

BMJ Open Are higher blood mercury levels associated with dry eye symptoms in adult Koreans? A population-based cross-sectional study

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ABSTRACT

Objectives: The purpose of this study was to investigate whether blood mercury concentrations associated with the presence of dry eye symptoms in a nationally representative Korean population.

Methods: Population-based prospective cross-sectional study using the heavy metal data set of the 2010–2012 Korean National Health and Nutrition Examination Survey (KNHANES). A total of 4761 adult Koreans were the eligible population in this study. Of the 7162 survey participants, 2401 were excluded because they were <19 years of age, there were missing data in the heavy metal data set, or they had diabetes, rheumatoid arthritis, thyroid disease, asthma, depression and/or under-the-eye surgery. Blood mercury levels were measured on the day the participants completed a questionnaire regarding the presence of dry eye symptoms (persistent dryness or eye irritation). The population was divided into low and high groups by median level (4.26 and 2.89 µg/L for males and females, respectively).

Results: Self-reported dry eye symptoms were present in 13.0% of the cohort. Participants with dry eye symptoms were significantly more likely to have blood mercury levels exceeding the median than those without dry eye symptoms (45.7% vs 51.7%, p=0.021). Logistic regression analysis showed that, after adjusting for age, gender, education, total household income, smoking status, heavy alcohol use, sleep time, perceived stress status, total cholesterol levels and atopy history, dry eye symptoms were significantly associated with blood mercury levels that exceeded the median (reference: lower mercury group; OR, 1.324; 95% CI 1.059 to 1.655; p<0.05).

Conclusions: High blood mercury levels were associated with dry eye symptoms in a nationally representative Korean population.

INTRODUCTION

Dry eye syndrome is the most common disease for which patients visit ophthalmologists. Large epidemiological studies show that the prevalence of dry eye at various ages

Strengths and limitations of this study

- This study identified the blood mercury levels and dry eye symptoms of a nationally representative population in South Korea.
- The study population was large and the weights were considered.
- Potential confounders were excluded.
- The cross-sectional design of the study means that this association cannot be interpreted as a cause–effect relationship.

ranges from 5%¹ to >35%.² It is currently regarded as tear film instability and ocular surface inflammation with ocular surface damage.¹ Dry eye symptoms include dryness, sensation of foreign body or burning, photophobia, pain and visual symptoms. These symptoms affect daily living activities, including important tasks such as driving.² Dry eye syndrome is most commonly diagnosed using symptom questionnaires because they yield reliable diagnoses.³

An international dry eye workshop reported that the mostly consistent risk factors of dry eye syndrome included older age, female gender, postmenopausal oestrogen therapy, ocular surface surgery history, antihistamine medications, connective tissue disease, radiation therapy, haematopoietic stem cell transplantation, vitamin A deficiency, hepatitis C infection and androgen deficiency.⁴

Mercury is a ubiquitous metal in the environment that adversely affects health after absorption. Organic/inorganic/metal mercury can enter the body through various routes, including the gastrointestinal tract, skin and respiratory tract. After entry, it accumulates from the blood in the brain, kidney, liver, hair, eye and skin.⁵ Ionic mercury in the blood is transported to the retina pigment epithelium, where it accumulates in



photoreceptors, the plexiform layer and ganglion cells, and is also found in the vitreous in animal studies.^{6–8} In human studies, chronic exposure to methylmercury can affect eye movement.⁹ With regard to the conjunctiva, one previous report demonstrated in rabbits that metallic mercury in the conjunctiva increased lymphocytes and macrophages and was also associated with increased amounts of altered mucus.¹⁰ Since inflammation has a prominent role in the development and amplification of the signs and symptoms of dry eye syndrome,¹¹ we hypothesised that altered mucus and conjunctiva inflammation by exposure to mercury might affect dry eye syndrome.

However, there are few studies that have investigated the association between dry eye and blood mercury level. This question was addressed by performing this prospective cross-sectional study of a general nationwide population in South Korea that is exposed to low levels of environmental mercury.

METHODS

Study design

The study design of the present study is a population-based prospective cross-sectional study using the heavy metal data set of the 2010–2012 Korean National Health and Nutrition Examination Survey.

