quartile 2, 835–877 ppm	8.40	1.05	(1.01, 1.09)*	1.08	(1.04, 1.12)**
Quartile 3, 877–949 ppm	16.9	2.26	(2.18, 2.34)**	2.41	(2.33, 2.49)**
Quartile 4, > 949 ppm	16.3	2.25	(2.17, 2.33)**	2.50	(2.41, 2.59)**
Methane (CH ₄)					
Quartile 1, < 735 ppm	8.93	Reference group		Reference group	
Quartile 2, 735–754 ppm	6.82	0.76	(0.73, 0.79)**	0.78	(0.75, 0.81)**
Quartile 3, 754–770 ppm	11.0	1.27	(1.22, 1.32)**	1.29	(1.24, 1.33)**
Quartile 4, > 770 ppm	24.1	3.16	(3.06, 3.26)**	3.22	(3.11, 3.33)**
Sulfur dioxide (SO ₂)					
Quartile 1, < 1346 ppb	13.7	Reference group		Reference group	
Quartile 2, 1346–1914 ppb	10.4	0.75	(0.72, 0.77)**	0.79	(0.76, 0.81)**
Quartile 3, 1914–2338 ppb	11.7	0.87	(0.84, 0.90)**	0.89	(0.86, 0.92)**

IR, incidence rate (per 1000 person-years)

cHR, crude hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval

The annual average air pollutant concentrations were categorized into 4 groups based on quartiles for each air pollutant.

†Adjusted HR, adjusted for age, sex, monthly income, urbanization level of residence, number of consultations/visits with a physician per year, and allergy diseases

* p < 0.01, ** p < 0.001

	IR	cHR	(95%CI)	aHR†	(95%CI)
Quartile 4, > 2338 ppb	12.3	0.90	(0.87, 0.92)**	0.93	(0.90, 0.96)**
Nitrogen dioxide (NO ₂)					
Quartile 1, < 7896 ppb	11.8	Reference group		Reference group	
Quartile 2, 7896–8894 ppb	12.0	1.02	(0.99, 1.05)	1.07	(1.03, 1.10)**
Quartile 3, 8894–10214 ppb	11.5	0.99	(0.96, 1.02)	1.05	(1.01, 1.09)*
Quartile 4, > 10214 ppb	12.9	1.13	(1.10, 1.17)**	1.23	(1.19, 1.27)**
IR, incidence rate (per 1000 person-years)					
cHR, crude hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval					
The annual average air pollutant concentrations were categorized into 4 groups based on quartiles for each air pollutant.					
†Adjusted HR, adjusted for age, sex, monthly income, urbanization level of residence, number of consultations/visits with a physician per year, and allergy diseases					
* p < 0.01, ** p < 0.001					

Table 3

Association between ambient temperature with interaction of ambient air pollutants and risks for migraine and headaches by Cox proportional hazard regression analysis

Ambient air pollutants	Ambient temperature	IR	aHR [†] (95% CI)	p-value for interaction
Fine particulate matter (PM _{2.5})				< 0.001
<Median	<Median	9.24	1.00 (Reference)	
<Median	≥Median	10.8	1.20 (1.15, 1.24)*	
≥Median	<Median	14.4	1.61 (1.53, 1.70)*	
≥Median	≥Median	14.3	1.55 (1.51, 1.60)*	
Total hydrocarbons (THC)				< 0.001
<Median <Median	<Median	6.97	1.00 (Reference)	
	≥Median	8.93	1.26 (1.21, 1.31)*	
≥Median	<Median	13.4	2.11 (2.02, 2.21)*	
≥Median	≥Median	18.6	3.21 (3.08, 3.34)*	
Methane (CH ₄)				< 0.001
<Median	<Median	7.5	1.00 (Reference)	
<Median	≥Median	7.97	1.04 (1.00, 1.08)	
IR, incidence rate (per 1000 person-years)				
aHR, adjusted hazard ratio; CI, confidence interval				
The ambient air pollutants and ambient temperature were all categorized into 2 groups based on the median value of annual average.				
†Adjusted HR, adjusted for age, sex, monthly income, urbanization level of residence, number of consultations/visits with a physician per year, and allergy diseases				
* p < 0.001				

