Low-level Mercury Exposure and Risk of Asthma in School-age Children

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Background: Mercury (Hg) has been reported to have adverse effects on the immune system. However, the association between Hg exposure and asthma remains unclear. We hypothesized that blood Hg concentrations are associated with asthma and immune system blood profile changes in school-age children.

Methods: Between 2005 and 2010, we evaluated 4,350 Korean children at 7–8 years of age with no previous asthma diagnosis. Follow-up surveys were conducted twice, each 2 years apart, until 11–12 years of age. For every survey, we evaluated asthma through a questionnaire and blood profile. We analyzed the association of Hg concentration with asthma by logistic and Cox regression models and the association with blood profile by generalized additive and linear mixed models.

Results: Blood Hg concentrations at 7–8 years of age were associated with an increased risk of asthma (odds ratio [OR] = 1.3; 95% confidence interval [CI] = 1.0, 1.6) at ages up to 11–12 years (n = 191). Hg concentration was also associated with wheezing (OR = 1.2; 95% CI = 1.0, 1.3), asthma medication use (OR = 1.4; 95% CI = 0.97, 2.0), and airway hyperresponsiveness (OR = 1.2; 95% CI = 1.0, 1.3). Further adjustment for fish consumption did not change the results appreciably.

Conclusions: Low-level Hg exposure was associated with asthma and blood profile changes in school-age children.

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Asthma is one of the most common respiratory diseases in children. Although it is reported that the prevalence of asthma has plateaued or declined in some countries,[1,2] asthma is still a major public health problem in industrialized countries and increasingly in developing countries.[3]

Mercury (Hg) is a ubiquitous heavy metal and of global concern due to its extensive distribution and serious adverse health effects. Hg exposure, even at the low levels typically experienced locally in developed countries, has been associated with various adverse health effects, such as reduced birth weight,[4] impaired infant growth within the first 2 years,[5] delayed performance on both psychomotor and mental developmental indices,[6] elevated blood pressure,[7] and coronary heart disease.[8,9]

The effect of Hg exposure on the immune system has also been reported. Several toxicologic studies have reported immunomodulatory effects of Hg.[10–12] Epidemiologic studies have suggested effects of Hg exposure on the proportion of immune cells and cytokine production.[13–15] However, only a few studies have examined the relation between Hg exposure and allergic disease, with mixed results. A birth cohort study of Japanese mother–child pairs found no association between Hg exposure and wheezing or eczema,[16] but a cross-sectional study of Korean adults showed an association of Hg exposure with increased risk of atopic dermatitis.[17]

However, to the best of our knowledge, the hypothesis that Hg exposure increases the risk of asthma has never been studied. Under the hypothesis that the potential effects of Hg on the immune system are related to the development of allergic diseases, such as asthma,[14–17] we conducted a longitudinal study to evaluate the association of low-level Hg exposure with the development of asthma and immune system blood profile changes in school-age children.

METHODS

Study Population and Data Collection

The Children's Health and Environment Research study was conducted between 2005 and 2010 to investigate the relation between environmental factors and allergic or neurodevelopmental disorders in school-age children. We recruited children from 33 elementary schools in 10 Korean cities. We performed three surveys, each 2 years apart. All of the parents of the participating children submitted written informed consent, and the ethical review board of the Dankook University College of Medicine approved the study protocols.

Of 5,826 participants enrolled at 7–8 years of age, we subsequently excluded those with a previous asthma history

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(n = 963) or with no Hg measurement (n = 502) and those who had been diagnosed with diabetes mellitus (n = 2), cancer (n = 3), or a developmental disorder (n =5) or whose mother had been diagnosed with schizophrenia (n = 1); 4,350 enrolled children were eligible for analysis (Figure 1).

Data collection comprised questionnaires completed by parents, blood samples, and anthropometric measurements conducted during each survey. The questionnaires contained demographic information, socioeconomic status, medical and family history, and symptoms of allergic disease.

Blood Sample Analysis

Whole blood samples (3–5 ml) were collected from each child and then sealed in a heparin-containing tube. Blood samples were sent to the laboratory (NeoDin Medical Institute, Seoul, Korea), and Hg levels were determined by cold vapor atomic absorption spectrophotometry (M-6000A; CETAC Technologies, Omaha, NE). To ensure quality control, an internal control was used at every series of analyses. The precision of Hg measurements was validated by an external quality control program based on interlaboratory calibration. The Hg concentrations in all of the blood samples were above the limit of detection (0.008 μg/liter).