Study population

Since 1998, the Korea Center for Disease Control and Prevention (KCDC) has conducted the Korean National Health and Nutrition Examination Survey (KNHANES) to assess the health and nutritional status of South Koreans. The survey employs a rolling sampling design to select representative population samples of non-institutionalised civilians. The fifth survey (KNHANES V) was performed between 2010 and 2012. Details concerning the sampling frames of participants are described elsewhere.^{12 13} The heavy metal data set in KNHANES V was the source of the raw data in this study. Participants were excluded if their age was <19 years, data in the heavy metal data set were missing, they had diagnosed diabetes, rheumatoid arthritis, asthma, depression, thyroid disease, or they had a history of eye surgery. Written informed consent was obtained from all KNHANES participants by KCDC. Moreover, KCDC has released the data, which are anonymised. All data are publicly available.

Measurement of blood mercury concentrations

Blood mercury analysis was performed by the Neodin Medical Institute in Seoul; this laboratory has been certified by KCDC and the Ministry of Labor for the measurement of heavy metals. As part of the health examinations of each KNHANES participant, an experienced medical technician drew 3 mL of whole blood into an EDTA tube for trace element measurement. The mercury levels in the whole blood were measured using

gold amalgam sampling methods with a Mercury analyser (DMA-80; Milestone, Bergamo, Italy). For external quality assurance, we followed several protocols, namely, those of the German External Quality Assessment Scheme (G-EQUAS; Friedrich Alexander University), US Centers for Disease Control and Prevention, and Korean National Institute of Environmental Research. Monthly internal quality assurance and control programmes were performed with three different reference materials (Bio-rad, G-EQUAS 7B, and G-EQUAS 1A). The coefficients of variation were 0.78–3.22%, 1.54–6.08% and 0.84–3.52% for Bio-rad, G-EQUAS 7B and G-EQUAS 1A, respectively. The lower limit of detection for mercury in the blood was 0.05 µL.

Definition of dry eye symptoms

Since July 2008, the South Korean Ophthalmological Society has participated in KNHANES by performing ophthalmological interviews and examinations of the study participants. Participants were deemed to have dry eye symptoms if they responded positively to the questionnaire item that asked if the person had dry eye symptoms, namely, persistent dryness or sense of eye irritation. If the participant said that they only had these symptoms ‘sometimes’ or ‘occasionally’, they were deemed not to have dry eye.

Other variables

Education status was divided into four groups: ≤6, 7–9, 10–12 and ≥13 years of schooling. Total household income was divided into quartiles (Q), where Q1 and Q4 reflect the lowest and highest incomes of the population, respectively. Smoking status was categorised as non-smoking, ex-smoker or current smoker. Heavy alcohol use was defined as consuming seven or more drinks (men) or five or more (women) on a single occasion on five or more days in a month. Sleeping time was categorised as sleeping <6 h or ≥6 h. Perceived stress and those diagnosed with atopic disease were classified as ‘yes/no’. Cholesterol level was determined during fasting and categorised as <240 and ≥240 mg/dL. Anaemia was defined as follows: for males with a haemoglobin level <13 g/dL, pregnant females with a haemoglobin level <11 g/dL, and non-pregnant females with a haemoglobin level <12 g/dL.

Statistical analysis

Since KNHANES is a stratified multistage clustered probability design, the sampling weights, strata and clusters were included in all survey analyses. Mercury in the blood was expressed as geometric mean with geometric SE. Participants were deemed to have high blood mercury levels if their levels exceeded the median level of the cohort, which was 4.26 and 2.89 µg/L for men and women, respectively. To determine whether dry eye symptoms associated with the categorical variables described above, Rao-Scott χ^2 analysis was performed. To determine whether dry eye symptoms were associated

with continuous variables, survey regression analysis was performed in accordance with KNHANES statistical guidelines.¹³ To evaluate the association between dry eye symptoms and blood mercury level, survey multiple logistic regression analysis was applied after adjustment for age, gender, education, household income, smoking status, heavy alcohol drinking, sleep time, perceived stress status, blood cholesterol levels and atopy history (SAS Syntax: PROC SURVEYREG). To determine the potential bias, the sensitivity test was done with the optimal cut-off level is the median±10% (ie, between the 45th (3.99 and 2.72 µg/L for males and females, respectively) and 55th (4.26 and 2.89 µg/L for males and females, respectively) centiles) as the ORs and p values for the relationship between dry eye symptoms and these alternative cut-offs. All statistical analyses were performed using SAS V.9.4 (Statistical Analysis Software Institute, Cary, North Carolina, USA).