Ambient air pollutants	Ambient temperature	IR	aHR [†] (95% CI)	p-value for interaction
≥Median	<Median	14.2	1.98 (1.90, 2.07)*	
≥Median	≥Median	18.6	2.74 (2.65, 2.84)*	
Sulfur dioxide (SO ₂)				< 0.001
<Median	<Median	11	1.00 (Reference)	
<Median	≥Median	12.4	1.13 (1.09, 1.17)*	
≥Median	<Median	9.35	0.86 (0.82, 0.90)*	
≥Median	≥Median	14.4	1.36 (1.31, 1.42)*	
Nitrogen dioxide (NO ₂)				< 0.001
<Median	<Median	9.58	1.00 (Reference)	
<Median	≥Median	13.0	1.38 (1.33, 1.44)*	
≥Median	<Median	10.3	1.16 (1.11, 1.21)*	
≥Median	≥Median	13.4	1.54 (1.48, 1.60)*	
IR, incidence rate (per 1000 person-years)				
aHR, adjusted hazard ratio; CI, confidence interval				
The ambient air pollutants and ambient temperature were all categorized into 2 groups based on the median value of annual average.				
†Adjusted HR, adjusted for age, sex, monthly income, urbanization level of residence, number of consultations/visits with a physician per year, and allergy diseases				
* p < 0.001				

Table 4

Comparisons of differences in migraine and recurrent headaches incidences and associated HRs in participants exposed to various annual average concentrations of air pollutants.

Pollutant levels	cHR	95%CI	aHR†	95%CI
Fine particulate matter (PM2.5)	1.000	(1.000, 1.000)*	1.000	(1.000, 1.001)*
Total hydrocarbons (THC)	1.003	(1.003, 1.003)*	1.004	(1.004, 1.004)*
Methane (CH4)	1.010	(1.010, 1.010)*	1.010	(1.010, 1.010)*
Sulfur dioxide (SO2)	1.000	(1.000, 1.000)*	1.000	(1.000, 1.001)*
Nitrogen dioxide (NO2)	1.000	(1.000, 1.000)*	1.000	(1.000, 1.001)*
IR, incidence rate (per 1000 person-years)				
cHR, crude hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval				
The annual average air pollutant concentrations were categorized into 4 groups based on quartiles for each air pollutant.				
†Adjusted HR, adjusted for age, sex, monthly income, urbanization level of residence, number of consultations/visits with a physician per year, and allergy diseases				
* p < 0.001				

Discussion

Air pollution has become the one of the most significant worldwide environmental health risks [5–8]. Currently, Southeast Asia is established to be most polluted area worldwide, with 2.6 and 3.3 million deaths ascribed to outdoor and indoor air pollution, respectively [20,21]. Taiwan is in east Asia, near the most polluted area of the world. Previously executed research has reported an association between air pollution and increased frequency and severity of migraine [12–14]. The prevalence of migraine in Taiwanese adolescents has risen over the past decade [22]. Motivated by these clinical, public health, and environmental concerns, as well as the lack of data on the childhood headaches–air pollution interaction, we executed the first nationwide study on the association of long-term exposure to air pollution with the incidence and risk of childhood migraine/headaches. The findings quantify how air pollution affects children's health, indicating higher ambient temperature and ambient air pollutant exposure levels to be associated with increased incidence and risk of childhood migraine/headaches. Our study thus demonstrates that ambient air pollutant exposures are indeed associated with migraine/headaches in Taiwanese children. According to the information released by the Environmental Protection Agency of Taiwan, the domestic air pollution emissions are mainly from two categories. First, mobile pollution sources (transportation), such as NO₂, lead, THC, CO and CH₄. Secondly, fixed pollution sources (industrial processes, power generation or waste disposal), including suspended particulates (PM_{2.5}). As

a representative, we chose THC and CH₄ on the behalf of mobile pollution sources and fine PM_{2.5} for the fixed pollution sources.

Lewis (2009) assessed epidemiological research executed over the past 25 years on migraine headache in adolescents and children; the researcher detected 64 cross-sectional studies that involved a total of 227,249 subjects and were published in 32 different countries. The overall mean prevalence values of headache and migraine were estimated to be 54.4% (95% CI 43.1–65.8) and 9.1% (95% CI 7.1–11.1) by adolescence, respectively [23]. Concerning specific regions, in the United States, up to 5% of the pediatric population was determined to endure migraine [24]. Another study executed in Sweden recruited 9000 school children for probing the migraine prevalence; the mentioned study reported that approximately 4% of the recruited children had migraine, with the average onset age being six years [25]. Furthermore, the migraine prevalence estimates for the ages of seven and 15 years were 1.4% and 5.3%, respectively [25]. In the present study, we defined recurrent migraine as visiting health care facilities more than 3 times because of migraine to avoid temporary headaches secondary to common cold or acute viral illness. Based on these criteria, the overall prevalence of migraine in children in Taiwan was 12.9%. The risk of migraine and recurrent headaches increased while exposed to higher level air pollutants in children older than 6. Although migraine is less common in children than in adults, it can begin in childhood and increase in prevalence with age.

