ASSOCIATION BETWEEN COMPLEX EXPOSURE TO CADMIUM AND MERCURY AND ATOPIC DERMATITIS IN ELEMENTARY SCHOOL STUDENTS: ANALYSIS USING DATA FROM THE KOREAN NATIONAL ENVIRONMENTAL HEALTH SURVEY (KONEHS) CYCLE 4

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SUMMARY

Objectives: Atopic dermatitis (AD) is a common allergic disease with potential links to environmental pollutants, including heavy metals. This study investigates the association between co-exposure to cadmium and mercury and AD among Korean children.

Methods: Data from the fourth cycle of the Korean National Environmental Health Survey (KoNEHS) included 736 elementary school students. Urinary cadmium and mercury levels were measured, and their association with lifetime prevalence of AD was analysed using logistic regression, weighted quantile sum (WQS) regression, quantile g-computation (QGC), and Bayesian kernel machine regression (BKMR). Confounders adjusted included age, sex, urinary cotinine, income, and body mass index. Sensitivity analyses used symptomatic AD and AD treatment as outcome variables.

Results: Among two metals, only cadmium in the highest tertile showed an odds ratio (OR) of 2.39 (95% CI: 1.12–5.10) compared with lowest tertile, with a significant trend per tertile increase (OR 1.58, 95% CI: 1.08–2.31) in multiple logistic regression. Co-exposure analysis using WQS and QGC revealed significant associations with AD prevalence, with WQS showing an OR of 1.47 (95% CI: 1.18–1.83) and QGC showing an OR of 1.60 (95% CI: 1.20–2.13) per tertile increase of exposure. BKMR indicated a dose-dependent relationship between overall exposure and AD risk. For symptomatic AD, similar trend was found. The treatment status of AD did not show a significant association with either heavy metal.

Conclusion: This study suggests a significant association between co-exposure to cadmium and mercury and atopic dermatitis, emphasizing the need to consider combined environmental exposures in epidemiological studies.

Key words: atopic dermatitis, cadmium, co-exposure, heavy metals, mercury

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https://doi.org/10.21101/cejph.a8437

INTRODUCTION

Atopic dermatitis, a prevalent allergic disease, manifests a lifetime prevalence of approximately 10–20%, underscoring its commonality (1). The aetiology of atopic dermatitis is multifactorial, encompassing genetic predispositions and environmental influences (2). Particularly, exposure to environmental pollutants during foetal development and early childhood has been documented to impact both the immune system and the integrity of the skin barrier (3). Among such pollutants, heavy metals have been implicated in allergic reactions and diseases (4, 5).

Traditionally, when elucidating the relationship between exposure to hazardous substances and specific diseases, the impact of each substance is analysed individually. However, in real-world settings, individuals are typically exposed to a myriad of substances at low concentrations concurrently. Thus, health impact assessments should involve the analysis of the combined exposure to multiple heavy metals. Epidemiological investigations have similarly reported on the health impacts of co-exposure to several heavy metals, including cadmium and mercury (6–8). However, epidemiologic studies considering the co-exposure to these metals and their association with allergic diseases remain scarce. Therefore, this study aims to investigate the association between co-exposure to cadmium and mercury and atopic dermatitis.

MATERIALS AND METHODS

Study Population, Sampling and Survey

The Korean National Environmental Health Survey (KoNEHS) is a nationally representative, population-based cross-sectional

study that began in 2009 and is repeated in 3-year cycles to assess the status of exposure to environmental chemicals, along with clinical, demographic, and behavioural characteristics among the population of the Republic of Korea (9). The KoNEHS Cycle 4 received ethical approval from the International Review Board (IRB) of the National Institute of Environmental Research (NIER), Korea (IRB No. NIER-2018-BR-003-02). The KoNEHS was conducted in accordance with the Declaration of Helsinki. All participants of the KoNEHS agreed to participate the survey and signed a written informed consent. In this study, we analysed all elementary school students who participated in KoNEHS Cycle 4. The details of the survey items and analytical methods used in KoNEHS are described in a separate publication (10). A detailed description of the collection and analysis of blood samples has been reported previously, though described in Korean (11). The translated explanations regarding the participants sampling, urine sampling and handling of samples have been provided in Supplementary Material 1. In this study, participants with no missing values in the variables among the survey and urine test to be analysed were selected.