RESULTS

KNHANES V was performed in 2010–2012. In 2010, 2011 and 2012, 8958, 8518 and 8058 participants were surveyed, respectively. The KNHANES V heavy metal data set consisted of the 7162 participants whose blood concentrations of heavy metals were determined. Of these 7162 participants, 2355, 2395 and 2412 were surveyed in 2010, 2011 and 2012, respectively. A total of 2401 participants were excluded because their age was <19 years (n=1112), there were missing data in the heavy metal data set (n=18), they had been diagnosed with diabetes (n=134), rheumatic arthritis (n=90), asthma (n=110), depression (n=171), thyroid disease (n=152), or they had a history of eye surgery (n=614). The remaining 4761 participants were included in this study.

The general characteristics, socioeconomic status and blood mercury levels of the study participants are shown in table 1. The mean age of the study population was 39.6±0.2 years. Men were disproportionately represented (59.7%). More than 30% were current smokers and 21% were heavy alcohol users. Thirteen per cent of participants reported having persistent dry eye symptoms.

Men with and without dry eye had median blood mercury levels of 4.530 and 4.250 µg/L, respectively. In women, these values were 2.985 and 2.867 µg/L, respectively.

Table 2 compares the participants with and without dry eye symptoms in terms of various demographic and clinical variables. Women, non-smokers, non-heavy alcohol drinkers, participants who perceived that they were stressed, and participants with higher levels of blood mercury (defined as≥ median levels of the study population) were more likely to have dry eye symptoms than the comparators (all p<0.05).

Table 3 shows the ORs and 95% CIs for the association between the presence of dry eye symptoms and the demographic and clinical variables. Simple survey logistic regression analyses showed that the presence of dry eye

symptoms was associated with an age of 70 years or older, female gender, less education, not smoking, not being a heavy alcohol drinker, perceiving oneself to be stressed, and higher levels (ie, ≥ median values) of blood mercury (all p<0.05). In multiple survey logistic regression analysis, after adjusting for age, gender, education, total household income, smoking status, heavy alcohol use, sleep time, perceived stress, total cholesterol levels and atopy history, higher blood mercury levels (\geq median value) were significantly associated with the presence of dry eye symptoms (reference: <median value; OR, 1.324; 95% CI 1.059 to 1.655; p<0.05) (table 3).

Moreover, when the multivariate survey logistic regression analysis on the whole cohort was repeated using the median–10% range (3.99 and 2.72 µg/L for men and women, respectively) or median+10% range (4.61 and 3.10 µg/L for men and women, respectively) values as the cut-off to discriminate between lower and higher blood mercury levels, similar associations between the presence of dry eye symptoms and higher blood mercury levels were observed as when the median values were used (table 4).

DISCUSSION

To the best of our knowledge, this study on a large population-based nationally representative cohort in South Korea is the first study to investigate the association between dry eye syndrome and blood mercury levels. Our results show an association between dry eye symptoms and blood mercury levels after adjusting for the relevant risk factors.

Mercury is a toxic metallic element that can have a significant impact on human health, even when the exposure is relatively small.¹⁴ Mercury pollution led to public health disasters in Minamata, Japan and in Iraq.^{5 15 16} Although high levels of mercury exposure in the world have decreased, environmental exposure to mercury continues through seafood consumption, waste incineration, energy production and use of dental amalgams.^{17 18} In Korea, the main source of mercury is likely to be the frequent consumption of fish, including shellfish: the epidemiological studies of Kim and Lee showed that, in Korea, people with a higher intake of fish and shellfish also have higher blood mercury levels.^{19 20} Notably, a recent study on the health effects of mercury in American adults showed that the participants had a median blood mercury level of about 1.0 µg/L, which is much lower than that in the Korean population.²¹ Since Koreans differ from Americans in their dietary habits, this observation suggests that the high blood mercury levels of Koreans reflects their diet.

