Journal of Microbiology, Immunology and Infection (2019) 52, 352–362

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Original Article

Associations between environmental heavy metal exposure and childhood asthma: A population-based study

Keh-Gong Wu*, Chia-Yuan Chang, Chun-Yu Yen, Chou-Cheng Lai

Division of Infectious Diseases, Department of Pediatrics, Taipei Veterans General Hospital and National Yang-Ming University, Taipei, Taiwan

Received 1 June 2018; received in revised form 1 August 2018; accepted 13 August 2018
Available online 22 August 2018

KEYWORDS
Asthma;
Children;
Environmental pollutants;
Heavy metals;
National Health and Nutrition Survey

Abstract *Background/purpose:* The health risks of environmental heavy metals have been of concern are well known. The greater likelihood of heavy metal contamination in the physical environment increases the risk of asthma, especially in children. This cross-sectional, population-based study sought to investigate associations between heavy metal exposure and childhood asthma or wheezing.
Methods: Data from 5866 subjects, stratified into age groups of 2–5, 6–11, and 12–15 years, from the National Health and Nutrition Examination Survey 2007–2012 conducted by the Centers for Disease Control and Prevention were analyzed retrospectively. The primary outcome was active asthma. Variables included demographics, anthropometric, and clinical data. Univariate and multivariate logistic regression analyses were used to identify associations between blood heavy metal concentrations and adjusted odds (aORs) of active asthma.
Results: Higher concentration of blood lead was associated with higher adjusted odds of having asthma (aOR = 1.08, 95% CI = 1.00–1.16), but no significant effect was shown for current wheezing or whistling. Age-stratified analysis showed that higher blood lead concentration was associated with higher risk for active asthma (aOR = 1.24, 95% CI = 1.08–1.42) and current wheezing or whistling (aOR = 1.19, 95% CI = 1.04–1.38) in the 6–11 years age group, while higher blood mercury concentration was associated with lower risk of current wheezing or whistling (aOR = 0.95, 95% CI = 0.90–0.99). The medium concentration of blood lead was associated with decreased risks of current wheezing or whistling (aOR = 0.54, 95% CI = 0.30–0.96) in the 2–5 years age group.
Conclusion: Higher concentrations of blood lead are associated with higher odds of asthma in children aged 2–15 years.

Abbreviations: Cd, cadmium; CDC, Centers for Disease Control and Prevention; CI, confidence interval; Hg, mercury; IgE, immunoglobulin E; OR, odds ratio; Pb, lead.

* Corresponding author. Division of Infectious Diseases, Department of Pediatrics, Taipei Veterans General Hospital and National Yang-Ming University, No. 201, Section 2, Shih-Pai Road, Taipei City 11217, Taiwan. Fax: +886 2 28739019.
E-mail address: kgwu@vghtpe.gov.tw (K.-G. Wu).

https://doi.org/10.1016/j.jmii.2018.08.001

Introduction

Asthma is a global health issue affecting millions of children and adults worldwide. A cross-sectional world health survey reported that about 14% of children throughout the world may have asthma symptoms annually,[1] although the actual prevalence of childhood asthma differs considerably between countries and between cities or regions in the same country.[2] Surveillance reports of the Centers for Disease Control and Prevention (CDC)[3] show that asthma has a global prevalence of 4.3%, and prevalence in the United States is about 6.8% in children and 7.6% in adults. Asthma-related morbidity in the United States is highest among members of minority groups and those with lower socioeconomic status, especially among African-American and Hispanic children, whose rates of hospitalization are up to four times higher than those in Caucasian children.[4] U.S. asthma diagnoses increased by 50% among black children in 2001—2009, and 3447 asthma-associated deaths were reported in 2007.[5] The global death rate was 5.2 per 100,000 population (0.7%) in 2010.[6] The lifelong disease involves recurrent wheezing, airway obstruction, impeded breathing, chest tightness, and coughing, resulting in significant disability and poor quality of life.[2] Asthma symptoms are managed through a range of medications and lifestyle measures, and attacks may be prevented by using inhaled corticosteroids and avoiding specific asthma triggers. Meanwhile, asthma was frequently associated with other co-morbidities such as allergic rhinitis.[7] Exercise-induced broncho-constriction presented in 52.5% of children with asthma.[8] The health risks of environmental heavy metals are well known and, in particular, the adverse effects of exposure to lead, mercury and cadmium have been of concern for more than twenty years.[9—13] Along with low socioeconomic status and sub-standard housing posing a greater likelihood of heavy metal contamination, toxic elements in the physical environment increase the risk of asthma, especially in children.[2,4,11] The most often reported environmental factors are infections, allergens, tobacco smoke and environmental toxins such as mercury and lead, the most common environmental heavy metals, although others (e.g., arsenic, chromium, iron, nickel, vanadium, zinc) are reported.[14,15] Children are exposed to these environmental substances in various ways, including through food and water, housing materials, toxic emissions from traffic and industry, mineral and metal dust in the home environment, cleaning products, and in soil.[15,16] Pediatric immune dysfunction and environmental triggers (e.g., infectious agents, drugs, physical factors, and stressors) combine to result in environmentally-induced immune alterations, or immunotoxicity, in early childhood, eventually giving way to allergic diseases.[14] Genetics also seem to play a role, increasing the risk for allergy with a minor impact on pediatric asthma.[17] Developmental immunotoxicity may lead, in turn, to the dysregulation of inflammation seen in allergic diseases and asthma.[18] In a basic study of the effects of heavy metal exposure, Zhang et al. describe developmental damage, oxidative stress and immunotoxicity resulting from exposure of zebrafish embryos-larvae to mercuric chloride.[19] Maternal prenatal cadmium exposure was found to alter postnatal immune system cell development and functioning.[20] Environmental exposure to lead and resulting increased blood lead levels were associated with an increase in immunoglobulin E (IgE) levels, explained as hypersensitivity mediated by IgE.[20] A Korean study found that more than 50% of asthma cases were associated with increased levels of total and allergen-specific IgE levels, some associated with blood lead and cadmium levels.[12] Similarly, Wang et al.[13] estimated that 38% of the effect of lead exposure was mediated by IgE levels. However, ongoing attempts to describe the underlying immune mechanism of asthma have still not provided sufficient evidence to support associations between blood levels of heavy metals and asthma.