Venous blood samples were taken after an overnight fast of more than 8 hours before the survey. The peripheral white blood cell (WBC) differential counts were measured by automated blood cell counters (Coulter STKS; Coulter Electronics, Hialeah, FL). Measurement for high-sensitivity C-reactive protein (hs-CRP) was performed by a particle-enhanced immunoturbidometric method (ADVIA 1650; Siemens Diagnostic Solutions, Tarrytown, NY). Serum total IgE was analyzed by fluorescent enzyme immunoassay method (Unicap; Pharmacia & Upjohn Diagnostics, Uppsala, Sweden).

Measure of Asthma-related Outcomes

Asthma was defined based on the parental response to the following question: "Did a doctor ever diagnose asthma in your child?" (n = 4,350 at 7–8 years; n = 3,197 at 9–10 years; n = 2,179 at 11–12 years). Incident asthma was defined as the first asthma occurrence without having been diagnosed previously. Wheezing in the past 12 months (n = 4,350 at 7–8 years; n = 3,208 at 9–10 years; n = 2,137 at 11–12 years) and asthma medication use in the past 12 months (n = 4,350 at 7–8 years; n = 3,207 at 9–10 years; n = 2,137 at 11–12 years) were also assessed based on parental reporting ("Has your child experienced wheezing in the past 12 months?" and "Did your child use asthma medication in the past 12 months?", respectively).

Airway hyperresponsiveness (n = 2,230 at 7–8 years; n = 1,717 at 9–10 years; n = 459 at 11–12 years) was evaluated by a methacholine challenge test and expressed as PC_{20}, which is the methacholine concentration that induces 20% fall in forced expiratory volume in 1 second as measured by a portable spirometer (Microspiro HI 298; Chest Corporation, Tokyo, Japan). $PC_{20} \leq 8$ mg/ml was defined as hyperresponsiveness.

Covariates

Paternal and maternal asthma history and children's gender were reported on the baseline questionnaire. Fetal tobacco smoke exposure was defined as positive when the children's mother had smoked during pregnancy or there had been a smoker at home during pregnancy. Environmental tobacco smoke exposure was defined as positive when there had ever been a smoker at home from delivery until the time of the survey. Paternal and maternal education level was categorized as less than a high school diploma, high school diploma, or more than a high school diploma. Fish consumption was categorized as none, once a week, two to three times a week, four to five times a week, or greater than five times a week. Pet ownership was defined as having ever kept pet dogs or cats until the time of the survey.

Statistical Analysis

We transformed blood Hg concentration to approximate a normal distribution. The associations of log-transformed Hg concentration (continuous) with asthma at ages up to

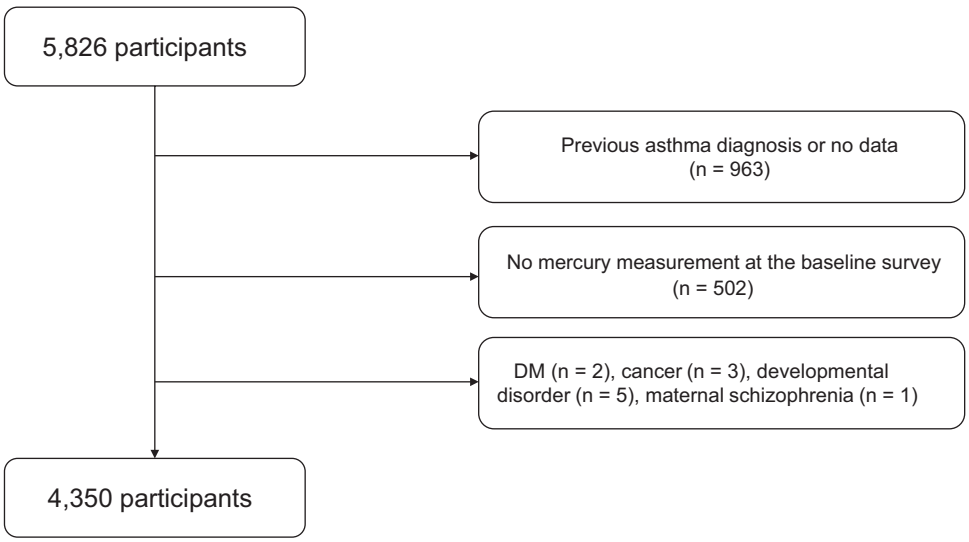

FIGURE 1. Overview of study population. DM indicates diabetes mellitus.