Outcome Variables

The main outcomes considered in this study were "ever diagnosed with atopic dermatitis", as the index of lifetime prevalence of atopic dermatitis. "current presence of skin lesions due to atopic dermatitis", and "current treatment for atopic dermatitis" were also used as outcome for sensitivity analysis.

Measurement of Urinary Heavy Metals and Cotinine

Urinary cadmium levels were measured using Graphite Furnace Atomic Absorption Spectroscopy. The analysis was performed using a Perkin Elmer 900Z (Perkin Elmer, Germany).

The method detection limit (MDL) for cadmium was 0.04 μg/L. Urinary mercury levels were measured using a mercury analyser (Gold amalgamation direct mercury analyser, DMA-80, Milestones, Italy). The MDL for mercury was 0.04 μg/L. Urinary cotinine was used as an indicator of second-hand smoke exposure. The MDL for cotinine was 0.2 μg/L. Detailed analysis methods for heavy metals and cotinine have been provided in Supplementary Material 1.

For both heavy metals and urinary cotinine, values below the MDL were substituted by the MDL divided by the square root of two. To adjust for urine concentration, the levels of heavy metals in urine were divided to urinary creatinine level (g). Urinary creatinine levels were analysed using the Jaffe reaction with the ADVIA 1800 automatic analyser (Siemens Medical Solutions, Germany).

Confounder

Confounders were selected based on their potential to influence both the exposure variable (heavy metals) and the outcome (atopic dermatitis). The variables sex, age, urinary cotinine, income, and body mass index (BMI) were identified as confounders that could potentially affect both the outcome and the independent variable. The principles for selecting confounders, preliminary research exploration, and directed acyclic graph have been provided in Supplementary Material 2.

Statistical Analysis

General characteristics were presented considering the complex sampling design. For continuous variables, the mean and standard deviation were reported, while for categorical variables, the raw data numbers, estimated numbers applying survey weights, and estimated proportions were provided. For variables with skewed distributions, the median, 1 and 2 tertile are presented. Before performing the analysis on combined exposure, the correlation between the two heavy metals was analysed.

Comparisons between the groups with and without atopic dermatitis were made for each characteristic. For continuous variables, t-tests were performed if the variables followed a normal distribution, and Mann-Whitney tests were conducted if they did not. Chi-square tests were used for categorical variables.

To assess the effects of exposure to each heavy metal, separate logistic regression models were performed using the quasi-binomial model, with urinary mercury and cadmium as independent variables and atopic dermatitis as the dependent variable. The independent variables, heavy metals, were analysed in two ways: odds ratio (OR) for tertiles compared to lowest tertile, and OR trend for tertile increase were calculated for atopic dermatitis. Models were presented including cadmium and mercury separately as well as combined in the same model.

For the analysis of complex toxic material exposure, the weighted quantile sum regression (WQS), quantile g-computation models (QGC), and Bayesian kernel machine regression (BKMR) were used.

WQS regression is a method for estimating the combined effect of correlated exposures by creating an index based on quantile-transformed exposures. Each exposure is assigned a weight, constrained to sum to one, reflecting its relative contribution to the overall effect. This approach helps identify key contributors within a mixture while reducing collinearity issues (12). QGC models the joint effect of an exposure mixture by summing the effects of quantile-transformed exposures. Unlike WQS, it allows for bidirectional effects and provides flexible estimates of exposure-response relationships, including potential nonlinearity and interaction effects (13).WQS and QGC analyses were performed to identify the weights of the effects of each of the two heavy metals on atopic dermatitis. Complex exposure variable for each model was divided into three tertiles, and the effect size for each tertile increase was calculated. For WQS calculation, repeated holdout validation for weighted quantile sum regression was used. The data were divided into 30% of the dataset for training and 70% for validation. This split procedure was repeated 100 times, with 100 bootstrap samples assigned for parameter estimation. QGC also calculates the effect of the exposure mixture, estimating the effect of a simultaneous increase in the exposure mixture by the same quantile. QGC estimates the parameters of a marginal structural model (14). In this study, models assuming linearity and additivity were used, and the trend per tertile increase was shown.

BKMR analysis is used to assess the interaction and nonlinear relationships between environmental pollutants and health outcomes. This method captures complex exposure-response patterns while accounting for potential confounding factors (15). BKMR uses a Gaussian predictive process approach and component-wise variable selection to estimate posterior inclusion probabilities. The final model was fitted using the Markov Chain Monte Carlo sampler for 50,000 iterations.