Age, gender and weight status (underweight for age and gender) have a noted association with childhood asthma and wheezing.[13,22,23] We hypothesized that evaluating heavy metal exposure in a large cohort of age-appropriate children may reveal distinct associations between environmental heavy metal exposure and childhood asthma or wheezing, and may highlight possible differences in relation to age, gender, and weight status. We planned to test our hypothesis using data from three cycles of the U.S. National Health and Nutrition Examination Survey (NHANES) from 2007 to 2012, which provides a nationwide probability sample organized by subject matter and representative of the whole U.S. population (http://www.cdc.gov/nchs/nhanes/). While an earlier study using data from 2003 to 2005 found no direct association of lead with asthma,[21] these results are not without controversy.[12,13,24] More recent studies of the NHANES data found declining lead levels in children, but did not evaluate the association with asthma.[25,26] NHANES data include laboratory values, anthropometric measures, and demographic and socioeconomic variables, including age, gender, race/ethnicity, family income to poverty ratio, exposure to maternal smoking or second-hand smoke, and premature status or intensive care at birth.[27] Given the lack of a cohesive understanding of environmentally-mediated asthma, this study aimed to further assess the associations between heavy metal exposure and childhood asthma or wheezing in a nationwide U.S. database.

Patients and methods

Data source

Data for this study were extracted from three cycles of the National Health and Nutrition Examination Survey (NHANES)

2007—2012, which is conducted by the National Center for Health Statistics (NCHS) of the CDC. All data were released as Public Data General Release file documents by the U.S. Department of Health and Human Services, CDC, Hyattsville, MD, USA (http://www.cdc.gov/nchs/nhanes/). Permission to use the data was granted by the NCHS. Since all NHANES data are de-identified, data analysis does not require IRB approval or written informed consent by the study subjects.

Study design and population

This cross-sectional population-based study screened the data of 8672 participants in the NHANES survey during 2007—2012. The inclusion criteria were: subjects aged 2—15 years with laboratory data on blood levels of lead, cadmium and mercury concentrations, and having complete data on key confounders (i.e., obesity status, underweight for age and gender, family income to poverty ratio, environmental tobacco exposure). Because adult-onset asthma is defined as starting as young as age 16 years,[28] the inclusion criteria of the present study described adult-onset asthma as age 16 years and older. Children below the 5th percentile of BMI for their age and sex were excluded since underweight is associated with increased risk for asthma.[22,23] Participants who did not have complete data of blood levels of lead, cadmium or mercury, or complete data on confounders such as obesity status, family income to poverty ratio and environmental tobacco exposure, were excluded. Finally, the data of 5866 subjects were retained for analysis.

Main outcome

The primary outcome of this study was active asthma, that is, those reporting ever having been told that they had asthma and/or who had an asthma attack in the past year. Active asthma was defined as those who responded "yes" to three questions: "Has a doctor or other health professional ever told you that you have asthma"? "Do you still have asthma"? and "During the past 12 months, have you had an episode of asthma or an asthma attack"?

Study variables

Asthma and wheezing

All participants aged 1 year and older were asked (by proxy if under age 16) whether a doctor or other health professional had ever said they had asthma. Those who answered "yes" were asked a series of additional questions, including whether they still had asthma, and whether they had experienced an asthma attack in the past year. (https://wwwn.cdc.gov/Nchs/Nhanes/2007-2008/MCQ_E.htm; https://wwwn.cdc.gov/Nchs/Nhanes/2003-2004/RDQ_C.htm). A separate set of questions was asked about wheezing. Wheezing outcomes analyzed in this study were patients' reports of wheezing or whistling in the chest in the past year (yes/no), as obtained by questionnaire or during the examination in the NHANES Medical Examination Center (MEC) (https://wwwn.cdc.gov/Nchs/Nhanes/2007-2008/MCQ_E.htm), as described previously.[28,29] Current wheezing or whistling was defined as those who responded "yes" to the question: "In the past 12 months have you had wheezing or whistling in your chest"?

Heavy metal levels

Whole blood mercury (Hg), lead (Pb) and cadmium (Cd) concentrations were determined using inductively coupled plasma mass spectrometry. The detailed description of the laboratory protocol and methods can be found at the NHANES Lab Protocol web page (https://wwwn.cdc.gov/Nchs/Nhanes/2003-2004/L06BMT_C.htm).

Demographic and anthropometric variables

Data of potential confounding variables were obtained from the demographic questionnaire filled out by NHANES interviewers for each participant, including: age, gender, race/ethnicity, family income to poverty ratio (shown as income/poverty ratio), prenatal maternal smoking, birth weight (low birth weight or not), received neonatal intensive care unit (NICU) care, close relative(s) had asthma and allergic rhinitis in past 12 months.

Physical examination by trained technicians at the NHANES MEC was used to calculate participants' body mass index (BMI; weight/height^2). Obesity or not was defined according to the NHANES Examination Protocol, which is based on the World Health Organization (WHO) standard BMI criteria of obesity as $\geq$30 kg/m^2 (National Health and Nutrition Examination Survey Body Mass Index data; http://wwwn.cdc.gov/Nchs/Nhanes/2007-2008/BMX_E.htm#BMXBMI). Gender-specific BMI percentiles-for-age were calculated using the CDC 2000 reference standards applied in NHANES data collection.[3] Children between the 5th and 85th percentiles of BMI for age were considered to be of normal weight, those between the 85th and 95th percentile were considered to be overweight, and those at or above the 95th percentile were considered to be obese, according to criteria of the American Medical Association.[30]

Environmental tobacco exposure was defined as those who responded "yes" to the question "Does anyone who lives here smoke cigarettes, cigars, or pipes anywhere inside this home"? Prenatal maternal smoking was defined as those who responded "yes" to the question: "Did (subject's) biological mother smoke at any time while she was pregnant with (him/her)"? Received NICU care was defined as those who responded "yes" to the question: "Did (subject's name) receive any newborn care in an intensive care unit, premature nursery, or any other type of special care facility"?

Having a close relative with asthma was defined as those who responded "yes" to the question: "Among family members living and deceased, were any of (subject's/your) close biological relatives (i.e., blood relatives) such as father, mother, sisters or brothers, ever told by a health professional that they had asthma"? Allergic rhinitis (hay fever) in past 12 months was defined as those who responded "yes" to the question: "During the past 12 months, have you (or has subject) had an episode of hay fever in the past year"?