9–10 years and 11–12 years were evaluated using logistic regression models adjusted for the potential confounders. We applied a Cox proportional hazards model to analyze the association between Hg concentration at 7–8 years of age and incident asthma and tested the proportional hazards assumption using a time-dependent explanatory variable. The time at risk for those with incident asthma was assigned as the number of months from the baseline survey to the midpoint between the previous survey and the survey when the current asthma was first observed. The time at risk for those without incident asthma was calculated as the number of months between the baseline survey and the last follow-up survey. The association between Hg concentration and repeatedly measured dichotomous outcome variables, such as wheezing, asthma medication use, and airway hyperresponsiveness, was analyzed using generalized estimating equations with a logit link to account for within-subject correlation of the observations.

We assessed the effects of Hg exposure on available blood indices related to the immune system after stratifying by asthma development during the study period. The WBC count, monocyte percentage, basophil percentage, hs-CRP, and total IgE were also log-transformed for normality. We constructed a linear mixed model to investigate the relation between Hg concentration and WBC count, segmented neutrophil percentage, lymphocyte percentage, monocyte percentage, basophil percentage, hs-CRP, and total IgE. We examined the linearity of associations with a generalized additive mixed model. Gender-specific associations were evaluated after children were stratified into subgroups based on gender.

We adjusted all models for the covariates, such as gender, paternal and maternal asthma history, fetal and environmental tobacco smoke exposure, paternal and maternal education level, and pet ownership, which was selected a priori based on an earlier literature review.

We also investigated the association between Hg and asthma among 2,705 children ages 10 years or younger using the 2011–2012 National Health and Nutrition Examination Survey (NHANES) data. We conducted logistic regression analyses adjusted for age, gender, family history of asthma, maternal smoking during pregnancy, smokers at home, and poverty income ratio with appropriate sample weights, strata, and cluster variables to account for complex, multistage sampling design.

We performed several sensitivity analyses. First, we conducted all analyses after weighting the follow-up observations that were more likely to be missing to account for loss of follow-up.[18] A weight of one was assigned to the observation at the baseline survey for each child, and the inverse of predicted probability of having a follow-up was assigned as an imputed weight to the subsequent observation.[19] Second, we conducted further adjustment for fish consumption with the children for whom this information was available (n = 2,850). Third, due to the concern for potential confounding, we further adjusted the main models for the city in which the study participants were recruited. Fourth, we assigned the time at risk for those with incident asthma as the number of months from the baseline survey to the survey when the current asthma was first observed. The time at risk for those without incident asthma was defined similarly to the main model.

We conducted all analyses with SAS version 9.4 (SAS Institute Inc., Cary, NC), and carried out all visualization with R version 3.1.0 (The Comprehensive R Archive Network: http://cran.r-project.org).

RESULTS

Table 1 shows the characteristics of children included in the present analyses, stratified by asthma occurrence during the study period. Of the 4,350 children included, 50% were boys, 2% had maternal asthma, 2% had paternal asthma, and most children ate fish fewer than four times a week. Children who had asthma during the study period were more likely to have parents with a history of asthma and to own a pet. When

TABLE 1. Baseline Characteristics of Study Participants by Occurrence of Asthma During the Study Period

	Total (n = 4,350), No. (%)	Children With Asthma (n = 191), No. (%)	Children Without Asthma (n = 4,159), No. (%)
Maternal asthma	65 (2)	14 (7)	51 (1)
Paternal asthma	83 (2)	14 (7)	69 (2)
Fetal tobacco smoke exposure[a]	925 (22)	38 (21)	887 (22)
Environmental tobacco smoke exposure[b]	1,377 (32)	61 (33)	1,316 (32)
Maternal education			
Less than high school diploma	196 (5)	11 (6)	185 (5)
High school diploma	2,348 (57)	99 (55)	2,249 (57)
More than high school diploma	1,612 (39)	71 (39)	1,541 (39)
Paternal education			
Less than high school diploma	185 (4)	6 (3)	179 (4)
High school diploma	1,846 (44)	91 (49)	1,755 (44)
More than high school diploma	2,157 (52)	87 (47)	2,070 (52)
Fish intake			
None	75 (3)	4 (4)	71 (3)
Once/week	1,379 (48)	53 (47)	1,326 (48)
2–3 times/week	1,227 (43)	46 (41)	1,181 (43)
4–5 times/week	126 (4)	7 (6)	119 (4)
>5 times/week	43 (2)	3 (3)	40 (1)
Pet ownership	1,271 (29)	66 (35)	1,205 (29)

