

The Association Between Mercury Exposure and Atopic Dermatitis in Early Childhood

A Mothers and Children's Environmental Health Study

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Background: Atopic dermatitis is a chronic and relapsing inflammatory skin disease. Although mercury has been suggested as a risk factor, the underlying mechanism and the relationship between mercury and atopic dermatitis remains unclear. The objective of the present study was to investigate the relationship between mercury exposure and the presence of atopic dermatitis in early childhood.

Methods: This study is part of the prospective Mothers and Children's Environmental Health cohort study. A total of 1,751 pregnant women were enrolled in Mothers and Children's Environmental Health. After delivery, children were followed up. Blood samples were collected and mothers were asked about the presence of atopic dermatitis in their children via a questionnaire at 6, 12, 24, 36, and 60 months of age.

Results: After excluding participants who did not meet the inclusion criteria, a total of 1,061 mother-children pairs were included in

the analysis. The geometric mean of mercury concentrations in cord blood was 5.1 µg/L. In adjusted models, cord blood mercury exposure (odds ratio [OR] = 1.1; 95% confidence interval [CI] = 1.0, 1.2 at 12–24 months) and postnatal mercury exposure (OR = 1.2; 95% CI = 1.0, 1.5 at 24–36 months, OR = 1.4; 95% CI = 1.1, 1.8 at 48–60 months) were associated with the presence of atopic dermatitis in children.

Conclusions: Postnatal mercury exposure at 24 months of age increases the risk of atopic dermatitis in children.

Keywords: Atopic dermatitis; Birth cohort; Blood mercury; Childhood; Heavy metal

(*Epidemiology* 2019;30: S3–S8)

Submitted May 11, 2017; accepted February 14, 2019.

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Supported by Mothers and Children's Environmental Health project of the National Institute of Environmental Research, Republic of Korea (<http://www.nier.go.kr>). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. Supported by the Ministry of Environment, Republic of Korea.

The authors report no conflicts of interest.

SDC Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.epidem.com).

J.S. is the first author of article. She interpreted the data, prepared the draft of this manuscript, and approved the final version of the manuscript. E.-H.H., H.-s.P., and M.H. designed this study and collected the data. B.-M.K., Y.-C.H., and Y.K. advised the design of this study. J.S. and B.-M.K. performed the statistical analyses. All authors interpreted the data, wrote the manuscript, and read and approved the final manuscript.

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ISSN: 1044-3983/19/3001-00S3

DOI: 10.1097/EDE.0000000000001002

Atopic dermatitis (AD) is a skin disease with an estimated prevalence of 2%–5% in young children and up to 20% in children overall.¹ The prevalence of AD in Korea ranges from 2.3% to 26.5% in children <18 years of age.^{2,3} AD presents as an inflammatory, pruritic skin disorder with chronically relapsing symptoms.⁴ These conditions occur over a large body surface area with enlarged lesions that can induce intense pruritus. Along with itching, sufferers often experience anxiety, depression, and sleep disorders which can lead to a poor quality of life.^{2,5,6} Researchers have also demonstrated that adults with AD may be prone to sleep deprivation with decreased quality of life and psychosocial effects of anxiety, shame, and self-consciousness.⁶ A comprehensive understanding of AD and its risk factors during infancy and early childhood can potentially lead to long-term benefits for patients in adulthood in addition to short-term impact on children's health.

A range of genetic, immunological, and environmental factors have been proposed to explain the etiology of AD. For example, a high serum level of total immunoglobulin E (IgE) is associated with clinical allergic diseases, including AD.⁵ Exposure to air pollutants composed of metals, organic compounds, and materials of biologic origin has also been suggested as the cause of disease.^{7,8} Additionally, high blood concentrations of several heavy metals such as mercury and

cadmium, are associated with the development of AD.^{9,10} Specifically, it has been suggested that mercury has the ability to modulate human immune systems via proliferation of T and B lymphocytes, leading to elevation of serum immunoglobulin levels and antibody production.¹¹