Statistical analysis

Categorical variables are presented as frequency and weighted percentage, and continuous variables as the

mean and standardized error (mean ± SE). A logistic regression model of survey data was used to estimate odds ratios (ORs) of blood concentrations of heavy metals (i.e., cadmium, lead, mercury) and other factors for active asthma and current chest wheezing or whistling. Statistically significant factors in univariate regression analysis other than blood heavy metal concentrations were included in multivariate regression models after adjusting for ORs of blood heavy metal concentrations for each event. Subgroup analysis was performed after stratifying subjects into three groups by age: 2—5 years, 6—11 years, and 12—15 years. All statistical analyses were performed using the two-tailed *t*-test and results were considered significant at $p < 0.05$. All statistical analyses were performed using the SAS 9.4 software program (SAS Institute Inc., Cary, NC, USA).

Results

Among 8672 eligible subjects whose data were extracted from the NHANES 2007—2012 database, the final analytic sample after exclusions was 5866 subjects (Fig. 1). Subjects were stratified into three groups by age: ages 2—5 years (n = 1626), ages 6—11 years (n = 2751), and ages 12—15 years (n = 1489). Distribution of subjects' demographic and clinical characteristics is shown in Table 1. Blood cadmium

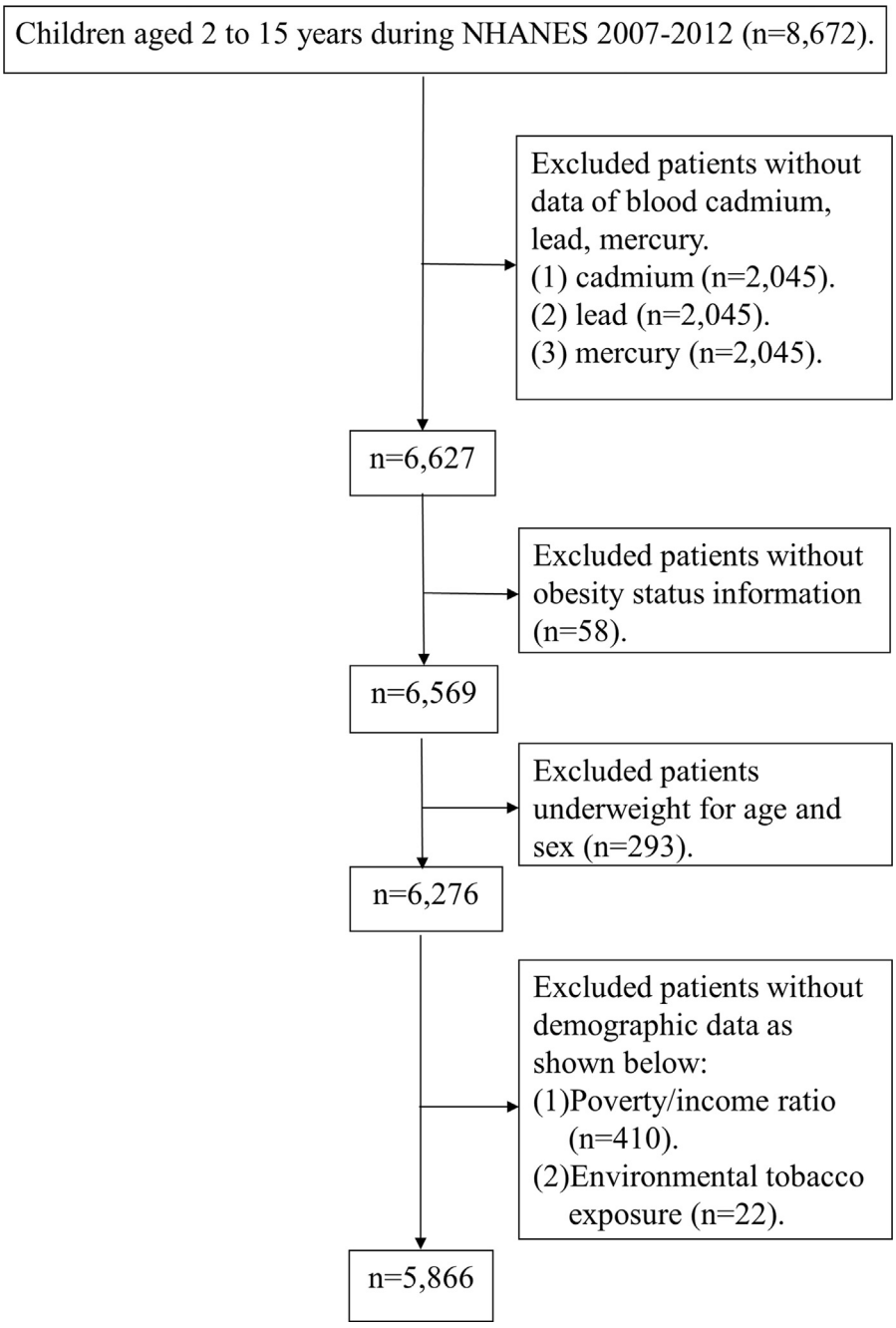

Figure 1. Study population selection flowchart.

Table 1 Characteristics distribution in study population, NHANES 2007–2012 (unweighted: 5866, weighted: 41,110,574.1).