[a]Active maternal smoking or the presence of a smoker at home during pregnancy.
[b]Presence of a smoker at home after delivery.
Hg indicates mercury.

comparing the children included in the current analyses with those excluded, more girls and children with less paternal or maternal asthma history were included (eTable 1; http://links.lww.com/EDE/A936).

The distribution of blood Hg concentration was right-skewed. The geometric means of the blood Hg concentration at 7–8, 9–10, and 11–12 years of age were 2.02 (first quartile, 1.42; second quartile, 2.17; third quartile, 3.24), 1.79 (first quartile, 1.30; second quartile, 1.89; third quartile, 2.64), and 1.96 (first quartile, 1.40; second quartile, 2.03; third quartile, 2.81) μg/liter, respectively (eTable 2; http://links.lww.com/EDE/A936). The log-transformed blood Hg concentrations at each age correlated with each other (r = 0.19, and 95% confidence interval [CI] = 0.16, 0.23 between Hg at 7–8 and 9–10 years; r = 0.14, and 95% CI = 0.10, 0.19 between Hg at 9–10 and 11–12 years; r = 0.13, and 95% CI = 0.09, 0.18 between Hg at 7–8 and 11–12 years).

Table 2 describes the adjusted associations between Hg exposure and asthma using logistic regression models. Hg concentration at 7–8 years of age was associated with asthma at ages up to 9–10 years (odds ratio [OR] = 1.6; 95% CI = 1.2, 2.1) and 11–12 years (OR = 1.3; 95% CI = 1.0, 1.6). An association between Hg concentration at 7–8 years of age and incident asthma up to 11–12 years was also found when analyzed by a Cox proportional hazards model (hazard ratio [HR] = 1.4; 95% CI = 1.1, 1.8).

Table 3 demonstrates the relation between blood Hg concentration and asthma-related outcomes, such as wheezing, asthma medication use, and airway hyperresponsiveness at ages up to 11–12 years, as determined using generalized estimating equations with a logit link. Blood Hg was associated with an increased risk of wheezing (OR = 1.2; 95% CI = 1.0, 1.3), asthma medication use (OR = 1.4; 95% CI = 0.97, 2.0), and airway hyperresponsiveness (OR = 1.2; 95% CI = 1.0, 1.3).

TABLE 2. Association Between Log-transformed Blood Hg Concentration (μg/Liter) and Asthma at 9–10 and 11–12 Years of Age[a]

	Asthma at 9–10 Years of Age		Asthma at 11–12 Years of Age	
	No.[b]	OR (95% CI)	No.[b]	OR (95% CI)
Hg at 7–8 years	129/3,197	1.6 (1.2, 2.1)	191/2,179	1.3 (1.0, 1.6)
Average Hg until 9–10 years[c]	129/3,197	1.7 (1.2, 2.4)	191/2,179	1.2 (0.89, 1.6)
Average Hg until 11–12 years[d]	NA	NA	191/2,179	1.2 (0.87, 1.8)

[a]Models were adjusted for gender, paternal and maternal asthma history, fetal and environmental tobacco smoke exposure, paternal and maternal education level, and pet ownership.
[b]Number with outcome/total number for analysis.
[c]Average blood Hg concentration at 7–8 (n = 4,350) and 9–10 (n = 3,165) years of age.
[d]Average blood Hg concentration at 7–8 (n = 4,350), 9–10 (n = 3,165), and 11–12 (n = 2,088) years of age.
Hg indicates mercury.