Mercury can be found in three forms: elemental mercury (Hg^0), inorganic mercury (Hg^+ and Hg^{2+}), and organic (methyl, ethyl, and phenyl) mercury.¹² Mercury has historically been used for cosmetic and medical purposes. At present, humans are most commonly in contact with vapor mercury found in amalgam tooth fillings, thimerosal (ethyl mercury) found in vaccines, and methylmercury from fish consumption.^{13,14} Methylmercury, especially, can accumulate in fish and top fish predators; humans are exposed to mercury by eating them.¹²

Despite widespread suggested risk factors and extant knowledge that mercury can lead to the development of allergic diseases, studies examining the role of prenatal and postnatal mercury exposure in AD remain limited.¹⁵ Therefore, the objective of the present study was to determine the relationship between prenatal and postnatal mercury exposure based on blood mercury concentrations and the presence of AD in children.

MATERIALS AND METHODS

Study Design and Subjects

This study was conducted as part of the Mothers and Children's Environmental Health (MOCEH) study. The cohort consisted of patients in multicenter hospitals located in Seoul (a metropolitan area), Ulsan (an industrial area), and Cheonan (a medium-sized urban area), Korea. The MOCEH cohort study was intended to investigate the relationship between pregnant women's exposure to harmful environmental substances and health outcomes for both themselves and their offspring.¹⁶ Individuals enrolled in the study made regular visits to designated hospitals or healthcare centers for follow-up investigations starting from early periods of pregnancy. Trained staff from each center asked pregnant women who visited the hospital about participating in the study. Informed consent was obtained at the initial prenatal visit. Once the mother gave birth, cord blood was collected at the time of delivery. After birth, their children were examined in pediatric departments to monitor their growth and health. Between May 2006 and December 2012, 1,751 pregnant women participated in the MOCEH study.^{16,17} The MOCEH study protocol has been reviewed and approved by the Institutional Review Board at Ewha Woman's University, Seoul, South Korea.

Data Collection

Blood samples were collected from the maternal cord blood at the time of delivery. After delivery, blood samples of children were collected at 24 and 36 months of age. Samples used to determine mercury exposure were analyzed using the gold amalgamation direct mercury analyzer (DMA-80;

Milestone, Bergamo, Italy). Analysis was performed using standardized quality control procedures. An internal control was included during each series of analyses.¹⁸ Total blood mercury level was measured by laboratory procedure, and the limit of detection was set at 0.07 $\mu\text{g/L}$.

During the first hospital visit, a comprehensive questionnaire was administered by trained staff at each time period to evaluate general characteristics, socioeconomic status (such as maternal age, marital status, parity, household monthly income, maternal educational level), parental history of allergic disease (such as asthma), and AD for participating women. We surveyed mothers using a semiquantitative food frequency questionnaire to evaluate fish consumption habit. Food frequency questionnaire consisted of a list of foods including fish and beverages with response categories to indicate the usual frequency of food consumption.¹⁹

After birth, the mother-child pair data were collected during the follow-up period. We determined children's AD outcomes for each period via a questionnaire administered by trained staff to evaluate children's health. The questionnaire for this period included questions about the baby's health status, including AD, with additional enquiries about changes in the mother's lifestyle. After excluding subjects without any mercury levels or AD diagnosis data based on infant questionnaires, 1,061 mother-infant pairs were included in this study.

At the age of 6, 12, 24, 36, and 60 months, AD outcomes were determined using the Korean version of the International Study on Allergies and Asthma in Childhood protocol. We obtained parents' answers to questions "Has your child ever had an AD?" for children at 6, 12, and 24 months of age and "Has your child ever had an AD in the past 12 months?"²⁰ for children at 36 and 60 months of age.

Statistical Analysis

For descriptive analysis, we categorized maternal age at the time of early pregnancy (<30 and ≥ 30 years), parity (0, 1, and ≥ 2), household income (<2500 , 2500–3500, and ≥ 3500 USD/month), education level (graduated high school, graduated college, and graduated higher than college), sex of the child, and maternal fish consumption (<1 servings/week and ≥ 1 servings/week). The number of children diagnosed with AD in each group was also determined. Geometric means, range, and 25th, 50th, and 75th percentiles of mercury levels were calculated.