Several hypothetical mechanisms may explain the association we observed between high blood mercury levels and dry eye symptoms. The first is that blood mercury accumulates in the eye and may alter the conjunctival mucus and induce conjunctival inflammation.⁵ The gel-like tear layer over the ocular surface is composed of

Table 1 General characteristics, socioeconomic status and blood mercury levels of the study cohort

Variables	No.	Weighted No.	Weighted mean	Weighted %	SE
Age (years)			39.6		0.2
<30	1015	3 844 732		30.6	0.8
30–39	999	2 717 085		21.6	0.6
40–49	1018	2 899 013		23.0	0.5
50–59	938	2 060 342		16.4	0.5
60–69	696	951 896		7.6	0.3
≥70	96	110 698		0.9	0.1
Gender					
Men	2498	7 512 566		59.7	0.6
Women	2263	5 071 200		40.3	0.6
Education status (years)*					
<6	639	1 156 795		9.5	0.5
6–9	453	1 096 297		8.9	0.5
10–12	1849	5 533 191		45.3	0.9
>12	1696	4 432 718		36.3	0.9
Household income†					
1Q	569	1 433 998		11.6	0.6
2Q	1282	3 483 839		28.1	1.0
3Q	1419	3 852 908		31.0	0.9
4Q	1431	3 636 772		29.3	1.0
Smoking status					
Non-smoker	2566	6 233 073		49.5	0.8
Ex-smoker	954	2 464 812		19.6	0.7
Current smoker	1241	3 885 881		30.9	0.8
Heavy alcohol drinking‡					
No	3818	9 731 102		79.0	0.7
Yes	855	2 593 067		21.0	0.7
Sleep time (h)					
≥6	4131	10 976 795		87.2	0.6
<6	630	1 606 971		12.8	0.6
Perceived stress status§					
No	3491	9 076 745		74.2	0.8
Yes	1154	3 160 474		25.8	0.8
Cholesterol (mg/dL)¶			186.5		0.7
<240	3963	10 666 938		89.6	0.5
≥240	578	1 236 374		10.4	0.5
Atopy history					
No	4624	12 123 239		96.3	0.4
Yes	137	460 527		3.7	0.4
Anaemia					
No	4443	11 843 579		94.1	0.4
Yes	317	738 388		5.9	0.4
Dry eye (symptoms)					
No	4103	10 952 964		87.0	0.7
Yes	658	1 630 802		13.0	0.7
Blood mercury levels			3.7		0.0
<Median	2379	6 740 444		53.6	1.0
≥Median	2382	5 843 322		46.4	1.0

Anaemia was defined as follows; for males with a haemoglobin level <13 g/dL, pregnant females with a haemoglobin level <11 g/dL, and non-pregnant females with a haemoglobin level <12 g/dL.

The median cut-off levels that discriminate between subjects with 'low' and 'high' blood mercury levels were 4.26 and 2.89 µg/L for males and females, respectively.

*124 missing values.

†60 missing values.

‡88 missing values.

§116 missing values.

¶220 missing values.

soluble mucus (which is secreted by conjunctival goblet cells) mixed with fluid and proteins secreted by the lacrimal glands.^{22 23} This hydrophilic gel moves over the

membrane mucins (glycocalyx) on the superficial corneal and conjunctival epithelial cells and serves as a medium to refresh the tear components and clear

Table 2 Comparison of the participants with and without dry eye symptoms in terms of general characteristics, socioeconomic status and blood mercury levels

