Epidemiology Publish Ahead of Print

DOI: 10.1097/EDE.0000000000000576

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

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Running Head: Mercury and asthma

Declaration of Conflicts of interest: none declared

Sources of financial support: Data collection and measurements of mercury were funded by a grant of Federal Agency of Environmental Protection, Germany.

Abstract

Background. Although mercury exposure has been associated with several adverse health effects, the association with childhood asthma is under-investigated. Therefore, we explore the association between mercury and childhood asthma in a population with low mercury levels.

Methods. Mercury levels were measured in blood and urine in 1,056 children aged 5-14 years. In addition to including questions about asthma diagnosis and wheezing, the study measured bronchial hyper-responsiveness and allergic sensitization to common aeroallergens. Logistic regression analysis adjusted for major potential confounders.

Results. Overall the adjusted odds ratios (aOR) between log blood mercury and the outcomes were 0.8 (95% CI 0.63, 1.11) for asthma, 0.9 (95% CI 0.79, 1.14) for wheeze, 1.1 (95% CI 0.60, 2.03) for bronchial hyperresponsiveness, and 1.0 (95% CI 0.80, 1.17) for allergic sensitization. Urine mercury adjusted for creatinine was also not associated with any of these allergy-related outcomes.

Conclusions. While the results did not support an association between mercury exposure and asthma, studies are needed to assess prenatal and lifetime exposure to mercury and asthma.

Introduction

While many studies have reported adverse health effects, including neurotoxicicity,[1,2,3] of mercury (Hg) exposure, few studies have investigated asthma and asthma-related outcomes. Recently, a prospective study of 4,350 Korean children found an increased risk of asthma, with increasing blood Hg during a two- and four-year follow-up period.[4] This result was supported by findings of increased risk for asthma medication, wheeze, and bronchial hyper-responsiveness. The increased risk for asthma was more pronounced among children younger than 10 years of age. Moreover, a cross-sectional analysis of 2,750 children aged 10 years found an association between urine Hg and life-time asthma prevalence and current asthma.[4] However, the results of three other studies on Hg and asthma did not find that Hg burden is related to increased risk asthma risk in children. A cohort study of 656 children in the Faroe Islands did not show any adverse impact of methylmercury exposure assessed prenatally and at ages 5 and 7 years with asthma and total IgE. The grass specific IgE levels were even lower in children higher exposures to methylmercury at age 7 years.[5] An ecological study aggregated Hg levels in hair of about 200 adolescents and 250 mothers across Belgium regions and found negative associations with asthma prevalence aggregated for these regions.[6] Finally, a cross-sectional study of 582 Japanese mother-child pairs did not show any increased risk for wheeze related to maternal or children's hair Hg levels.[7] Although the study by Kim et al (2015) has several strengths such as a large sample size, internal consistency across several asthma-related outcomes, and the prospective study design, that study's authors concluded that additional epidemiologic studies are needed to assess the association between Hg and asthma before drawing any final conclusion.[4] We followed this suggestion and analyzed previously collected data from school-aged children three regions of former East Germany.

Methods

This secondary analysis used data from the first survey of repeated cross-sectional studies comparing respiratory health indicators and the internal burden of heavy metals across three regions in former East

Germany. These three regions, Bitterfeld, Hettstedt, and Zerbst, are known to have been affected by different industrial emissions over decades and in ambient air pollution levels.[8,9,10] Details about the study population and methods are given elsewhere.[8,9,10] Ethical approval was granted by University of Rostock. The parents or guardians of the children gave written informed consent. During 1992-1993 the first survey was conducted and included 1,056 children aged 5-14 years with Hg data. Internal Hg burden was measured in blood and urine by atomic absorption spectroscopy; see details on chemical analysis in Trepka et al.[9] Mercury levels in urine were adjusted for creatinine. We defined asthma as parental reported doctor's diagnosis of asthma, asthmoid bronchitis, or spastic bronchitis, because East German doctors avoided the label "asthma" and commonly used labels as "asthmoid bronchitis" or "spastic bronchitis" even years after German reunification. We gathered data on wheezing during the 12 months prior to the study from the parents. We evaluated allergic sensitization to common aeroallergens by a radio-absorbance test (RAST) to birch and grass pollen allergens, to mite and cat allergens, and to *Cladosporium herbarum* using a cut-off of 0.35 kU/L.[8] We assessed bronchial hyper-responsiveness after a cold air challenge in a smaller subset of the children.[8] We applied logistic regression analysis and used log transformed Hg levels as exposure, to correct for the skewed distribution of Hg levels. We adjusted the association for age, gender, paternal, and maternal history of asthma, maternal smoking during pregnancy, passive smoking at home, paternal, and maternal educational level, furred pet ownership, and region. We used an almost identical set of covariates to increase comparability of our findings with that of Kim et al (2015).[4] As sensitivity analyses we also adjusted our models for utmost the same set of covariates as Grandjean et al (2010)[5] In addition age-specific effects were modelled, because Kim et al observed the strongest association for children aged 7 to 10 years. Odds ratios are reported per increase in log-transformed mercury concentration.