TABLE 3. Association Between Blood Hg Concentration and Asthma-related Outcomes at Ages up to 11–12 Years[a]

	Wheezing[b]	Asthma Medication Use[c]	Airway Hyperresponsiveness[d]
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Log Hg (μg/liter)	1.2 (1.0, 1.3)	1.4 (0.97, 2.0)	1.2 (1.0, 1.3)

[a]Models were adjusted for gender, paternal and maternal asthma history, fetal and environmental tobacco smoke exposure, paternal and maternal education level, and pet ownership.
[b]Positive response to the question "Has your child experienced wheezing in the past 12 months?."
[c]Positive response to the question "Did your child use asthma medication in the past 12 months?."
[d]Defined as a methacholine provocative concentration producing a 20% fall in forced expiratory volume in 1 second of ≤8 mg/ml.
Hg indicates mercury.

Table 4 presents the association between the Hg concentration at 7–8 years of age and the immune system blood profile using linear mixed models. Blood Hg was associated with hs-CRP (β = 0.29; 95% CI = 0.07, 0.51), segmented neutrophil percentage (β = 1.38; 95% CI = 0.11, 2.65), and lymphocyte percentage (β = −1.26; 95% CI = −2.61, 0.08) in children who had asthma during the study period. Figure 2 shows the penalized regression spline, which addresses linear relations, visualizing the associations of Hg concentration at 7–8 years of age with segmented neutrophil percentage, lymphocyte percentage, monocyte percentage, and basophil percentage at ages up to 11–12 years in children who had asthma during the study period.

When we performed analysis stratified by gender using a Cox proportional hazards model, boys showed an increased risk of incident asthma from exposure to Hg at 7–8 years of age (HR = 1.5, and 95% CI = 1.1, 2.1 in boys; HR = 1.3, and 95% CI = 0.9, 1.8 in girls; P value for interaction = 0.3452; eTable 3; http://links.lww.com/EDE/A936).

Due to the concern that the present result might be attributable to random error, we investigated the association between Hg and asthma among 2,705 children ages 10 years or younger using NHANES data. Analyses using the NHANES data also showed that one unit increase in log-transformed urinary Hg was positively associated with lifetime asthma prevalence (OR = 1.4; 95% CI = 1.0, 1.9) and current asthma (OR = 1.8; 95% CI = 1.3, 2.6) after adjusting for age, gender, family history of asthma, maternal smoking during pregnancy, smokers at home, and poverty income ratio.

Sensitivity analyses were performed to consider follow-up loss. After weighting follow-up observations by the inverse probability of having a follow-up response, the results showed no essential changes (eTable 4; http://links.lww.com/EDE/A936). When we further adjusted for fish consumption, the trend was also robust, with some relations attenuated to the null (eTables 5 and 6; http://links.lww.com/EDE/A936). After adjusting for the city from which the study participants were recruited, the results did

TABLE 4. Stratified Association of Log Hg Concentration at 7–8 Years of Age with Immune System Blood Profile at Ages up to 11–12 Years, by Occurrence of Asthma[a]

	Total (n = 4,350)		Children With Asthma (n = 191)		Children Without Asthma (n = 4,159)	
	B	95% CI	*β*	95% CI	*β* (SE)	95% CI
WBC count	−0.01	−0.02, 0.003	0.03	−0.01, 0.08	−0.003	−0.01, 0.01
Segmented neutrophil %	0.19	−0.12, 0.50	1.38	0.11, 2.65	0.21	−0.20, 0.63
Lymphocyte %	−0.13	−0.43, 0.18	−1.26	−2.61, 0.08	−0.19	−0.60, 0.23
Monocyte %	−0.004	−0.01, 0.01	−0.01	−0.05, 0.03	−0.002	−0.01, 0.01
Basophil %	0.02	0.01, 0.04	0.04	−0.03, 0.11	0.04	0.02, 0.06
hs-CRP	0.08	0.03, 0.12	0.29	0.07, 0.51	0.09	0.02, 0.15
Total IgE	−0.03	−0.09, 0.02	0.07	−0.20, 0.35	−0.01	−0.09, 0.07

[a]Models were adjusted for gender, paternal and maternal asthma history, fetal and environmental tobacco smoke exposure, paternal and maternal education level, and pet ownership. WBC count, monocyte percentage, basophil percentage, hs-CRP, and total IgE were log-transformed to approximate normality.

Hg indicates mercury; SE, standard error.