Airborne pollutants have long been regarded as environmental factors that trigger migraine/headaches. However, most previously published studies have accentuated the short-term influences engendered by air pollution on migraine/headaches [10,12–14]. The current state of knowledge suggests that a primary neuronal dysfunction leading to an increased sensitivity to a broad range of stimuli accounts for human migraine disorders [11,26]. Both genetic and environmental factors are likely to be pivotal to migraine phenomena [27,28]; a child's brain develops in response to genes, the environment, and their interactions [29]. Although beyond the scope of the present study, future study exploring the interactions of gene, air pollution exposure and migraine headaches is crucial to improve understanding of the mechanisms of childhood migraine/headaches.

Previously published studies regarding the influences exerted by air pollution on migraine headaches have offered inconsistent results. Chen et al executed a similar investigation in 2015 and determined that high PM_{2.5} levels raise the risk of migraine-related clinic visits in Taipei (the capital city of Taiwan) [10]. Research in a Canadian population analyzed patients who visited emergency rooms for migraine between 1992 and 2002; the results showed PM_{2.5} to be associated with 3.3% increases in visits for migraine (95% CI: 0.6–6.0) as well as 3.4% increases in visits for headache (95% CI: 0.3–6.6) (12). Dales et al (2009) studied seven Chilean urban centers; they observed an association between acute increases in ambient air pollution and increases in the number of headache-related hospital admissions [13]. However, Mukamal et al (2009), who executed their work in Boston, did not find a clear association of air pollutants with risk of emergency room visits for migraine [14]. Our results support the association of long-term exposure to THC, PM_{2.5}, and CH₄ and high AMB TEMP to increased incidence and risk of childhood migraine.

Furthermore, our results indicate that most individuals living in areas with higher urbanization levels had higher air pollutant exposure, most likely due to the high vehicle density and population density in urban areas. Hence, the consumption of large amounts of energy and resources results in the emission of large amounts of air pollutants into the atmosphere in urban settings. On the other hand, although there are many sources of PM_{2.5}, it is mainly from fixed pollution source (industrial processes, power generation or waste disposal) and dust raised by the public works (constructions) based on the statistics of the Environmental Protection Agency of Taiwan. Domestic data also revealed numerous large factories and heavy industries (such as cement, petrochemical, oil refining, steel and shipbuilding, and other related factories) are mostly concentrated in areas with low population density. In addition, due to the high degree of construction in Taiwan city, most public works have been transferred to suburbs or low population density areas in recent years. Therefore, the concentration of PM_{2.5} in these areas is relatively high. To date, the mechanism by which ambient temperature influences headache remains largely unknown. From a physiological view, headache is associated with hemodynamic variations, and cold weather might aggravate such variations [30]. In addition, regarding both particulate air pollution and ambient temperature, PM_{2.5} was previously reported to be associated with migraine-related visits in the cold season, especially in female patients [12]. Additionally, during cold-front passages, the concentration of PM_{2.5} is relatively high [31]. Thus, it is inferred that when the temperature is low, it may cause poor vertical diffusion conditions and thus may result in a relatively high PM_{2.5} concentration under ordinary discharge conditions [31].

Our results reveal children who lived in areas with relatively a high ambient temperature had a relatively high accumulated incidence of migraine/headaches, in accordance with previously published studies [32]. Chen et al and Roberts et al [9,33] have emphasized the daily particulate air pollution–daily mean temperature interaction and gave several plausible explanations for this finding. In Taiwan, people have a higher likelihood of opening their windows or going outdoors in the warm season than they do in the cool season, leading to increased exposure; accordingly, monitored air pollutant concentrations could be more closely correlated with personal exposure in the warm season than in the cool season. However, extremely cold or extremely hot weather can be a triggering factor for migraine headache [34–38]. In Taiwan, a subtropical country, summer temperatures are often above 38 °C, and annual average temperatures are often above 25 °C; hence, the effect of high temperatures is significantly higher than that of low temperatures.