Results

Several selected characteristics of the study population are showed in Table 1. Asthma was reported for 10% (101/1056), wheeze during last 12 months for 29% (290/995), and allergic sensitization assessed by RAST test for 40% (345/853) children, and bronchial hyper-responsiveness for 7% (23/342). The blood Hg levels ranged from 0.1 to 4.0 μg Hg/L with a geometric mean of 0.36 μg Hg/L.

Results of logistic regression analysis for blood levels and the impact of covariates are reported in Table 2. Overall, the adjusted odds ratios (aOR) between log blood Hg and the outcomes were 0.8 (95% CI 0.63, 1.11) for asthma, 0.9 (95% CI 0.79, 1.14) for wheeze, 1.1 (95% CI 0.60, 2.03) for bronchial hyper-responsiveness, and 1.0 (95% CI 0.80, 1.17) for allergic sensitization. Asthma was not associated with blood Hg among any of the age groups. The age-specific adjusted OR and 95% CI were 1.11 (0.65, 1.87) for 5-7 year olds, 0.63 (0.37, 1.07) for 8-10 year olds, and 0.67 (0.40, 1.14) for 11-14-year-olds. Because Hg in blood reflects recent exposure, while urinary Hg levels better reflect chronic exposure, we also analyzed the association between asthma and urinary Hg adjusted for creatinine and did not find any substantial increased risk of asthma (OR =1.0 [95% CI 0.82, 1.25]), wheeze (0.9 [0.77, 1.02]), bronchial hyper-responsiveness (0.8 [0.49, 1.22]), or allergic sensitization (1.1 [0.96, 1.28]) (Table 2). For those children younger than 10 years of age the creatinine adjusted odds plus 95% CI was 1.23 (0.95, 1.59). As sensitivity analyses we also ran model adjusting for additional variables such as season of birth, preterm birth, low birth weight (<2500g), children's fish consumption, day care attendance, and body mass index, which were almost the same as those used by the Grandjean et al study, and the effect estimates for mercury burden on tested outcomes were mostly identical (data not shown).

Discussion

We found no association between blood Hg levels or urine Hg levels and childhood asthma or related

outcomes. This is in contrast to the results of a prospective study of blood mercury and a cross-sectional analysis of urinary Hg by Kim et al.[4] Our findings, however, are consistent with those of a study of a birth cohort followed for 7 years by Grandjean et al who found no association between methylmercury measurements and asthma.[5] They are also consistent with a cross-sectional study by Miyake et al who did not observe any association between hair Hg and wheeze, and an ecologic study by Croes et al that found a negative association between hair Hg and asthma prevalence.[6,7]

There are several potential reasons for the inconsistent results between our study and the studies by Kim et al, the only other studies to find a positive relationship between asthma and mercury exposure. First, the setting and consequently the sources of internal burden of Hg are different between our population and the cohort studied by Kim et al.[4] While for the Korean population, fish consumption could be the main source, our own study estimated that amalgam fillings in combination with fish consumption were influential.[9] This impacts the relative exposure to inorganic and organic Hg, which cannot specifically be measured by atomic absorption spectrometry, and which was applied in both studies. Second, the average level of blood Hg is approximately six-fold higher in the Korean children compared to that of children in our study. One might speculate that there may be a threshold level of Hg needed to increase the risk for asthma. Third, blood Hg reflects recent mercury exposure. Repeated blood tests correlated only weakly ($r<0.2$), which was also shown by Kim and colleagues.[4] Since the exposure assessment is mainly recent and asthma development starts over a long period of time, the exposure assessment by blood test is not ideal, and the follow-up time not long enough. Fourth, the proposed biologic mechanisms for the development of asthma are mainly related to immune-modulating effects, and associations were found neither for total IgE[4,5] nor for specific IgE to grass pollen allergens.[5] Asthma in childhood is predominantly allergic asthma. Therefore, we would have expected an increased risk for IgE assuming a causal impact of Hg exposure on asthma, but no study has shown that so far. A further explanation for the different results of the study by Kim et al and ours

is the definition of the outcome. While Kim et al also considered new onset of asthma, our own study is based on prevalent asthma. However, Kim et al also reported increased risks for prevalent asthma using NHANES data, when mercury was averaged until age 9-10 years and associations with asthma at 9-10 years were reported (OR 1.7[95%CI 1.2,2.4]). Moreover, the cross-sectional association between the urinary mercury burden and current asthma was also reported as positive (OR= 1.4[95%CI 1.0,1.9]. Thus, it is not clear that incidence versus prevalence is the reason for the different results. Finally, there is a design-related difference between the prospective cohort study by Kim et al and our study. While Kim et al (2015) assessed the health impact of blood Hg for an average of two or three Hg measurements at age 7-8, 9-10, and 11-12 years and measured asthma incidence, our study was cross-sectional and measured prevalence, similar to the cross-sectional analysis by Kim et al of the NHANES data. However, since the follow-up of the blood Hg cohort by Kim is less than 2 or 4 years for the youngest age group, we would not expect a strong design-related impact as explanation for the overall differences of study findings.