	Total N = 5866	Age group		
	N (%)	Age 2–5 N = 1626 N (%)	Age 6–11 N = 2751 N (%)	Age 12–15 N = 1489 N (%)
Cadmium (nmol/L)[a]				
Mean ± SE.	1.46 ± 0.02	1.28 ± 0.02	1.34 ± 0.02	1.74 ± 0.06
Q1	1312 (25.6)	395 (27.4)	656 (24.6)	261 (19.6)
Q2	3082 (51.5)	969 (58.1)	1478 (54.6)	635 (42.6)
Q3	1472 (25.0)	262 (14.4)	617 (20.9)	593 (37.8)
Lead (μg/dL)[b]				
Mean ± SE.	1.03 ± 0.03	1.47 ± 0.07	0.97 ± 0.03	0.78 ± 0.02
Q1	1976 (40.7)	268 (21.4)	956 (40.5)	752 (54.8)
Q2	1951 (32.1)	489 (30.3)	984 (34.6)	478 (30.1)
Q3	1939 (27.2)	869 (48.3)	811 (24.9)	259 (15.1)
Mercury (μmol/L)[c]				
Mean ± SE.	2.71 ± 0.10	2.15 ± 0.12	2.73 ± 0.11	3.09 ± 0.17
Q1	1367 (26.5)	497 (34.6)	596 (24.7)	274 (23.1)
Q2	2506 (42.1)	755 (44.7)	1150 (42.1)	601 (40.2)
Q3	1993 (31.4)	374 (20.7)	1005 (33.2)	614 (36.7)
Data release cycle				
2007–2008	1945 (32.7)	564 (34.2)	909 (32.9)	472 (31.4)
2009–2010	1950 (32.6)	550 (32.8)	891 (32.4)	509 (32.7)
2011–2012	1971 (34.7)	512 (33.1)	951 (34.6)	508 (35.8)
Male (years)	3053 (51.9)	869 (52.3)	1408 (52.3)	776 (51.2)
Age				
2–5	1626 (23.6)			
6–11	2751 (43.3)			
12–15	1489 (33.1)			
Race/ethnicity				
Mexican American	1489 (15.6)	412 (17.4)	725 (16.1)	352 (13.7)
Other Hispanic	709 (7.3)	193 (8.4)	325 (7.1)	191 (6.9)
Non-Hispanic White	1699 (55.6)	483 (51.8)	779 (55.3)	437 (58.7)
Non-Hispanic Black	1459 (14.4)	397 (15.0)	692 (14.4)	370 (13.8)
Other race, including multi-racial	510 (7.0)	141 (7.3)	230 (7.0)	139 (6.9)
Poverty/income ratio				
Not poor	3720 (74.0)	942 (68.7)	1746 (73.3)	1032 (78.6)
Poor	2146 (26.0)	684 (31.3)	1005 (26.7)	457 (21.4)
Obesity status				
Normal weight	4904 (85.4)	1347 (83.8)	2276 (84.4)	1281 (87.9)
Overweight	633 (9.8)	182 (10.8)	309 (10.4)	142 (8.3)
Obese	329 (4.8)	97 (5.4)	166 (5.2)	66 (3.8)
Low birth weight				
No	5007 (87.1)	1384 (87.0)	2364 (87.2)	1259 (87.1)
Yes	733 (10.7)	224 (12.0)	327 (10.4)	182 (10.3)
Unknown	126 (2.1)	18 (1.1)	60 (2.4)	48 (2.6)
Received NICU care				
No	1715 (28.9)	504 (30.9)	811 (29.3)	400 (27.1)
Yes	220 (3.6)	58 (3.2)	94 (3.4)	68 (4.1)
Unknown	3931 (67.5)	1064 (65.9)	1846 (67.3)	1021 (68.8)
Prenatal maternal smoking				
No	4993 (84.0)	1371 (84.0)	2349 (83.9)	1273 (84.2)
Yes	800 (14.9)	248 (15.7)	362 (14.7)	190 (14.6)
Unknown	73 (1.05)	7 (0.3)	40 (1.4)	26 (1.2)
Environmental tobacco exposure				
No	875 (14.3)	244 (13.2)	425 (15.7)	206 (13.4)
Yes	4991 (85.7)	1382 (86.8)	2326 (84.3)	1283 (86.6)

Table 1 (*continued*)

	Total N = 5866	Age group		
	N (%)	Age 2–5 N = 1626 N (%)	Age 6–11 N = 2751 N (%)	Age 12–15 N = 1489 N (%)
Close relative with asthma				
No	2852 (51.6)	0	1845 (67.0)	1007 (68.3)
Yes	1316 (23.5)	0	863 (31.4)	453 (29.9)
Unknown	1698 (24.9)	1626 (100.0)	43 (1.6)	29 (1.9)
Allergic rhinitis past 12 months				
No	5235 (86.8)	1515 (91.3)	2431 (85.7)	1289 (85.2)
Yes	620 (13.0)	110 (8.6)	313 (14.2)	197 (14.5)
Unknown	11 (0.2)	1 (0.03)	7 (0.2)	3 (0.3)

[a] Trisection of cadmium: Q1: ≤1.24 nmol/L; Q2: 1.24–1.25 nmol/L; Q3: >1.25 nmol/L.
[b] Trisection of lead: Q1: ≤0.68 μg/dL; Q2: 0.68–1.12 μg/dL; Q3: >1.12 μg/dL.
[c] Trisection of mercury: Q1: <1.1 μmol/L; Q2: 1.1–2.5 μmol/L; Q3: ≥2.5 μmol/L.

and mercury concentrations both increased with age, while blood lead concentrations decreased with age. Non-Hispanic white was the most prevalent racial/ethnic group (55.6%). The weighted percentage of income/poverty ratio was 26.0%. The majority of the study population (85.4%) was normally weighted. About 14.9% and 85.7% of subjects were exposed to prenatal maternal smoking and environmental tobacco, respectively. About 23.5% and 13.0% of subjects had blood relatives with asthma and had experienced allergic rhinitis, respectively, in the past 12 months (Table 1).

Univariate logistic regression analysis revealed that ORs for active asthma increased with elevated lead concentrations only (OR = 1.06, 95% CI = 0.98–1.313) among the three types of heavy metals (lead, cadmium, mercury), but without statistically significant differences. Male gender (OR = 1.36 and 1.32), non-Hispanic black race/ethnicity (OR = 2.02 and 1.57), obese (OR = 1.82 and 1.60), close relative having asthma (OR = 5.50 and 3.12), and having allergic rhinitis in the past 12 months (OR = 3.97 and 4.05) were associated with higher risk of having active asthma and current wheezing or whistling (Table 2).

After adjusting for significant factors identified in the univariate analysis, higher concentrations of blood lead were associated with higher odds of having asthma (adjusted OR [aOR] = 1.08, 95% CI = 1.00–1.16), but no statistical effect was shown for current wheezing or whistling. Also, while no statistically significant differences were found in different concentrations of blood cadmium, lead and mercury were associated with active asthma and current wheezing or whistling. In the age-stratified analysis, higher blood lead concentration was associated with higher risk for active asthma (aOR = 1.24, 95% CI = 1.08–1.42) and current wheezing or whistling (aOR = 1.19, 95% CI = 1.04–1.38) in the 6–11 years age group; however, higher blood mercury concentration was associated with lower risk of current wheezing or whistling (aOR = 0.95, 95% CI = 0.90–0.99). No statistically significant differences were shown between the different concentrations of blood lead, cadmium, and mercury leading to active asthma and current wheezing or whistling in the 2–5 years and 12–15 years age groups. For heavy metal in the categorical variable, the result shows that children aged 2–5 years with medium levels of blood lead had lower risks for current wheezing or whistling compared to those with the lowest level of blood lead concentration (aOR = 0.54, 95% CI = 0.30–0.96) (Table 3).