Variable	Dry eye symptom			Yes			p Value	
	No	Weighted Number	W %* (mean)	SE†	Weighted Number	W %* (mean)	SE	
Age (years)			(39.6)	(0.2)		(39.7)	(0.6)	0.861
<30	3 311 990	30.2	0.8	532 742	32.7	2.3	0.242	
30–39	2 408 526	22.0	0.6	308 558	18.9	1.8		
40–49	2 535 770	23.2	0.6	363 243	22.3	2.1		
50–59	1 799 287	16.4	0.5	261 054	16.0	1.7		
60–69	811 313	7.4	0.3	140 583	8.6	1.0		
≥70	86 077	0.8	0.1	24 621	1.5	0.4		
Gender								
Men	6 853 988	62.6	0.7	658 578	40.4	2.4	<0.001	
Women	4 098 976	37.4	0.7	972 225	39.6	2.4		
Education status (years)†								
<6	949 924	8.9	0.5	206 871	12.9	1.6	0.062	
6–9	969 900	9.2	0.5	126 397	7.9	1.3		
10–12	4 844 638	45.6	1.0	688 553	43.0	2.6		
>12	3 853 297	36.3	1.0	579 421	36.2	2.4		
Household income‡								
1Q	1 225 036	11.4	0.6	208 962	13.0	1.8	0.516	
2Q	3 068 394	28.4	1.0	415 444	25.8	2.2		
3Q	3 368 980	31.2	1.0	483 928	30.1	2.3		
4Q	3 136 600	29.0	1.0	500 172	31.1	2.5		
Smoking status								
Non-smoker	5 249 125	47.9	0.9	983 948	60.3	2.2	<0.001	
Ex-smoker	2 181 991	19.9	0.7	282 821	17.3	1.8		
Current smoker	3 521 847	32.2	0.9	364 033	22.3	2.1		
Heavy alcohol drinking§								
No	8 344 969	77.9	0.8	1 386 133	86.0	1.7	<0.001	
Yes	2 366 814	22.1	0.8	226 253	14.0	1.7		
Sleep time (h)								
≥6	9 587 631	87.5	0.7	1 389 164	85.2	1.7	0.179	
<6	1 365 333	12.5	0.7	241 638	14.8	1.7		
Perceived stress status¶								
No	7 998 429	75.2	0.9	1 078 316	67.6	2.3	0.001	
Yes	2 642 978	24.8	0.9	517 496	32.4	2.3		
Cholesterol** (mg/dL)		(186.4)	(0.7)		(187.4)	(1.9)	0.607	
<240	9 274 285	89.7	0.6	1 392 653	89.7	1.4	0.517	
≥240	1 060 494	10.3	0.6	175 880	10.3	1.4		
Anaemia							0.823	
No	10 322 544	94.3	0.4	1 521 035	93.3	1.1		
Yes	628 621	5.7	0.4	109 767	6.7	1.1		
Atopy history								
No	10 552 820	96.3	0.4	1 570 419	96.3	1.0	0.963	
Yes	400 144	3.7	0.4	60 383	3.7	1.0		
Blood mercury level								
<Median	5 953 407	54.4	1.1	787 037	48.3	2.5	0.021	
≥Median	4 999 557	45.7	1.1	843 765	51.7	2.5		

Anaemia was defined as follows; for males with a haemoglobin level <13 g/dL, pregnant females with a haemoglobin level <11 g/dL, and non-pregnant females with a haemoglobin level <12 g/dL.

The median cut-off levels that discriminated between participants with 'low' and 'high' blood mercury levels were 4.26 and 2.89 µg/L for males and females, respectively.

The p values were obtained by comparing the participants with and without dry eye symptoms using Rao-Scott χ^2 analysis.

*Weighted per cent.

†124 missing values.

‡60 missing values.

§88 missing values.

¶116 missing values.

**220 missing values.

Table 3 Logistic regression analysis of the association between dry eye symptom prevalence and demographic and clinical variables before and after adjustment for confounding factors

	Crude		Model 1	
	OR	95% CI	OR	95% CI
Age (years) (<i>continuous</i>)	1.001	(0.993 to 1.008)	0.964	(0.874 to 1.064)
<30	reference		reference	
30–39	0.831	(0.617 to 1.119)	0.798	(0.589 to 1.079)
40–49	0.876	(0.654 to 1.173)	0.809	(0.588 to 1.113)
50–59	0.904	(0.649 to 1.260)	0.811	(0.547 to 1.201)
60–69	1.092	(0.799 to 1.493)	0.923	(0.608 to 1.402)
≥70	2.032	(1.155 to 3.576)	1.570	(0.767 to 3.210)
Gender				
Men	reference		reference	
Women	2.502	(2.005 to 3.124)	2.378	(1.676 to 3.372)
Education status (years)				
<6	reference		reference	
6–9	0.564	(0.361 to 0.881)	0.720	(0.415 to 1.169)
10–12	0.645	(0.463 to 0.900)	0.824	(0.538 to 1.263)
>12	0.629	(0.489 to 0.942)	0.862	(0.554 to 1.340)
Household income				
1Q	reference		reference	
2Q	0.695	(0.483 to 1.002)	0.800	(0.530 to 1.207)
3Q	0.733	(0.507 to 1.060)	0.879	(0.577 to 1.337)
4Q	0.841	(0.579 to 1.223)	0.956	(0.625 to 1.463)
Smoking status				
Non-smoker	reference		reference	
Ex-smoker	0.698	(0.532 to 0.915)	1.124	(0.797 to 1.585)
Current smoker	0.527	(0.400 to 0.694)	0.900	(0.622 to 1.304)
Heavy alcohol drinking				
No	reference		reference	
Yes	0.564	(0.414 to 0.768)	0.945	(0.643 to 1.391)
Sleep time (h)				
≥6	reference		reference	
<6	1.338	(0.978 to 1.831)	1.141	(0.815 to 1.597)
Perceived stress status				
No	reference		reference	
Yes	1.357	(1.071 to 1.719)	1.330	(1.046 to 1.692)
Cholesterol (mg/dL)				
<240	reference		reference	
≥240	1.129	(0.836 to 1.524)	1.055	(0.768 to 1.450)
Atopy history				
No	reference		reference	
Yes	0.848	(0.457 to 1.574)	0.777	(0.415 to 1.453)
Anaemia				
No	reference		reference	
Yes	1.215	(0.830 to 1.778)	0.803	(0.430 to 1.499)
Blood mercury levels				
<Median	reference		reference	
≥Median	1.303	(1.056 to 1.607)	1.324	(1.059 to 1.655)