For the main analysis, we analyzed the relationship between blood concentration of mercury and AD at each period through logistic regression. Each model had a different total number for analysis because of missing data of mercury or AD ($n = 693$ for cord blood mercury and AD at 0–6 months; $n = 516$ for cord blood mercury and AD at 6–12 months; $n = 451$ for cord blood mercury and AD at 12–24 months; $n = 448$ for cord blood mercury and AD at 24–36 months; $n = 283$ for cord blood mercury and AD at 48–60 months; $n = 363$ for mercury at 24 months and AD at 24–36 months; $n = 217$ for

mercury at 24 months and AD at 48–60 months; $n = 230$ for mercury at 36 months and AD at 48–60 months). We excluded missing data of each main exposure and outcome variable. In multiple logistic regression model 1, we considered the possible confounding effects of other covariates such as maternal age, sex of child, maternal education level, household income, and parity. Thus, we adjusted them as confounding factors. In model 2, we used all confounding factors included in model 1 in addition to maternal fish consumption, a covariate with biologic significance. Missing covariates were included in the model by categorizing them into a separate category of missing. We conducted all analyses with SAS statistical software version 9.4 (SAS institute Inc., Cary, NC).

RESULTS

Figure shows the flowchart of study population. We excluded 79 participants with low birth weight or premature babies. We also excluded 611 participants who did not have any data of mercury level or response data of AD reported in children's questionnaires. Therefore, 1,061 mother-child pairs were included in our study population at the baseline. To estimate incident number of AD, we excluded children who had previous history of AD for each period.

Among 1751 participants recruited, 690 participants were excluded based on our exclusion criteria. Characteristics of participants and nonparticipants in our study are summarized in Table 1. Compared with those who were excluded, study participants included in current analyses were more likely to have higher education levels and more likely to be >30-year-old.

The average maternal age was 30.6 years. The largest group based on parity was those who were nulliparous at the registration period. Those who earned \$2500–3500 per month, including their entire household income, constituted the largest (53%) portion of all income groups of participants. The largest group based on education comprised individuals who graduated college (65%) whereas those who graduated higher than college represented the smallest group (6%). There were more male children included in the study than excluded. However, the distribution of sex of child did not differ substantially between participants and nonparticipants.

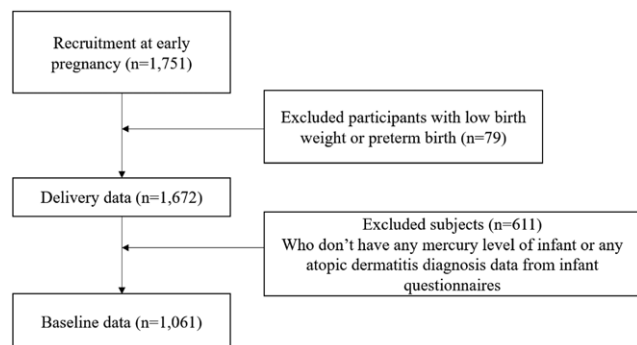


FIGURE. Flowchart of the study population.

TABLE 1. Comparison Between participants and Nonparticipants

Characteristic	No. (%)	
	Participants (N = 1,061)	Nonparticipants (N = 690)
Maternal age group (year)		
<30	450 (42)	321 (47)
≥30	589 (56)	328 (48)
Missing	22 (2)	41 (6)
Parity		
0	516 (49)	313 (45)
1	346 (33)	206 (30)
+2	63 (6)	42 (6)
Missing	136 (13)	129 (19)
Household income (USD/month)		
<2,500	281 (26)	247 (36)
2,500–3,500	560 (53)	343 (50)
≥3,500	192 (18)	93 (13)
Missing	28 (3)	7 (1)
Education level		
Low (graduated high school)	306 (29)	231 (33)
Medium (graduated college)	686 (65)	438 (63)
High (graduated higher than college)	68 (6)	20 (3)
Missing	1 (0.1)	1 (0.1)
Sex of child		
Male	541 (51)	320 (46)
Female	495 (47)	284 (41)
Missing	25 (2)	86 (12)
Maternal fish consumption		
<1 servings/week	201 (19)	136 (20)
≥1 servings/week	679 (64)	437 (63)
Missing	181 (17)	117 (17)