Discussion

Results of the present study show that higher concentrations of blood lead are associated with higher odds of asthma in children aged 2–15 years. However, no statistically significant differences are found between different blood concentrations of cadmium and mercury associated with active asthma and current wheezing or whistling. Also, no statistically significant differences are shown between the different concentrations of blood lead, cadmium, and mercury associated with active asthma and current wheezing or whistling in those aged 2–5 years and 12–15 years. Compared to the lowest trisected concentration of blood lead, the medium and highest levels of blood lead are associated with lower odds of current wheezing or whistling in children aged 2–5 years, while the highest concentration of blood lead is associated with higher odds of asthma in those aged 12–15 years.

Results of the present study are compatible with those of previous studies by other authors. Wang et al.[13] compared blood lead levels in 930 children with and without allergic diseases or asthma, finding that lead was positively associated with asthma as well as with serum IgE, the latter occurring only in males, who also had higher concentrations of blood lead. The authors estimated that 38% of the total effect of lead exposure on asthma was mediated by IgE levels. The present study also found higher levels in males. Results of Wang et al.[13] strongly suggest an IgE immune mechanism that explains asthma in children exposed to lead, which also helps to explain the report of Mohammad et al.[24] that blood lead levels correlate with children's asthma severity. Linear trends were also seen across age groups in a Korean study[12] that linked whole blood lead levels with IgE and asthma, but this was not seen in children with cadmium exposure even though blood levels were increased.

Table 2 Results of univariate logistic regression for asthma and associated factors in study population, NHANES 2007–2012.

	Active asthma	Current wheezing or whistling
	Crude OR (95% CI)	Crude OR (95% CI)
Cadmium (nmol/L)[a]		
Continuous var.	1.01 (0.87–1.17)	0.98 (0.83–1.15)
Q1	1.0	1.0
Q2	0.85 (0.64–1.13)	0.84 (0.63–1.14)
Q3	0.99 (0.66–1.48)	0.84 (0.60–1.18)
Lead (μg/dL)[b]		
Continuous var.	1.06 (0.98–1.13)	1.01 (0.94–1.09)
Q1	1.0	1.0
Q2	0.93 (0.64–1.35)	0.84 (0.64–1.12)
Q3	1.09 (0.81–1.49)	1.08 (0.83–1.41)
Mercury (μmol/L) [c]		
Continuous var.	1.00 (0.95–1.05)	0.98 (0.94–1.02)
Q1	1.0	1.0
Q2	1.35 (0.99–1.82)	1.02 (0.79–1.30)
Q3	1.01 (0.69–1.47)	0.83 (0.65–1.07)
Male vs. Female	1.36 (1.002–1.85)*	1.32 (1.05–1.65)*
Age (vs. 2–5)		
6–11	1.14 (0.87–1.50)	0.79 (0.65–0.96)*
12–19	1.31 (0.98–1.76)	0.84 (0.64–1.13)
Race/ethnicity (vs. Non-Hispanic White)		
Mexican American	0.79 (0.57–1.11)	0.74 (0.56–0.97)*
Other Hispanic	1.65 (1.16–2.34)*	1.11 (0.81–1.52)
Non-Hispanic Black	2.02 (1.52–2.67)***	1.57 (1.24–1.97)**
Other race including multi-racial	1.73 (1.14–2.61)*	1.13 (0.86–1.51)
Poverty/income ratio		
Poor vs. Not poor	1.29 (0.86–1.94)	0.97 (0.73–1.28)
Obesity status (vs. Normal weight)		
Overweight	1.18 (0.80–1.72)	1.29 (0.97–1.71)
Obese	1.82 (1.02–3.26)*	1.60 (1.08–2.37)*
Low birth weight		
Yes vs. No	1.42 (0.94–2.14)	1.14 (0.85–1.53)
Received NICU care		
Yes vs. No	1.68 (0.95–2.97)	1.41 (0.98–2.04)
Prenatal maternal smoking		
Yes vs. No	1.07 (0.73–1.57)	1.07 (0.78–1.47)
Environmental tobacco exposure		
Yes vs. No	1.06 (0.74–1.52)	1.04 (0.81–1.35)
Close relative with asthma		
Yes vs. No	5.50 (3.79–7.98)***	3.12 (2.38–4.10)***
Allergic rhinitis past 12 months		
Yes vs. No	3.97 (3.08–5.10)***	4.05 (2.97–5.51)***

[a] Trisection of cadmium: Q1: ≤1.24 nmol/L; Q2: 1.24–1.25 nmol/L; Q3: >1.25 nmol/L.
[b] Trisection of lead: Q1: ≤0.68 μg/dL; Q2: 0.68–1.12 μg/dL; Q3: >1.12 μg/dL.
[c] Trisection of mercury: Q1: <1.1 μmol/L; Q2: 1.1–2.5 μmol/L; Q3: ≥2.5 μmol/L.
* $p < 0.05$, ** $p < 0.001$, *** $p < 0.0001$.

In the present study, although both cadmium and mercury levels increased with age, association with asthma was not significant. However, a study of 224 children in Poland found that even very low levels of prenatal exposure to lead had more than doubled the relative risk (RR) at 5 years for atopic skin sensitization (RR = 2.25, 95% CI: 1.21–4.19).[9] In Korea, a cross-sectional analysis of urinary mercury in 4350 children aged 10 years found an association between mercury exposure and current and lifetime risk of asthma.[31] Kim et al.[32] found an association between prenatal exposure to cadmium and development of atopic dermatitis in infants exposed to the cadmium in utero. In South Africa, prenatal cadmium exposure was associated with lower birth weight in female neonates but not males; maternal smoking was shown to be the source of cadmium and cadmium levels in cord blood suggested that protection from exposure was not offered by the placenta.[33] These findings suggest a possible enhanced sensitivity to aeroallergens in children with prenatal exposure to heavy metals, and this type of sensitization is a common precursor

Table 3 Results of multiple logistic regression analysis for asthma and associated factors in study population, NHANES 2007–2012.