Table 1. *General characteristics of study population*

	Total			With atopic dermatitis (lifetime prevalence)			Without atopic dermatitis			p-value
	Raw n	Estimated n	Estimated %	Raw n	Estimated n	Estimated %	Raw n	Estimated n	Estimated %	
	736	2,743,523		181	710,032	0	555	2,033,491	74	
Sex										
Male	348	1,410,675	51.4	85	365,093	51.4	263	1,045,582	51.4	0.988
Female	388	1,332,848	48.6	96	344,939	48.6	292	987,909	48.6	
BMI, mean (SD)	18.7 (3.76)			18.5 (3.70)			18.7 (3.78)			0.450
Urinary cotinine (ug/g creatinine)	1.63 (1.11, 2.21)			2.00 (0.90, 2.69)			2.00 (1.15, 2.18)			0.882
Income										0.576
< 3 million KRW	119	447,277	16.3	27	119,418	16.8	92	327,859	16.1	
≥ 3 million KRW	591	2,203,492	80.3	150	576,570	81.2	441	1,626,923	80	
Do not respond	26	92,754	3.4	4	14,044	2.0	22	78,709	3.9	
Age (years), mean (SD)	8.5 (1.69)			8.4 (1.61)			8.4 (1.72)	0		0.743
6	114	452,075	16.5	27	105,859	14.9	87	346,215	17	0.752
7	126	468,862	17.1	28	120,117	16.9	98	348,745	17.2	
8	119	460,353	16.8	32	137,434	19.4	87	322,919	15.9	
9	126	470,825	17.2	35	136,761	19.3	91	334,065	16.4	
10	131	458,377	16.7	34	119,595	16.8	97	338,782	16.7	
11	120	433,032	15.8	25	90,267	12.7	95	342,765	16.9	
Urinary mercury (ug/g creatinine)	0.34 (0.29, 0.43)			0.37 (0.32, 0.46)			0.33 (0.28, 0.42)			0.071
1st tertile	249	912,603	33.3	53	202,350	28.5	196	710,253	34.9	
2nd tertile	245	918,226	33.5	62	256,440	36.1	183	661,786	32.5	
3rd tertile	242	912,694	33.3	66	251,242	35.4	176	661,452	32.5	
Urinary cadmium (ug/g creatinine)	0.20 (0.16, 0.24)			0.22 (0.18, 0.25)			0.19 (0.15, 0.23)			**0.002**
1st tertile	252	912,971	33.3	49	184,911	26.0	203	728,060	35.8	
2nd tertile	245	918,306	33.5	61	239,406	33.7	184	678,900	33.4	
3rd tertile	239	912,246	33.3	71	285,715	40.2	168	626,531	30.8	
Presence of symptomatic atopic dermatitis										
Yes	679	2,511,387	91.5	124	477,896	67.3	555	2,033,491	100	
No	57	232,136	8.5	57	232,136	32.7	–	–	–	–

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Table 1. *General characteristics of study population*

Present treatment of atopic dermatitis										
Yes	714	2,655,721	96.8	159	622,230	87.6	555	2,033,491	100	
No	22	87,802	3.2	22	87,802	12.4	–	–	–	

The estimated number (n) and estimated proportion (%) were calculated considering the complex sample design weights.
Continuous variables are expressed as mean (standard deviation), but variables deviating from a normal distribution are presented as median (1st quartile, 3rd quartile). Normally distributed continuous variables were analysed using the t-test, non-normally distributed continuous variables were analysed using the Mann-Whitney test, and categorical variables were analysed using the chi-square test.

Statistical analyses were performed using R Project 4.3.0*. For the statistical analysis of complex samples, "survey" package was used. BKMR, WQS regression, and QGC models were performed using the "bkmr", "gwqs", and "qgcomp" packages, respectively.

Sensitivity Analysis

We presented the results of models adjusting for the same variables but replacing the outcome variables with "current presence of skin lesions due to atopic dermatitis" and "current treatment for atopic dermatitis".

Considering that various environmental pollutants and endocrine-disrupting chemicals may potentially influence the prevalence of atopic dermatitis, we presented all biomonitoring exposure indicators for environmental pollutants assessed in KoNEHS Cycle 4 according to atopic dermatitis status. Additionally, we provided the odds ratios ORs for urinary mercury and cadmium in relation to atopic dermatitis from a fully adjusted QGC model.