Italics indicate that the variable was inserted in the survey logistic regression as a continuous variable.

The data from Model 1 are after adjusting for age, gender, education, total household income, smoking status, heavy alcohol status, sleep time, perceived stress status, cholesterol levels and atopy history.

Anaemia was defined as follows; for males with a haemoglobin level <13 g/dL, pregnant females with a haemoglobin level <11 g/dL, and non-pregnant females with a haemoglobin level <12 g/dL.

The median cut-off levels that discriminated between participants with 'low' and 'high' blood mercury levels were 4.26 and 2.89 µg/L for males and females, respectively.

debris. In dry eye syndrome, the mucins are altered²⁴ and inflammatory/immune cells on the ocular surface (particularly CD4+ and CD17+ T cells) are activated or recruited to the conjunctival epithelium.^{25 26} The

inflammation on ocular surface promotes the corneal epithelial disease in dry eye syndrome and evokes dry eye symptoms such as persistent dryness or sense of eye irritation. The possibility that mercury induces dry eye

Table 4 Multiple survey logistic regression analysis of the association between dry eye symptom prevalence and blood mercury levels using median±10% range (45th, 50th and 55th percentile) mercury values as the cut-off

Cut-off mercury level	Dry eye symptom	
	OR	95% CI
Median—10% range	1.321	(1.055 to 1.653)
Median	1.324	(1.059 to 1.655)
Median+10% range	1.329	(1.061 to 1.664)

The median—10% range cut-off levels that discriminated between participants with 'low' and 'high' blood mercury levels were 3.99 and 2.72 µg/L for males and females, respectively.

The median cut-off levels that discriminated between participants with 'low' and 'high' blood mercury levels were 4.26 and 2.89 µg/L for males and females, respectively.

The median+10% range cut-off levels that discriminated between participants with 'low' and 'high' blood mercury levels were 4.61 and 3.10 µg/L for males and females, respectively.

syndrome by promoting ocular surface inflammation is supported by a study on 12 rabbits that showed that metallic mercury in the conjunctiva increases the numbers of conjunctival lymphocytes and macrophages; it also associates with increased amounts of altered mucus.¹⁰ A previous report demonstrated that the subcutaneous injection of mercury can develop an autoimmune syndrome with infiltration of mononuclear cells into the oral mucosa, salivary and lacrimal glands.²⁷ We speculate that mercury induced autoimmunity in the lacrimal glands might reduce tear production and induce conjunctival inflammation, resulting in dry eye syndrome.

The second possible mechanism that explains the relationship between mercury and dry eye syndrome is that mercury depletes the conjunctivae of antioxidant proteins such as metallothioneins. These cysteine-rich low-molecular-weight proteins help to prevent tissue inflammation.²⁸ They are thought to bind heavy metals such as mercury in the blood, thereby removing heavy metals that can induce oxidative stress.^{5 28 29} We speculate that a persistent, albeit low level, exposure of the conjunctiva to mercury, such as in our Korean population, may reduce the availability of free metallothioneins in the lacrimal glands and conjunctiva. This, in turn, may increase the susceptibility of the ocular surface to inflammation and dry eye symptoms. Experimental studies that test these potential mechanisms by which mercury may promote dry eye syndrome are warranted.