	Active asthma[d]	Current wheezing or whistling[e]
	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Continuous var.		
Cadmium (nmol/L)	1.02 (0.88–1.18)	0.99 (0.84–1.18)
Lead (μg/dL)	1.08 (1.00–1.16)*	0.99 (0.92–1.08)
Mercury (μmol/L)	0.99 (0.94–1.04)	0.98 (0.95–1.01)
Trisection of heavy metal concentrations		
Cadmium[a] (nmol/L) (vs. Q1)		
Q2	0.97 (0.74–1.27)	0.94 (0.71–1.25)
Q3	1.02 (0.72–1.43)	0.89 (0.64–1.24)
Lead[b] (μg/dL) (vs. Q1)		
Q2	0.93 (0.63–1.37)	0.83 (0.62–1.11)
Q3	1.18 (0.82–1.68)	1.08 (0.81–1.43)
Mercury[c] (μmol/L) (vs. Q1)		
Q2	1.39 (0.99–1.97)	1.06 (0.81–1.39)
Q3	0.95 (0.61–1.47)	0.85 (0.66–1.11)
Ages 2–5 years		
Continuous var.		
Cadmium (nmol/L)	1.15 (0.64–2.08)	0.69 (0.37–1.30)
Lead (μg/dL)	0.99 (0.86–1.14)	0.87 (0.75–1.01)
Mercury (μmol/L)	0.96 (0.87–1.05)	0.94 (0.88–1.01)
Trisection of heavy metal concentrations		
Cadmium[a] (nmol/L) (vs. Q1)		
Q2	1.33 (0.71–2.51)	0.89 (0.57–1.39)
Q3	1.13 (0.49–2.61)	0.69 (0.36–1.29)
Lead[b] (μg/dL) (vs. Q1)		
Q2	0.56 (0.24–1.32)	0.54 (0.30–0.96)*
Q3	0.76 (0.40–1.44)	0.64 (0.39–1.04)
Mercury[c] (μmol/L) (vs. Q1)		
Q2	1.56 (0.79–3.10)	0.81 (0.53–1.23)
Q3	1.17 (0.53–2.57)	0.83 (0.54–1.27)
Ages 6–11 years		
Continuous var.		
Cadmium (nmol/L)	0.81 (0.56–1.19)	0.80 (0.55–1.17)
Lead (μg/dL)	1.24 (1.08–1.42)*	1.19 (1.04–1.38)*
Mercury (μmol/L)	0.95 (0.90–0.99)*	0.96 (0.92–1.00)
Trisection of heavy metal concentrations		
Cadmium[a] (nmol/L) (vs. Q1)		
Q2	0.91 (0.92–1.37)	1.09 (0.74–1.59)
Q3	0.75 (0.46–1.22)	0.78 (0.49–1.23)
Lead[b] (μg/dL) (vs. Q1)		
Q2	1.05 (0.68–1.62)	0.85 (0.63–1.48)
Q3	1.31 (0.82–2.07)	1.31 (0.88–1.96)
Mercury[c] (μmol/L) (vs. Q1)		
Q2	0.96 (0.62–1.49)	1.15 (0.74–1.77)
Q3	0.75 (0.44–1.28)	0.91 (0.61–1.37)
Ages 12–15 years		
Continuous var.		
Cadmium (nmol/L)	1.00 (0.84–1.19)	1.03 (0.87–1.22)
Lead (μg/dL)	1.22 (0.90–1.64)	1.02 (0.79–1.31)
Mercury (μmol/L)	1.02 (0.93–1.11)	1.01 (0.95–1.06)
Trisection of heavy metal concentrations		
Cadmium[a] (nmol/L) (vs. Q1)		
Q2	0.78 (0.36–1.72)	0.77 (0.38–1.53)
Q3	0.99 (0.41–2.35)	0.99 (0.43–2.31)

(*continued on next page*)

Table 3 (*continued*)

	Active asthma[d]	Current wheezing or whistling[e]
	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Lead[b] (μg/dL) (vs. Q1)		
Q2	1.15 (0.56–2.38)	1.05 (0.59–1.85)
Q3	1.48 (0.82–2.68)	1.24 (0.64–2.41)
Mercury[c] (μmol/L) (vs. Q1)		
Q2	2.09 (0.79–5.53)	1.24 (0.69–2.23)
Q3	1.06 (0.33–3.44)	0.81 (0.48–1.37)

[a] Trisection of cadmium: Q1: ≤1.24 nmol/L; Q2: 1.24–1.25 nmol/L; Q3: >1.25 nmol/L.
[b] Trisection of lead: Q1: ≤0.68 μg/dL; Q2: 0.68–1.12 μg/dL; Q3: >1.12 μg/dL.
[c] Trisection of mercury: Q1: <1.1 μmol/L; Q2: 1.1–2.5 μmol/L; Q3: ≥2.5 μmol/L.
[d] Model adjusted for blood cadmium, blood lead, blood mercury, sex, race, obesity status, close relative with asthma, allergic rhinitis past 12 months.
[e] Model adjusted for blood cadmium, blood lead, blood mercury, sex, age, race, obesity status, close relative with asthma, allergic rhinitis past 12 months.
* $p < 0.05$, ** $p < 0.001$, *** $p < 0.0001$.

to asthma and allergic rhinitis from infancy into early childhood.

While many studies agree on heavy metal-induced allergic disease, controversy remains over the association of heavy metal exposure and asthma, particularly in terms of mercury. A noted discrepancy is found between the lack of association between mercury exposure and risk of wheeze and eczema in Japanese children[34] and the more recent report of Kim et al.,[31] who found a correlation between asthma risk and mercury exposure in school-age Korean children. An earlier report from Korea also showed a positive association between blood mercury levels and atopic dermatitis in adults.[35] The controversy can be considered simply as "mixed results," or it may indicate that changes in the immune system blood profile of children with elevated mercury concentration and asthma suggest immunotoxicity.[31] A German study[36] also explored the associations between mercury and childhood asthma in subjects with low mercury levels, finding no significant association; the authors explained their null findings as differences in setting and source of mercury exposure between their study in Germany and the study of Kim et al.[31] in Korea, suggesting that further studies are needed to assess prenatal and childhood mercury exposure.