RESULTS

General Characteristics

The study included a total of 736 participants, representing an estimated population of approximately 2,743,523 when considering the sampling method. The general characteristics of population are presented in Table 1. The sample consisted of 348 males and 388 females, representing 51.4% and 48.6% of the population, respectively, after weighting. The average age was 8.5 ± 1.69 years. The median urinary mercury level was 0.34 μg/g creatinine, with the 1st tertile at 0.29 μg/g creatinine and the 2nd tertile at 0.43 μg/g creatinine. The median urinary cadmium level was 0.20 μg/g creatinine, with the 1st tertile at 0.16 μg/g creatinine and the 2nd tertile at 0.24 μg/g creatinine. There were 181 participants with lifetime prevalence of atopic dermatitis (estimated proportion: 25.9%) and 555 without (estimated proportion: 74.1%). Among population, 57 had current symptoms of dermatitis (estimated proportion: 8.5%), and 22 were receiving treatment of atopic dermatitis (estimated proportion: 3.2%).

In univariate comparisons, only urinary cadmium tertiles showed significant differences between the groups with and without atopic dermatitis ($p=0.002$). The lifetime prevalence of atopic dermatitis for each tertile of heavy metals and the levels of heavy metals according to the lifetime prevalence of atopic dermatitis are illustrated in supplementary S Fig. 2.

The lifetime prevalence of atopic dermatitis according to tertiles of cadmium and mercury, as well as the levels of cadmium and mercury in urine by atopic dermatitis status, are presented in Supplementary Material 3.

Multiple Logistic Regression

In separate models considering urinary cadmium and mercury as exposure variables, when categorized into tertiles, the highest

*https://r-project.org; R Foundation, Vienna, Austria

tertile of cadmium showed a significant association with atopic dermatitis, with an OR of 2.39 (95% CI: 1.12–5.10, p = 0.030), and a trend per tertile increase with an OR of 1.58 (95% CI: 1.08–2.31, p = 0.024). Mercury did not show significant differences across tertiles or trends.

In a multiple logistic regression model including both cadmium and mercury, cadmium showed a significant association, with the highest tertile having an OR of 1.79 (95% CI: 1.20–2.66, p = 0.007) and a trend per tertile increase of 1.58 (95% CI: 1.08–2.31, p = 0.023). Mercury did not show significant differences in any tertile comparisons or trends (p = 0.178, p = 0.208, and trend p = 0.913, respectively).

Mixture Analysis

In the WQS analysis, the complex exposure to mercury and cadmium showed an OR of 1.47 (95% CI: 1.18–1.83) per tertile increase, which was statistically significant (p = 0.001). The weights for mercury and cadmium were 0.41 (95% CI: 0.07–0.85) and 0.58 (95% CI: 0.15–0.93), respectively. In the QGC, the complex exposure to mercury and cadmium showed an OR of 1.60 (95% CI: 1.20–2.13, p = 0.001) for atopic dermatitis. The scaled effect sizes were 0.62 for cadmium and 0.38 for mercury (Table 2).

In BKMR, assuming a simultaneous increase of 1 percentile in both mercury and cadmium, there was a significant decrease in the prevalence of atopic dermatitis below the 50th percentile and a significant increase above the 50th percentile (Fig. 1). However, when examining the effects of each substance at specific quantiles (5%, 50%, 95%) while holding the other constant, no clear trend changes were observed, indicating no synergistic or protective effects (Supplementary Material 4).

Sensitivity Analysis

The results of the sensitivity analysis by different outcome variables are presented in Supplementary Material 5. When limiting the outcome variable to those with current symptoms of atopic dermatitis, urinary cadmium showed a significant difference

Table 2. *Association between lifetime prevalence of atopic dermatitis and complex exposure of mercury and cadmium*