Conclusion

Although the one prospective cohort[4] and one cross-sectional study[4] found a positive association between mercury exposure and asthma are superior to our study in several aspects, the null findings of our study along with those of the three other studies suggest that the health impact of internal burden of Hg in relation to asthma and allergic diseases needs to be studied further. Given what is known about how asthma develops, it would be useful for additional studies to be conducted that use a life-course approach and that assess both prenatal and early childhood Hg exposure.

References

1. Grandjean P, and Landrigan PJ. Developmental neurotoxicity of industrial chemicals. *Lancet*. 2006; 368(9553):2167-78.

2. Bose-O'Reilly S, McCarty MK, Steckling N, Lettmeier B. Mercury exposure and children's health. *Curr Probl Pediatr Adolesc Health Care*. 2010; 40(8):186-215.

3. Karagas MR, Choi AL, Oken E, et al. Evidence on the human health effects of low-level methylmercury exposure. *Environ Health Perspect*. 2012; 120(6):799-806.

4. 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(5):733-9.

5. Grandjean P, Poulsen LK, Heilmann C, Steuerwald U, Weihe P. Allergy and sensitization during childhood associated with prenatal and lactational exposure to marine pollutants. *Environ Health Perspect*. 2010; 118(10):1429-33

6. Croes K, De Coster S, De Galan S, et al. Health effects in the Flemish population in relation to low levels of mercury exposure: from organ to transcriptome level. *Int J Hyg Environ Health*. 2014; 217(2-3):239-47.

7. Miyake Y, Tanaka K, Yasutake A, Sasaki S, Hirota Y, et al. 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(8): 1180-4.

8. Heinrich J, Hoelscher B, Wjst M, Ritz B, Cyrys J, Wichmann H. Respiratory diseases and allergies in two polluted areas in East Germany. *Environ Health Perspect.* 1999; 107(1):53-62.

9. Trepka MJ, Heinrich J, Krause C, et al. Factors affecting internal mercury burdens among eastern German children. *Arch Environ Health.* 1997; 52(2):134-8.

10. Heinrich J, Hoelscher B, Frye C, et al. Improved air quality in reunified Germany and decreases in respiratory symptoms. *Epidemiology*. 2002; 13(4):394-401.

Table1: Distribution of population characteristic and health outcomes for the analysis of blood mercury level (Total N=1,056)

Characteristics	No. with characteristics or outcome/total available for analysis	%	No. without available result
Gender			-
Male	504/1056	48	
Female	552/1056	52	
Age			-
5-7 years	322/1056	30	
8-10 years	318/1056	30	
11-14 years	416/1056	40	
Region			-
Bitterfeld	177/1056	17	
Hettstedt	682/1056	64	
Zerbst	197/1056	19	
Parental history of asthma			80
Yes	27/976	3	
No	949/976	97	
Parental educational level[a]			22
<10 years	67/1034	7	
10 years	488/1034	47	
12 or more years	479/1034	46	
Own a pet with fur			15
Yes	701/1041	67	
No	340/1041	33	
Tobacco smoke exposure[b]			5
Yes	604/1051	57	
No	447/1051	43	
Outcomes			
Asthma[c]	101/1056	10	-
Wheeze at last 12 months	290/995	29	61
Bronchial hyperresponsiveness[d]	23/342	7	714
RAST positivity[e]	345/853	40	203

[a] Defined as the number of years of school for parent with highest achieved educational level
[b] Maternal smoking during pregnancy or postnatal exposure to tobacco smoke at home
[c] Defined as any doctor-diagnosed asthma, asthmatic bronchitis or spastic bronchitis.
[d] Defined as bronchial hyperresponsiveness when a cold air provocative caused a 9% fall in FEV1
[e] At least one of five measured specific IgE>0.35kU/L

Table 2: Odds ratio (OR) and 95% confidence interval for asthma-related outcomes per one unit of log-transformed blood or urine mercury.

Logistic regression models for mercury exposure and asthma related outcomes among children aged 5-14 years old[a]

	Blood Hg	Urine Hg
	adjusted OR (95%CI)	adjusted OR (95%CI)
Asthma	0.8 (0.63, 1.11)	1.0 (0.82, 1.25)
Wheezing at last 12 months	0.9 (0.79, 1.14)	0.9 (0.77, 1.02)
Bronchial Hyperresponsiveness	1.1 (0.60, 2.03)	0.8 (0.49, 1.22)
Radio Absorbance Test Positivity	1.0 (0.80, 1.17)	1.1 (0.96, 1.28)