The geometric mean of blood mercury level at each period was described. Cord blood recorded the highest level of mercury at 5.1 $\mu\text{g/L}$ (first quartile = 3.8 $\mu\text{g/L}$; second quartile = 5.1 $\mu\text{g/L}$; third quartile = 6.9 $\mu\text{g/L}$). This level was higher than that in children 2.2 $\mu\text{g/L}$ (first quartile = 1.6 $\mu\text{g/L}$; second quartile = 2.1 $\mu\text{g/L}$; third quartile = 3.0 $\mu\text{g/L}$) at 24 months and 2.2 $\mu\text{g/L}$ (first quartile = 1.5 $\mu\text{g/L}$; second quartile = 2.1 $\mu\text{g/L}$; third quartile = 2.8 $\mu\text{g/L}$) at 36 months. All participants' mercury levels were below the reference level of 5.8 $\mu\text{g/L}$ recommended by the National Research Council. All blood mercury levels exceeded the minimum detection limit. Geometric mean and percentiles of blood mercury levels divided by AD status of children were also calculated. Children who had AD in any study period had higher mercury levels at all study periods, including cord blood, mercury level at 24 months, and mercury level at 36 months (see eTable 1; <http://links.lww.com/EDE/B489>).

Table 3 presents the geometric mean of blood mercury levels in study participants by characteristics. Cord blood

TABLE 2. The Number of Children by Each Characteristic Stratified by the Presence of AD

Characteristic	No. (%)	
	Children With AD (N = 281)	Children Without AD (N = 780)
Maternal age group (year)		
<30	128 (46)	322 (41)
≥30	149 (53)	440 (56)
Missing	4 (1)	18 (2)
Parity		
0	145 (52)	371 (48)
+1	86 (31)	260 (33)
+2	13 (5)	50 (6)
Missing	37 (13)	99 (13)
Household income (USD/month)		
<2,500	75 (27)	206 (26)
2,500–3,500	148 (53)	412 (53)
≥3,500	52 (19)	140 (18)
Missing	6 (2)	22 (3)
Education level		
Low (graduated high school)	64 (23)	242 (31)
Medium (graduated college)	199 (71)	487 (62)
High (graduated higher than college)	18 (6)	50 (6)
Missing	0 (0)	1 (0.1)
Sex of child		
Male	154 (55)	387 (50)
Female	120 (43)	375 (48)
Missing	7 (2)	18 (2)
Maternal fish consumption		
<1 servings/week	60 (21)	141 (18)
≥1 servings/week	181 (64)	498 (64)
Missing	40 (14)	141 (18)

mercury level was higher than mercury level in children at 24- and 36-months by all characteristics. Moreover, higher maternal fish consumption group (≥1 serving/week) showed higher mercury level than lower maternal fish consumption group at all periods.

Table 4 shows results of logistic regression analysis of the association between mercury levels and incidence of AD. Cord blood mercury level was associated with an increase of AD at 12–24 months in model 1 (OR = 1.1; 95% confidence interval [CI] = 1.0, 1.2) and model 2 (OR = 1.1; 95% CI = 1.0, 1.2). Mercury level at 24 months of age was more likely to be associated with AD in the crude model (OR = 1.2; 95% CI = 1.1, 1.4 at 24–36 months; OR = 1.3; 95% CI = 1.1, 1.6 at 48–60 months), model 1 (OR = 1.2; 95% CI = 1.1, 1.5 at 24–36 months; OR = 1.4; 95% CI = 1.1, 1.7 at 48–60 months). Model 1 was adjusted for maternal age, sex of child, educational level, household income, and parity. Model 2 was adjusted for variables in model 1 and maternal fish consumption. It also

TABLE 3. Geometric Mean of Blood Mercury Level (μg/L) Among Study Participants at Each Period