There seems to be an association between smoking status and dry eye symptoms.^{30 31} However, in this study, smoking status is not statistically significant. The gender difference in smoking status may be the possible reason why the discrepancy remains. In tables 2 and 3, females were likely to have a higher association with dry eye symptoms. According to previous research on smoking status by gender,³² the smoking rate in Korean females was much lower than that in Korean males. We speculate that different smoking status by gender in this population might cause these results.

This study has a few limitations. First, its cross-sectional design means that the association observed in this study cannot be interpreted as a cause-and-effect relationship. A large-scale population-based longitudinal study that can assess causality is warranted. Second, we did not adjust for other factors that could confound the relationship between mercury and dry eye symptoms, including the use of contact lenses or systemic drugs (including traditional oriental medicines). Third, we did not examine the effect of occupational exposure because KNHANES does not ask about occupation. Fourth, we used the median blood mercury concentration of our population as the cut-off level to distinguish participants with 'low' and 'high' blood mercury levels. Whether this is the best approach or not may be debatable. However, the sensitivity tests shown in table 4 indicated that the optimal cut-off level is the median±10% (ie, between the 45th and 55th centiles) as the ORs and p values for the relationship between dry eye symptoms and these alternative cut-offs were similar to those when the 50th centile was employed. Fifth, we could not analyse the relationship between physician-diagnosed dry eye and blood mercury levels. However, physician-diagnosed dry eye is not a good index for health outcomes for several reasons. First, mercury has a relatively short half-life in the blood due to its rapid distribution to other tissues while its half-life in the body is about 2 months.^{5 33} We hypothesised, therefore, that questionnaire-determined dry eye symptoms would mirror recent exposure to mercury better than physician-diagnosed dry eye syndrome, which could reflect earlier exposure to mercury that has long ago left the circulation a long time ago. Second, the KNHANES design did not include a direct physical examination to define dry eye, namely using a slit-lamp. This is because the survey was large and its main purpose was to evaluate the prevalence of and risk factors for dry eye. If dry eye syndrome would be diagnosed according to standard guidelines, the association between mercury and dry eye symptoms observed in this study might be altered. To reduce this information bias, further evaluation with an objective tool for diagnosing dry eye syndrome should be incorporated into a nationwide survey in Korea.

This study also had several strengths. First, it was a large-scale study that was based on a nationally representative Korean population. Second, potential confounders reported in the literature were excluded or the analyses were adjusted for them.

CONCLUSIONS

In conclusion, recent environmental exposure to mercury was associated with the presence of dry eye symptoms. To elucidate a causal relationship between mercury exposure and dry eye syndrome, further longitudinal and experimental studies are needed. Our observations also suggest that to reduce the prevalence of dry eye syndrome, public health measures that control the dietary and polluted air sources of mercury are needed.



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Patient consent Obtained.