	Exposure variables	OR (95% CI)	p-value
OR for individual model per each metal (as category of each tertile)	Urinary cadmium		
	1st tertile	Reference	
	2nd tertile	1.30 (0.60–2.8)	0.508
	3rd tertile	2.39 (1.12–5.1)	**0.030**
	Urinary mercury		
	1st tertile	Reference	
	2nd tertile	1.26 (0.67–2.35)	0.475
	3rd tertile	1.02 (0.49–2.13)	0.958
OR for individual model per each metal (trend increase of tertile)	Urinary mercury (trend per tertile increase)	1.01 (0.72–1.42)	0.957
	Urinary cadmium (trend per tertile increase)	1.58 (1.08–2.31)	**0.024**
Within one model	Urinary cadmium		
	1st tertile	Reference	
	2nd tertile	1.43 (0.96–2.15)	0.088
	3rd tertile	1.79 (1.2–2.66)	**0.007**
	Urinary mercury		
	1st tertile	Reference	
	2nd tertile	1.35 (0.88–2.08)	0.178
	3rd tertile	1.33 (0.86–2.04)	0.208
Within one model	Urinary mercury (trend per tertile increase)	0.98 (0.70–1.38)	0.913
	Urinary cadmium (trend per tertile increase)	1.58 (1.08–2.3)	**0.023**
WQS	Complex exposure	1.47 (1.18–1.83)	**0.001**
	Weight for mercury	0.41 (0.07–0.85)	
	Weight for cadmium	0.58 (0.15–0.93)	
QGC	Complex exposure	1.61 (1.21–2.15)	**0.001**
	Weight for mercury	0.38	
	Weight for cadmium	0.62	

CI – confidence interval; OR – odds ratio; WQS – weighted quantile sum regression; QGC – quantile g-computation
The results of WQS and GQC represent the change in OR for each increase in tertile.

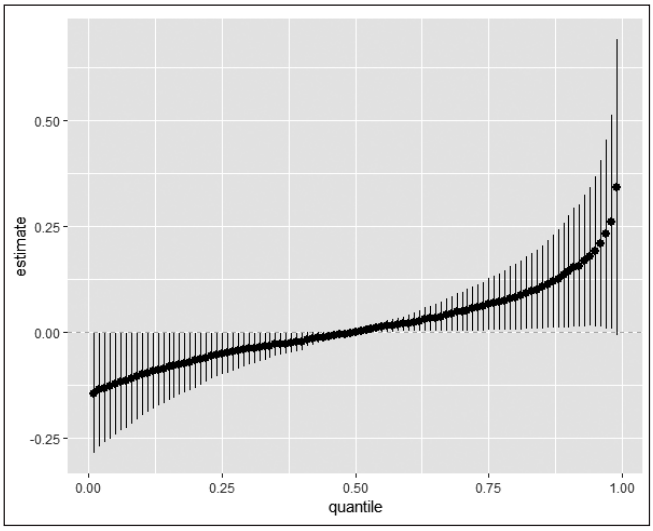

Fig. 1. *Association between lifetime prevalence of atopic dermatitis and combined exposure to mercury and cadmium.*

Calculated using Bayesian kernel machine regression. Each unit movement on the x-axis represents a simultaneous 1 percentile increase in both mercury and cadmium, and the y-axis represents the log (odds ratio).

between the 1st and 3rd tertiles, and the trend was significant in both single and combined variable models. Mercury did not show statistical significance.

WQS and QGC analyses showed significant results, with an OR of 1.75 (95% CI: 1.15–2.65) per tertile increase. In WQS, the weights were 0.71 (95% CI: 0.33–0.97) for cadmium and 0.29 (95% CI: 0.03–0.67) for mercury. In QGC, the OR change per tertile was 1.75 (95% CI: 1.10–2.78), with scaled effect sizes of 0.90 for cadmium and 0.10 for mercury. In BKMR, assuming a simultaneous increase of 1 percentile in both mercury and cadmium, there was no significant increase or decrease below or above the 50th percentile. However, comparing the 1st to the 99th percentile, there was a significant positive association with current symptoms of atopic dermatitis.

When the outcome variable was limited to current treatment for atopic dermatitis, neither heavy metal showed a significant relationship with the outcome variable. Similarly, WQS and QGC analyses did not show a significant relationship between complex exposure and current treatment for atopic dermatitis. BKMR also did not show a significant relationship between overall complex exposure and current treatment for atopic dermatitis.

The results of the QGC model, adjusted for all environmental pollutants, indicate that complex exposure to urinary mercury and cadmium is significantly associated with atopic dermatitis, with an odds ratio (OR) of 1.69 (95% CI: 1.24–2.30, p = 0.001). The estimated weights for mercury and cadmium were 0.49 and 0.51, respectively, suggesting that both metals contributed almost equally to the overall effect of complex exposure (Supplementary Material 6).