Characteristics	Total Hg Level, GM (GSD)		
	Cord Blood	24 Months	36 Months
Maternal age group			
<30	5.1 (1.6)	2.3 (1.7)	2.2 (1.7)
≥30	5.2 (1.6)	2.1 (1.7)	2.0 (1.6)
Parity			
0	5.2 (1.6)	2.3 (1.7)	2.2 (1.7)
1	5.2 (1.6)	2.1 (1.7)	2.0 (1.6)
+2	5.2 (2.0)	1.9 (1.7)	2.2 (1.6)
Household income (USD/month)			
<2,500	4.9 (1.6)	2.2 (1.6)	2.1 (1.7)
2,500–3,500	5.1 (1.6)	2.2 (1.8)	2.1 (1.7)
≥3,500	5.5 (1.7)	2.2 (1.5)	2.0 (1.5)
Education level			
Low (graduated high school)	4.9 (1.7)	2.1 (1.8)	2.0 (1.7)
Medium (graduated college)	5.3 (1.6)	2.2 (1.7)	2.2 (1.6)
High (graduated higher than college)	4.5 (1.5)	2.0 (1.6)	1.8 (1.6)
Sex of child			
Male	5.1 (1.6)	2.1 (1.7)	2.0 (1.6)
Female	5.2 (1.7)	2.2 (1.7)	2.2 (1.7)
Maternal fish consumption			
<1 servings/week	4.5 (1.7)	2.1 (1.7)	2.0 (1.7)
≥1 servings/week	5.4 (1.6)	2.2 (1.7)	2.1 (1.7)

showed a positive association between mercury level and incidence of AD (OR = 1.2; 95% CI = 1.1, 1.4 at 24–36 months; OR = 1.5; 95% CI = 1.1, 1.9 at 48–60 months). Mercury levels during other periods such as mercury levels found at 36 months did not show a noticeable association with the presence of AD at any period. Average mercury level of cord blood or children blood mercury level at 24 months did not show a meaningful relationship with incidence of AD (see eTable 2; <http://links.lww.com/EDE/B489>).

DISCUSSION

In our study, we found that mercury exposure at 24 months of age was positively associated with the presence of AD at 24–36 and 48–60 months of age after adjusting for maternal age, sex of child, educational level, household income, parity, and maternal fish consumption. Cord blood mercury level was also associated with the risk of AD at 12–24 months in adjusted model. However, blood mercury levels at other periods such as cord blood mercury level or blood mercury levels at 36 months did not show a meaningful association with AD.

The geometric median of blood mercury level was 2.2 μg/L at 24 months of age and 2.1 μg/L at 36 months of age, which was higher than the median blood mercury level reported in the Korean Environmental Health Survey in Children

TABLE 4. Association Between Blood Mercury Level and Incidence of AD in Children

Measured Period		No., OR (95% CI)					
Mercury (µg/L)	Period of AD (months)	No. ^a	Crude	No.	Model 1 ^b	No.	Model 2 ^c
Cord blood	0–6	90/693	0.99 (0.92, 1.1)	90/693	0.99 (0.92, 1.1)	90/693	1.0 (0.92, 1.1)
	6–12	35/516	1.0 (0.93, 1.1)	35/516	1.0 (0.92, 1.1)	35/516	1.0 (0.92, 1.1)
	12–24	31/451	1.1 (1.0, 1.1)	31/451	1.1 (1.0, 1.2)	31/451	1.1 (1.0, 1.2)
	24–36	52/448	1.0 (0.92, 1.1)	52/448	1.0 (0.91, 1.1)	52/448	1.0 (0.91, 1.1)
	48–60	23/283	1.0 (0.86, 1.2)	23/283	1.1 (0.87, 1.2)	23/283	1.0 (0.87, 1.2)
24 months	24–36	48/363	1.2 (1.1, 1.4)	48/363	1.2 (1.1, 1.5)	48/363	1.2 (1.1, 1.4)
	48–60	18/217	1.3 (1.1, 1.6)	18/217	1.4 (1.1, 1.7)	18/217	1.5 (1.1, 1.9)
36 months	48–60	17/230	1.1 (0.74, 1.5)	17/230	1.3 (0.83, 2.1)	17/230	1.4 (0.86, 2.2)

^aNumber with outcome/total number for analysis.^bModel 1 was adjusted for maternal age, sex of child, educational level, household income, and parity.^cModel 2 was adjusted for model 1 and maternal fish consumption.

and Adolescents (1.7 µg/L in 3- to 5-year-old children).²¹ The geometric mean of blood mercury level in our study was also higher than that (0.40 ± 0.02 µg/L) in children who were 1–19 years of age in the National Health and Nutrition Examination Survey, a nationally representative survey of civilian, noninstitutionalized US population.^{21,22}