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REFERENCES

- Chia EM, Mitchell P, Rochtchina E, et al. Prevalence and associations of dry eye syndrome in an older population: the Blue Mountains Eye Study. *Clin Experiment Ophthalmol* 2003;31: 229–32.
- McCarty CA, Bansal AK, Livingston PM, et al. The epidemiology of dry eye in Melbourne, Australia. *Ophthalmology* 1998;105:1114–19.
- The committee of the International Dry Eye WorkShop. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf* 2007;5:75–92.
- The committee of the International Dry Eye WorkShop. The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf* 2007;5:93–107.
- Bernhoff RA. Mercury toxicity and treatment: a review of the literature. *J Environ Public Health* 2012;2012:460508.
- Warfvinge K, Bruun A. Mercury distribution in the squirrel monkey retina after in Utero exposure to mercury vapor. *Environ Res* 2000;83:102–9.
- Bridges CC, Battle JR, Zalups RK. Transport of thiol-conjugates of inorganic mercury in human retinal pigment epithelial cells. *Toxicol Appl Pharmacol* 2007;221:251–60.
- Tanan CL, Ventura DF, de Souza JM, et al. Effects of mercury intoxication on the response of horizontal cells of the retina of thrairai fish (*Hoplias malabaricus*). *Braz J Med Biol Res* 2006;39:987–95.
- Beuter A, Edwards R. Effect of chronic exposure to methylmercury on eye movements in Cree subjects. *Int Arch Occup Environ Health* 2004;77:97–107.
- Kulczycka B. Resorption of metallic mercury by the conjunctiva. *Nature* 1965;206:943.
- Stevenson W, Chauhan SK, Dana R. Dry eye disease: an immune-mediated ocular surface disorder. *Arch Ophthalmol* 2012;130:90–100.
- Jeong H, Hong S, Heo Y, et al. Vitamin D status and associated occupational factors in Korean wage workers: data from the 5th Korea national health and nutrition examination survey (KNHANES 2010–2012). *Ann Occup Environ Med* 2014;26:28.
- Korea Center for Disease Control and Prevention. Korea National Health and Nutrition Examination Survey V. 2010–2012. <http://knhanes.cdc.go.kr/> (accessed 1 Dec 2014).
- Karagas MR, Choi AL, Oken E, et al. Evidence on the human health effects of low-level methylmercury exposure. *Environ Health Perspect* 2012;120:799–806.
- Bakir F, Damluji SF, Amin-Zaki L, et al. Methylmercury poisoning in Iraq. *Science* 1973;181:230–41.
- Skerfving SB, Copplestone JF. Poisoning caused by the consumption of organomercury-dressed seed in Iraq. *Bull World Health Organ* 1976;54:101–12.
- Baughman TA. Elemental mercury spills. *Environ Health Perspect* 2006;114:147–52.
- Gabal MS, Raslan OA. Ocular disorders among workers exposed to mercury. *J Egypt Public Health Assoc* 1995;70:1–14.
- Kim NS, Lee BK. Blood total mercury and fish consumption in the Korean general population in KNHANES III, 2005. *Sci Total Environ* 2010;408:4841–7.
- Korea Ministry of Food and Drug Safety. Library of Toxic Substances. 2000. http://foodnara.go.kr/foodnara/board-list.do?boardId=series&mid=S07_05_03 (accessed 27 Aug 2014).
- Ng TH, Mossey JM, Lee BK. Total blood mercury levels and depression among adults in the United States: National Health and Nutrition Examination Survey 2005–2008. *PLoS ONE* 2013;8:e79339.
- Dursun D, Monroy D, Knighton R, et al. The effects of experimental tear film removal on corneal surface regularity and barrier function. *Ophthalmology* 2000;107:1754–60.
- Nichols BA, Chiappino ML, Dawson CR. Demonstration of the mucous layer of the tear film by electron microscopy. *Invest Ophthalmol Vis Sci* 1985;26:464–73.
- Spurr-Michaud S, Argueso P, Gipson I. Assay of mucins in human tear fluid. *Exp Eye Res* 2007;84:939–50.
- De Paiva CS, Chotikavanich S, Pangellian SB, et al. IL-17 disrupts corneal barrier following desiccating stress. *Mucosal Immunol* 2009;2:243–53.
- De Paiva CS, Villarreal AL, Corrales RM, et al. Dry eye-induced conjunctival epithelial squamous metaplasia is modulated by interferon-gamma. *Invest Ophthalmol Vis Sci* 2007;48:2553–60.
- Warfvinge G, Warfvinge K, Larsson A. Histochemical visualization of mercury in the oral mucosa, salivary and lacrimal glands of BN rats with HgCl₂-induced autoimmunity. *Exp Toxicol Pathol* 1994;46:329–34.
- Kumari MV, Hiramatsu M, Ebadi M. Free radical scavenging actions of metallothionein isoforms I and II. *Free Radic Res* 1998;29:93–101.
- Sinaie M, Bastami KD, Ghorbanpour M, et al. Metallothionein biosynthesis as a detoxification mechanism in mercury exposure in fish, spotted scat (*Scatophagus argus*). *Fish Physiol Biochem* 2010;36:1235–42.
- Moss SE, Klein R, Klein BE. Prevalence of and risk factors for dry eye syndrome. *Arch Ophthalmol* 2000;118:1264–8.
- Uchino M, Nishiwaki Y, Michikawa T, et al. Prevalence and risk factors of dry eye disease in Japan: Koumi study. *Ophthalmology* 2011;118:2361–7.
- Jung-Choi KH, Khang YH, Cho HJ. Hidden female smokers in Asia: a comparison of self-reported with cotinine-verified smoking prevalence rates in representative national data from an Asian population. *Tob Control* 2012;21:536–42.
- Mela M, Cambier S, Mesmer-Dudons N, et al. Methylmercury localization in *Danio rerio* retina after trophic and subchronic exposure: a basis for neurotoxicology. *Neurotoxicology* 2010;31:448–53.