The WHO ambient air quality guidelines suggest an annual mean PM_{2.5} concentration limit of 10 µg/m³ and 25 µg/m³ for the 24-hourly mean [39]. In the United States (US), the EPA reduces particle pollution by tightening the annual National Ambient Air Quality Standard for PM_{2.5} from 15 to 12 µg/m³ in 2012 [39]. Populations in large parts of the world, especially in East and Southeast Asia and the Middle East, are exposed to levels of fine particulate pollution that far exceed the WHO guidelines. In our study, the limit of international guideline for PM_{2.5} (25 µg/m³) is only within the first quartile of current study. Hence, most of our population exposed to levels of PM_{2.5} that far exceed the WHO guidelines. Taiwan is in east Asia, near the most polluted area of the world. The prevalence of migraine in Taiwanese adolescents has risen

over the past decade. Our findings show ambient air pollutant exposure levels to be associated with increased incidence and risk of childhood migraine/headaches.

Potential limitations that could serve as confounders to this study should be acknowledged. First, genetic and environmental factors (such as stress, family member's smoking habits, physical activity, occupational exposures, dietary habits, family history of migraine, and emotional factors), severity of migraine, and subtype of migraine were not captured in administrative claims databases. Second, children with high exposure to air pollution lived in areas with relatively high urbanization levels. Children living in relatively crowded environments might have relatively high stress associated with notably crowded housing. Moreover, children in highly polluted areas may have numerous diseases other than migraine/headaches, their consultations for respiratory tract infections and allergic diseases may be more frequent than the national average; the more frequently a child consults the doctor, the more opportunities that child has of being diagnosed with migraine/headaches. Thus, we adjusted for possible confounders such as numbers of consultations/visits with a physician (both per year and overall), monthly income, residence area urbanization level, and allergic diseases. Third, coding accuracy and financial incentives may lead to bias when ICD-9 CM codes are used for diagnosis in large insurance claims data for research. Although migraine is said to be the most common cause of primary headache in children, most children with headache were coded as 'unspecified headache'. Some physicians were accustomed to give a diagnosis of headache rather than migraine for patients by only few visits. This implies that migraine may be underdiagnosed, particularly in young children and those with mild or infrequent symptoms. Children with mild symptoms, which may not be recognized by caregivers may be only treated with over-the-counter medications. Doctors' specializations may also interfere with the diagnosis. Therefore, we defined the studying children should have at least 3 times medical visits and were given diagnosis of "migraine " and/or "headache" in any diagnosis field during any inpatient or ambulatory claim process to capture more cases of migraine. Fourth, data from fixed monitoring stations may not reflect the true exposure level to air pollutants in patients and residence may change over the course of the study. In Taiwan, because of 12-year compulsory education law, children usually study at a fixed school district of residence area before entering college (> 18-year-old). Hence, residence changed over the course of the study is not quite often seen for children. Sixth, weather change was previously mentioned as a trigger of migraine [38]. Because Taiwan has a subtropical climate, it does not have 4 distinct seasons; thus, climate should not be responsible for changes in prevalence throughout the year.

Conclusions

We herein demonstrate that long-term exposure to ambient air pollutants and relatively high ambient temperature are associated with migraine not only in adults but also in children. With this study, we hope to facilitate the implementation of an appropriate policy of public health for monitoring and further improving air quality—for the health of our children, who are the backbone of the future.

Declarations

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Authors' contributions

Syuan-Yu Hong, Lei Wan, Hui-Ju Lin and Chang-Ching Wei conceptualized and designed the study. Syuan-Yu Hong drafted the initial manuscript. Cheng-Li Lin carried out the analysis, reviewed and approved the final manuscript as submitted. Chang-Ching Wei coordinated and supervised data collection, critically reviewed the manuscript, and approved the final manuscript as submitted.

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Availability of data and materials

All data related to this case report are contained within the manuscript.

Ethics approval and consent to participate

Consent for discussion of the clinical history was provided by the family. The study protocol was approved by the Ethics Review Board of the China Medical University ethics committee (Approval # CMUH104-REC2-115). Written informed consent of participation was obtained from the legal guardians. A copy of the written consent is available for review by the Editor of this journal.

Consent for publication

The patient's guardians have consented to submission of this case report to the journal, and we have obtained a written informed consent.

Competing Interest: None.

Abbreviations

EPA: Environmental Protection Administration; HRs: hazard ratios; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; IDW: inverse distance weighting; NHIRD: National Health Insurance Research Database; NT: New Taiwan Dollar; PIN: personal identification number; TAQMD: Taiwan Air Quality Monitoring Database

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Figures

Figure 1

Kaplan-Meier curves of the accumulative incidence rate of migraine and recurrent headaches during the follow-up period among the four quartiles of each air pollutant. (A) PM2.5 (B) THC (C) CH4 (D) SO2 (E) NO2

Figure 2

The distribution of annual air pollution exposures during the follow up time. (A) PM2.5 (B) THC (C) CH4 (D) SO2 (E) NO2

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