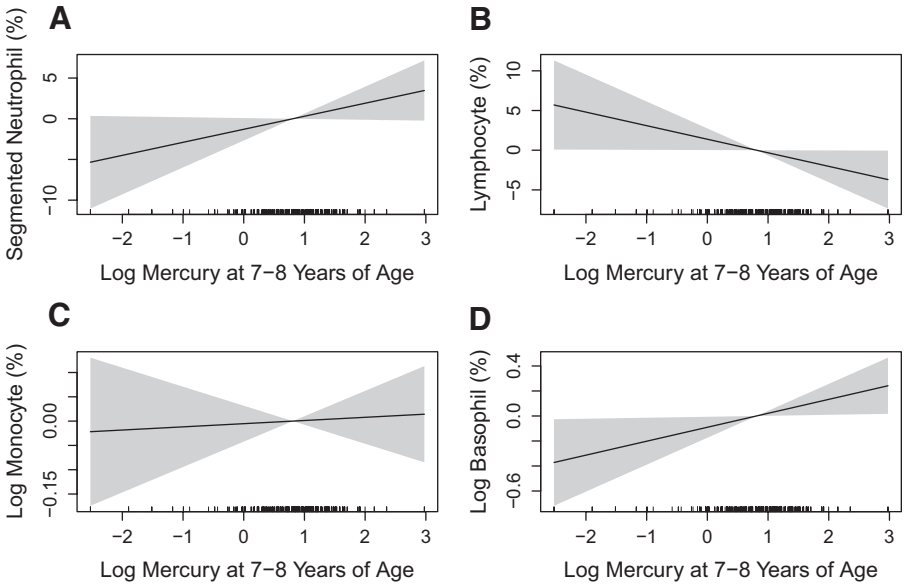

FIGURE 2. Penalized regression spline of log-transformed mercury concentrations at 7–8 years of age on segmented neutrophil percentage (A), lymphocyte percentage (B), monocyte percentage (C), and basophil percentage (D) at ages up to 11–12 years in children who had asthma during the study period. *Solid lines* Spline curves; *shaded areas* 95% confidence intervals. The models were adjusted for gender, maternal asthma history, fetal and environmental tobacco smoke exposure, paternal and maternal education level, and pet ownership.

not change appreciably (eTables 7 and 8; http://links.lww.com/EDE/A936). Finally, the results did not change substantially when time at risk was defined as the number of months from the baseline survey to the survey when the current asthma was first observed or to the last follow-up survey if current asthma was not observed during the study period (data not shown).

DISCUSSION

We found an association between blood Hg concentrations and risk of asthma in school-age children. Hg level was also associated with asthma-related outcomes such as wheezing, asthma medication use, and airway hyperresponsiveness. In children who had asthma during the study period, Hg level was associated with hs-CRP, segmented neutrophil percentage, and lymphocyte percentage.

In this study, blood Hg concentration was related to asthma among school-age children. A previous Japanese birth cohort study reported no evidence for the association of mothers' and children's hair Hg level with wheeze and eczema assessed at 29–39 months postpartum.[16] Discrepancy between our results and the results of the previous birth cohort study might be related to different windows of exposure, different ages of the study populations, smaller sample size of the previous study, and different sites of Hg measurement, such as hair and blood. More epidemiologic studies with diverse study populations are needed to assess not only the relation between Hg exposure and asthma but also the windows of vulnerability to Hg exposure.

Hg exposure has been associated with mitochondrial dysfunction, increased oxidative stress, and inactivation of antioxidant defenses.[20,21] Higher levels of oxidative stress and

disturbed anti-inflammatory capacity could lower children's defense against other insults, such as air pollution, and provoke chronic airway inflammatory status, including asthma.[22,23] Several studies have reported that hs-CRP, a sensitive marker of inflammation, is associated with asthma development and severity.[24,25] In this study, we found that the association of Hg with hs-CRP was greater in children who had asthma during the study period. If causal, this association could be explained by Hg exposure resulting in an impaired capacity to deal with oxidative stress, which often leads to inflammation, due to an already high level of oxidative stress or lowered antioxidant function.