Examples of immunotoxicity from environmental toxicants have been reported. The immune system is shown to be one of the most sensitive targets for lead toxicity.[37] The immunotoxic effects of heavy metals were demonstrated by polyclonal B cell activation and the induction of autoantibodies in subjects with oral exposure to cadmium at environmental levels; similar B cell activation was seen with lead and mercury.[38] In a study of prenatal cadmium exposure, postnatal immune cell development and function were altered in all cadmium-exposed offspring; even low cadmium exposure is suggested to have long-term detrimental effects.[20] Associations were found between IgE, eosinophils, and asthma in a study of 1788 children from NHANES 2005–2006; although they found no direct association between current blood levels of lead and asthma, the authors concluded that early life exposure to lead and other heavy metals may alter immune function and predispose children to develop allergic diseases, including asthma.[21] Pre- and post-natal exposure to heavy metals, such as lead, elevate production of IgE, which may have the potential to increase the risk of allergic disease and asthma.[14] Increased recognition that heavy metals alter immune system function has advanced the understanding of environmentally-induced immunotoxicity, particularly how environmental agents may trigger the immune process and autoimmune response.[18] The immune effects of environmental substances may, therefore, serve as potential biomarkers for evaluating the health effects of heavy metal exposure, ultimately confirming associations between heavy metals and asthma as shown in the present study and others.

There is no doubt that environmental exposure to industrial- and traffic-based fine-particle metal pollutants has an impact on the health of populations, particularly the respiratory health of children.[39] Children in New York City between ages nine and eleven who were found to have fractional exhaled nitric oxide (FeNO) also had positive associations with blood iron, nickel, and vanadium.[40] One study found elevated blood levels in preschoolers associated with incense burning in the home.[41] In a Korean population-based study of children and adolescents,[42] sociodemographic factors such as age, sex, and fathers' education levels were associated with increased environmental exposure to heavy metals, pointing out the importance of these data in performing ongoing surveillance to help understand environmental exposure and public health trends. As in the present study, the lead was more positively associated with sociodemographic variables such as age, and higher levels were associated with health risks. Public health policies and programs are urgently needed to reduce the levels of toxicants and the environmental exposure to them that may present public health risks, particularly in children.

The present study has several limitations. First, the NHANES database is cross-sectional, and cross-sectional analysis does not allow causal inferences to be made. Also, the NHANES questionnaire and interview data are based on self-reports or reports of adult proxy and may be

subject to recall issues, misunderstanding of questions, and other factors that may limit interpretation of results. Further, although the NHANES database is comprehensive and nationally representative of the U.S. population, including representative of different racial/ethnic groups, findings of the present study are generalizable to the overall U.S. population but are not likely generalizable to other populations or locations. Additional studies in other locations are still needed. Future prospective longitudinal and interventional studies of large samples of children aged 2—15 are warranted to confirm the findings of the present study and to further examine the effects of heavy metals on childhood asthma and wheezing.

In conclusion, higher concentrations of blood lead are associated with higher odds of asthma in children aged 2—15 years, especially those 12—15, but no associations are found between blood levels of cadmium and mercury and active asthma and current wheezing or whistling in children aged 2—15. Results of the present study regarding the effects of heavy metals may inspire public health efforts to expand focused interventions directed at reducing the sources of environmental exposure.

Funding source

None.

Financial disclosure

None.

Contributors' statement

Keh-Gong Wu: guarantor of integrity of the entire study; study concepts; study design; definition of intellectual content; literature research; clinical studies; experimental studies; data acquisition; data analysis; statistical analysis; manuscript preparation; manuscript editing; manuscript review.

Chun-Yu Yen: study concepts; literature research; data acquisition; data analysis; statistical analysis; manuscript review.

Chia-Yuan Chang: study concepts; literature research; data acquisition; data analysis; statistical analysis; manuscript review.

Chou-Cheng Lai: study concepts; literature research; data acquisition; data analysis; manuscript editing; manuscript review.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflicts of interest

All authors have no conflicts of interest to declare.

Acknowledgments

The authors wish to thank the National Center for Health Statistics (NCHS) for creating the NHANES database and making it available for research. We understand that interpretation and reporting of these data are the sole responsibility of the authors.

References

1. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Publ Health* 2012;**12**:204.
2. Asher I, Pearce N. Global burden of asthma among children. *Int J Tubercul Lung Dis* 2014;**18**:1269—78.
3. Centers for Disease Control and Prevention. *Data, statistics, and surveillance. Asthma surveillance data*. 2016. Available at: http://www.cdc.gov/asthma/asthmadata.html [accessed 7 August 2018].
4. Joseph CL, Havstad S, Ownby DR, Peterson EL, Maliarik M, McCabe Jr MJ, et al. Blood lead level and risk of asthma. *Environ Health Perspect* 2005;**113**:900—4.
5. Centers for Disease Control and Prevention. *Asthma in the US. Growing every year*. 2011. Available at: https://www.cdc.gov/vitalsigns/asthma/index.html [accessed 7 August 2018].
6. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;**380**:2163—96.
7. Tsao SM, Ko YK, Chen MZ, Chiu MH, Lin CS, Lin MS, et al. A survey of allergic rhinitis in Taiwanese asthma patients. *J Microbiol Immunol Infect* 2011;**44**:139—43.
8. Lin LL, Huang SJ, Ou LS, Yao TC, Tsao KC, Yeh KW, et al. Exercise-induced bronchoconstriction in children with asthma: an observational cohort study. *J Microbiol Immunol Infect* 2017 Sep 6. https://doi.org/10.1016/j.jmii.2017.08.013. pii: S1684-1182(17)30196-2 [Epub ahead of print].
9. Jedrychowski W, Perera F, Maugeri U, Miller RL, Rembiasz M, Flak E, et al. Intrauterine exposure to lead may enhance sensitization to common inhalant allergens in early childhood: a prospective prebirth cohort study. *Environ Res* 2011;**111**:119—24.
10. Razi CH, Akin O, Harmanci K, Akin B, Renda R. Serum heavy metal and antioxidant element levels of children with recurrent wheezing. *Allergol Immunopathol* 2011;**39**:85—9.
11. Rabito FA, Horter L, Langlois EC, Carlson JC, White LE, Schwartz K, et al. Blood lead and pediatric asthma. *Epidemiology* 2013;**24**:474—6.
12. Park S, Lee EH, Kho Y. The association of asthma, total IgE, and blood lead and cadmium levels. *J Allergy Clin Immunol* 2016;**138**:1701—1703. e6.
13. Wang IJ, Karmaus WJJ, Yang CC. Lead exposure, IgE, and the risk of asthma in children. *J Expo Sci Environ Epidemiol* 2017;**27**:478—83.
14. Dietert RR, Zelikoff JT. Early-life environment, developmental immunotoxicology, and the risk of pediatric allergic disease including asthma. *Birth Defects Res B Dev Reprod Toxicol* 2008;**83**:547—60.
15. Godri Pollitt KJ, Maikawa CL, Wheeler AJ, Weichenthal S, Dobbin NA, Liu L, et al. Trace metal exposure is associated with increased exhaled nitric oxide in asthmatic children. *Environ Health* 2016;**15**:94.
16. Dunea D, Iordache S, Liu HY, Bohler T, Pohoata A, Radulescu C. Quantifying the impact of PM2.5 and associated heavy metals on respiratory health of children near metallurgical facilities. *Environ Sci Pollut Res Int* 2016;**23**:15395—406.
17. Wang JY, Shyur SD, Lam FW, Wu LS. Polymorphisms of EHF-ELF5 genomic region and its association with pediatric asthma in the Taiwanese population. *J Microbiol Immunol Infect* 2016;**49**:879—84.