Our results suggest that increased cord blood mercury or blood mercury levels in children at 24 months of age are associated with the presence of AD in early childhood. Adjustment for the relationship between childhood mercury exposure and AD did not change this result substantially. Our adjusted results represent a lower association than results of a previous Korean research on the relationship between lifetime prevalence of AD and high mercury levels (>6.0 µg/L; OR = 1.5; 95% CI = 1.0, 2.2) in adults after adjusting for age, sex, cigarette smoking status, alcohol drinking status, income, fish or shellfish consumption, body mass index, and education level.⁹ We used blood mercury levels in children as the exposure variable. Our results were comparable to results of previous research investigating the association between urinary concentrations of mercury in German school beginner's children and acute atopic eczema (AE).²³ Previous results also showed a positive association between mercury and acute AE after adjusting for sex, social status, number of persons at home, parental history of AE, exposure to environmental tobacco smoke, and urinary creatinine (OR = 1.7; 95% CI = 1.1, 2.7, ORs when changing exposure from the 5th to 95th percentile).

Although we found a notable relationship between postnatal mercury exposure at 24 months of age and the incidence of AD in young children, we could not find association between mercury exposure at 36 months of age and AD. Previous studies have also indicated that there is no association between postnatal methylmercury level in children and AD at 5 years of age.^{15,24}

Although the exact mechanism linking mercury exposure to the presence of AD remains unclear, many metals are known as immunotoxins that can adversely affect the immune system.²⁵ Heavy metals can lead to increased expression of major histocompatibility complex (MHC) class 2 molecule.²⁶ MHC class 2 is one of the primary elements of the immune system associated with antigen presentation and allergic inflammatory responses. Thus, increased expression of MHC class 2 molecule due to heavy metal exposure might have increased allergic immune response. Several studies have shown that mercury exposure can lead to increased autoantibody production, higher levels of serum IgG1 in mice, and higher IgE levels in humans, suggesting that mercury may affect B cells.^{27,28} However, it has also been shown that mercury does not directly induce B cell proliferation.²⁹ Further research is needed to elucidate the exact mechanism involved in mercury induced allergic immune responses.

The present study has several limitations. Other environmental factors including food allergies and other sociodemographic factors can also affect the relationship between mercury exposure and the presence of AD. Fish consumption among children may have also affect the result. One study has reported that inflammatory parameters are reduced in mice fed high n-3 polyunsaturated fatty acids (PUFA) (fish oil source) diet and suggested that PUFA can reduce allergic inflammatory response.³⁰ Although fish consumption is a primary source of methylmercury exposure, it also has nutritional benefits that may outweigh this risk. It might also affect the relationship between mercury exposure at 36 months of age and AD in children, particularly in the direction of attenuating the relationship. In our study, we adjusted for maternal fish consumption in main analyses. However, due to the lack of available data, we were unable to investigate fish consumption habits among children. If PUFA diet reduces allergic responses, the association between children mercury exposure and AD adjusted for fish consumption among children would

increase. Selection bias due to loss to follow-up in our cohort study might have affected the association. When we compared characteristics between baseline participants and nonparticipants, there were no major differences in the number of children diagnosed with AD among all periods. However, the impact of attrition on our sample size at another follow-up period might have introduced selection bias.

Nevertheless, our findings are based on data obtained from the birth cohort study to identify the relationship between prenatal and postnatal mercury exposure and AD in young children. Our longitudinal study design lowered the possibility of recall bias. In addition, participants were enrolled in our study from an early pregnancy period before they knew their children's future diseases. Especially, mercury levels and health outcome data of children were collected prospectively, allowing analysis of an association between mercury exposure and the presence of AD in children. We also considered prenatal and postnatal mercury factors in one of our models to simultaneously adjust for both effects.

In conclusion, the primary finding of this study is that mercury exposure has a positive association with the presence of AD in children. Further studies are required to investigate other possible factors related to mercury and the development of allergic diseases. Our results support actions to reduce blood mercury level known to be risk factor for AD in children. These results may also be used to guide future studies to develop guidelines for mercury exposure levels in children with the aim to prevent allergic diseases, including AD.

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