DISCUSSION

In this study, we examined the association between co-exposure to mercury and cadmium and atopic dermatitis. The WQS and QGC analyses revealed that considering the co-exposure to cadmium and mercury, the combined exposure had a significant association with the lifetime prevalence of atopic dermatitis. The BKMR analysis also indicated that overall exposure increased the risk of atopic dermatitis in a relatively dose-dependent manner, however, no clear synergistic or protective effects were observed.

Before interpreting the results of this study, it is essential to consider the characteristics of heavy metal exposure among Korean population. In a study analysing adults who participated in KoNEHS, the primary routes of heavy metal exposure were reported in the order of ingestion > inhalation > dermal absorption, with dietary intake being the predominant source of exposure for both mercury and cadmium (16). While systematic studies on the exposure pathways of heavy metals among Korean children remain limited, Korea is a country with high consumption of rice and seafood. Several studies have reported that seafood consumption is the major dietary source of mercury exposure (17, 18), whereas rice consumption contributes significantly to cadmium exposure (19, 20). In an analysis of middle and high school students from KoNEHS, it has been reported that the intake of large fish, tuna, and fish is associated with urinary mercury levels in specific groups, with higher BMI (21). Additionally, some studies have suggested an association between cadmium exposure and the consumption of vegetables and fruits (22) Furthermore, residential environment and geographic location have been reported to influence body burdens of mercury and cadmium (17). While studies conducted up until the 2000s indicated that heavy metal concentrations in Korean children were generally higher than those observed in populations in the United States and Europe (23), more recent studies suggest that the levels are now comparable. For comparison, a study reported a median urinary mercury concentration of 0.37 μg/g creatinine in Czech children aged 8–10 years (24) which is similar to the median level of 0.34 μg/g creatinine observed in our study. In the DEMOCOPHES cohort from the Czech Republic, the geometric mean urinary cadmium concentration was reported as 0.11 μg/g creatinine, while our study reported a median of 0.20 μg/g creatinine and a geometric mean of 0.17 μg/g creatinine, suggesting a slightly higher level of cadmium exposure in our study population.

Cadmium is a heavy metal involved in the immunomodulation of T helper cells (25). An animal studies have reported that oral cadmium administration induces a proinflammatory epidermal cell response (26). Mercury is also known to induce generalized activation of the immune system and is recognized for promoting the release of inflammatory mediators from mast cells (27, 28). Numerous epidemiological studies have explored the associations between heavy metals, including cadmium and mercury, and immune and allergic diseases. For instance, a study in Korea reported that prenatal exposure to cadmium, inferred from cadmium levels in cord blood, was associated with atopic dermatitis within the first six months of life (29). A cohort study in Taiwan involving 586 mother-child pairs found that prenatal co-exposure to arsenic and cadmium was linked to the development of atopic dermatitis (30). There is also evidence linking blood mercury levels in Korean adults to the occurrence of atopic dermatitis (31). Another study reported that prenatal and postnatal mercury exposure, inferred from mercury levels in cord blood and maternal blood samples collected shortly after birth, was associated with the prevalence of atopic dermatitis in children (32). However, some studies have found no association between mercury and allergic conditions.

A Japanese study on children reported no correlation between mercury exposure and the occurrence of wheeze and eczema (33). Similarly, an analysis of data from the United States National Health and Nutrition Examination Survey found no significant association between cadmium, lead, mercury, and the prevalence of eczema (34). Thus, while there are multiple reports on the relationship between individual heavy metals and allergic diseases, the evidence remains controversial. Environmental exposure to heavy metals typically occurs at very low levels compared to occupational or accidental exposures, where exposure levels are significantly higher. As a result, even if clinical-level health impacts exist, it is challenging to demonstrate them clearly due to the minimal differences in exposure levels between groups categorized as "high" and "low" exposure. This makes it difficult to accumulate robust evidence on the health effects of low-level exposure to pollutants (35).