18. Mishra KP. Lead exposure and its impact on immune system: a review. *Toxicol In Vitro* 2009;**23**:969—72.
19. Zhang QF, Li YW, Liu ZH, Chen QL. Exposure to mercuric chloride induces developmental damage, oxidative stress and immunotoxicity in zebrafish embryos-larvae. *Aquat Toxicol* 2016;**181**:76—85.
20. Hanson ML, Holaskova I, Elliott M, Brundage KM, Schafer R, Barnett JB. Prenatal cadmium exposure alters postnatal immune cell development and function. *Toxicol Appl Pharmacol* 2012;**261**:196—203.
21. Wells EM, Bonfield TL, Dearborn DG, Jackson LW. The relationship of blood lead with immunoglobulin E, eosinophils, and asthma among children: NHANES 2005-2006. *Int J Hyg Environ Health* 2014;**217**:196—204.
22. Braback L, Hjern A, Rasmussen F. Body mass index, asthma and allergic rhinoconjunctivitis in Swedish conscripts-a national cohort study over three decades. *Respir Med* 2005;**99**: 1010—4.
23. Kwon HL, Ortiz B, Swaner R, Shoemaker K, Jean-Louis B, Northridge ME, et al. Childhood asthma and extreme values of body mass index: the Harlem Children's Zone Asthma Initiative. *J Urban Health* 2006;**83**:421—33.
24. Mohammed AA, Mohamed FY, El-Okda el S, Ahmed AB. Blood lead levels and childhood asthma. *Indian Pediatr* 2015;**52**: 303—6.
25. Jain RB. Trends and variability in blood lead concentrations among US children and adolescents. *Environ Sci Pollut Res Int* 2016;**23**:7880—9.
26. Jain RB. Trends over 1999—2014 in the concentrations of Ba, Cs, Co, Mo, Pb, Sb, Tl, and W in urine of US children aged 6—11 years. *Toxicol Environ Chem* 2018;**100**:115—33.
27. Zipf G, Chiappa M, Porter KS, Ostchega Y, Lewis BG, Dostal J. National health and nutrition examination survey: plan and operations, 1999-2010. *Vital Health Stat* 2013;**1**(56):1—37.
28. Huang X, Xie J, Cui X, Zhou Y, Wu X, Lu W, et al. Association between concentrations of metals in urine and adult asthma: a case-control study in Wuhan, China. *PLoS One* 2016;**11**: e0155818.
29. Visness CM, London SJ, Daniels JL, Kaufman JS, Yeatts KB, Siega-Riz AM, et al. Association of childhood obesity with atopic and nonatopic asthma: results from the National Health and Nutrition Examination Survey 1999-2006. *J Asthma* 2010; **47**:822—9.
30. Krebs NF, Himes JH, Jacobson D, Nicklas TA, Guilday P, Styne D. Assessment of child and adolescent overweight and obesity. *Pediatrics* 2007;**120**(Suppl 4):S193—228.
31. Kim KN, Bae S, Park HY, Kwon HJ, Hong YC. Low-level mercury exposure and risk of asthma in school-age children. *Epidemiology* 2015;**26**:733—9.
32. Kim JH, Jeong KS, Ha EH, Park H, Ha M, Hong YC, et al. Association between prenatal exposure to cadmium and atopic dermatitis in infancy. *J Kor Med Sci* 2013;**28**:516—21.
33. Rollin HB, Kootbodien T, Channa K, Odland JO. Prenatal exposure to cadmium, placental permeability and birth outcomes in coastal populations of South Africa. *PLoS One* 2015; **10**:e0142455.
34. Miyake Y, Tanaka K, Yasutake A, Sasaki S, Hirota Y. Lack of association of mercury with risk of wheeze and eczema in Japanese children: the Osaka Maternal and Child Health Study. *Environ Res* 2011;**111**:1180—4.
35. Park H, Kim K. Association of blood mercury concentrations with atopic dermatitis in adults: a population-based study in Korea. *Environ Res* 2011;**111**:573—8.
36. Heinrich J, Guo F, Trepka MJ. Low-level mercury exposure and risk of asthma in school-age children. *Epidemiology* 2017;**28**:116—8.
37. Min JY, Min KB, Kim R, Cho SI, Paek D. Blood lead levels and increased bronchial responsiveness. *Biol Trace Elem Res* 2008; **123**:41—6.
38. Ohsawa M. Heavy metal-induced immunotoxicity and its mechanisms. *Yakugaku Zasshi* 2009;**129**:305—19 (article in Japanese).
39. Cara AC, Degryse J, van den Akker M, Dinant GJ, Manolovici C, Buntinx F. Impact of early childhood air pollution on respiratory status of school children. *Eur J Gen Pract* 2010;**16**:133—8.
40. Rosa MJ, Benedetti C, Peli M, Donna F, Nazzaro M, Fedrighi C, et al. Association between personal exposure to ambient metals and respiratory disease in Italian adolescents: a cross-sectional study. *BMC Pulm Med* 2016;**16**:6.
41. Hwang YH, Lin YS, Lin CY, Wang IJ. Incense burning at home and the blood lead level of preschoolers in Taiwan. *Environ Sci Pollut Res Int* 2014;**21**:13480—7.
42. Burm E, Song I, Ha M, Kim YM, Lee KJ, Kim HC, et al. Representative levels of blood lead, mercury, and urinary cadmium in youth: Korean Environmental Health Survey in Children and Adolescents (KorEHS-C), 2012-2014. *Int J Hyg Environ Health* 2016;**219**:412—8.