We found an association between Hg exposure and an increased segmented neutrophil percentage, as well as reduced lymphocyte percentage, predominantly in children who had asthma during the study period. One in vitro study demonstrated that Hg exposure causes mitochondrial dysfunction and enhances the apoptosis of T-cells.[26] Another in vitro study showed that Hg exposure inhibits spontaneous apoptosis of human neutrophils and prolongs neutrophil survival but enhances apoptosis of mononuclear cells including lymphocytes, which implies that segmented neutrophils are more resistant to Hg cytotoxicity than lymphocytes.[27] Due to reduced antioxidant capacity, the cytotoxicity of Hg could is prominent in asthmatics, which suggests that the changes in the profile of inflammatory blood cells were due to Hg exposure in children who developed asthma.

We also observed an association between Hg exposure and increased basophil percentage. Although basophils had been overlooked because of their phenotypic similarities to mast cells and relative rarity, recent studies have shown that basophils play important roles in development and progression of allergic inflammation and contribute to the pathogenesis of allergic diseases including asthma.[28,29] Because we did not find an association between Hg exposure and IgE, we suspect that Hg exposure might provoke asthma and changes in the blood profile of the immune system not only through IgE-mediated basophils but also through an IgE-independent pathway mediated by thymic stromal lymphopoietin-activated basophils.[30,31] It is not clear why Hg exposure showed no association with basophils in children with asthma, in contrast to other blood indices, such as segmented neutrophil or lymphocyte counts. However, considering the heterogeneity of asthma with regard to clinical and pathophysiological characteristics,[32,33] the mechanism by which Hg exposure affects asthma and the immune system, particularly related to basophils, might also be complex and should be further investigated.

We found an association between Hg exposure and asthma only in boys. Previous studies investigating gender-specific effects of Hg have focused primarily on gender differences in the neurotoxicity of Hg exposure.[34,35] However, we could not find previous studies exploring gender-specific effects of Hg exposure on allergic outcomes. One possible explanation for our findings is provided by a study reporting the gender-dependent Hg accumulation and excretion profile in mice.[36] Another possible explanation is gender-specific interplay between Hg and hormones. Sex hormones such as estrogen could affect the oxidative stress level by controlling the expression of antioxidant enzymes and reduced nicotinamide adenine dinucleotide phosphate oxidases.[37] Oxidative stress levels induced by Hg differ according to estrogen exposure status, which could lead to the phenotypically different effects we observed.

Our study has several strengths. First, to the best of our knowledge, this is the first cohort study investigating the association of low-level Hg exposure with asthma development and immune system blood profiles in school-age children. Due to the lack of studies investigating the observed association, the possibility that the present result might be attributable to random error could not be excluded. However, when we assessed the association between Hg and asthma using the 2011–2012 NHANES data, we found consistent associations. Second, the relatively large number of participating children residing in 10 Korean cities provided sufficient power to investigate the possible association. Third, the longitudinal study design lowered the possibility of temporal ambiguity and recall bias. Fourth, all analyses in this study were adjusted for multiple potential confounders, thereby increasing the likelihood of true association.

Some weaknesses of this study should be discussed. First, asthma was assessed based mainly on questionnaires completed by parents rather than a diagnosis by an allergist. Therefore, there could be a misclassification of asthma. However, confirmation of doctor's diagnoses via parental questionnaire is reported to be reasonably accurate,[38] and the possibility of limited access to healthcare was relatively low because of the universal health insurance coverage in the Republic of Korea.[39] Furthermore, several asthma-related outcomes, including objective methacholine challenge test result, showed consistent associations. Second, in a longitudinal study like this study, follow-up loss can lead to selection bias when the loss is not random. However, although this study showed notable follow-up loss, the sensitivity analysis that was conducted after weighting follow-up observations by the inverse probability of having a follow-up response showed no substantial changes in the results. Third, we measured only total Hg and could not assess any specific effects of the organic or inorganic form of Hg. However, total Hg concentrations in whole blood are generally considered to reflect organic Hg exposure, predominantly methylmercury.[40] Fourth, although previous studies have reported that serum cytokines, such as interleukin (IL)-4, IL-6, IL-7, interferon-γ, and antinuclear antibody, are associated with Hg exposure,[14,15] data regarding levels of these cytokines were not available in this study and therefore could not be assessed. Future studies with more thorough measurement of biomarkers related to the immune system are needed to understand the biological mechanisms underlying Hg exposure.

CONCLUSION

We found that low-level blood Hg concentration was associated with an increased risk of asthma at ages up to 11–12 years. We also observed changes in the immune system blood profile associated with Hg concentration in children who had asthma during the study period.

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