To overcome some of these limitations, we considered the co-exposure of two or more substances, which can more clearly delineate the differences in exposure levels between groups with low and high exposures. In this study, we focused on the co-exposure of two heavy metals, cadmium and mercury. In vitro studies on the co-exposure of these metals and their effects on the immune system have shown that mercury and lead inhibit interleukin (IL) -2 production regardless of T cell activation state, while cadmium stimulates IL-2 production only in preactivated T cells. However, when co-exposed to mercury, cadmium, and lead, the effects seem to nullify each other, suggesting possible interactions between the substances (36). Both cadmium and mercury have been reported to exhibit inhibitory effects on B-cell activation by inhibiting deoxyribonucleic acid, ribonucleic acid, and antibody synthesis (37). Despite numerous animal and in vitro studies reporting the health effects of cadmium and mercury on allergic diseases, epidemiological studies on the co-exposure of these heavy metals have mainly focused on target organs such as the lungs (38), kidneys (6, 7), nervous system (8), and liver (39), with fewer studies on allergic diseases. In this study, we aimed to investigate the association between the co-exposure to cadmium and mercury and atopic dermatitis, a representative allergic disease. Our findings showed a clearer association with co-exposure compared to the exposure of each heavy metal individually. Previous studies using the same dataset (KoNEHS Cycle 4) did not find a significant association between mercury and atopic dermatitis (40), likely due to the small differences in exposure levels between the low and high exposure groups and the failure to account for co-exposure to multiple substances. By employing advanced statistical methods such as WQS, QGC and BKMR, this study demonstrated the association between the co-exposure to cadmium and mercury and atopic dermatitis.

In this study, the resent treatment of atopic dermatitis did not show an association with heavy metal exposure, which can be interpreted as evidence against a reverse causal relationship. Specifically, it suggests that the process of treating atopic dermatitis does not lead to increased heavy metal exposure. Many atopic dermatitis patients in Korea opt for alternative therapies such as herbal medicine (41), which can contain relatively high concentrations of heavy metals (42), potentially influencing urinary heavy metal levels. However, the lack of a significant relationship between heavy metal levels and the treatment of current atopic dermatitis supports the exclusion of such a reverse causal relationship.

One limitation of this study is that the timing of urinary mercury and cadmium measurements, used as exposure indices, was after the diagnosis of atopic dermatitis. However, urinary mercury and cadmium reflect relatively long-term cumulative exposure compared to blood levels, indicating not just the current body burden but also serving as proxies for lifetime exposure. High urinary heavy metal levels likely reflect consistent high-level exposure over time. Moreover, since the study population consisted of elementary school students, the likelihood of high-level exposure from smoking or occupational sources is minimal, making it reasonable to use urinary heavy metals as proxies for lifetime exposure. By using "current symptoms of atopic dermatitis" as the outcome variable, we aimed to demonstrate the relationship between the current body burden of heavy metals and atopic dermatitis, partially addressing this limitation. Other limitations of this study include the cross-sectional design, which makes it difficult to establish causality, the possibility of unaccounted confounders, and the fact that it is a secondary analysis of previously collected data, which did not consider co-exposure to a broader range of heavy metals. Additionally, reliance on self-reported diagnoses through questionnaires may introduce bias. However, in this study, we used urinary heavy metal levels as a biological exposure index to indicate environmental exposure. Since most individuals are unaware of their exposure levels prior to testing, it is unlikely that recall bias occurred differentially based on exposure status. This study was conducted using secondary data from a survey designed for exposure assessment of environmental pollutants, which presents a limitation in that clinical evaluations for atopic dermatitis and assessments of common allergens were not available for adjustment. However, for a factor to be a true confounder, it must influence both exposure and outcome (43), yet there is no clear evidence that specific common allergens directly affect heavy metal exposure or its metabolism, thus, potential bias is expected to be non-differential. Even if differential bias were present, adjusting for multiple environmental pollutants would likely account for co-exposures, including potential allergens that share common exposure pathways with pollutants other than heavy metals. Importantly, the effect size and statistical significance remained largely unchanged in models adjusted for various environmental pollutant exposure indicators, supporting the robustness of our findings.

CONCLUSION

In summary, while this study shows a significant association between the co-exposure to cadmium and mercury and atopic dermatitis using advanced statistical methods such as WQS, QGC, and BKMR, it also highlights the necessity for future research to address these limitations and further investigate the complex interactions between multiple environmental exposures and health outcomes.

Electronic Supplementary Materials

This article contains supplementary material available at https://doi.org/10.21101/cejph.a8437

Acknowledgement

We would like to thank the Dongguk University College of Medicine for their support through the 2024 Research Fund.

Funding

This work was supported by Dongguk University College of Medicine 2024 Research Fund.

Conflicts of Interest

None declared

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Received October 11, 2024
Accepted in revised March 14, 2025