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Relationship between Blood Mercury Level and Risk of Cardiovascular Diseases: Results from the Fourth Korea National Health and Nutrition Examination Survey (KNHANES IV) 2008-2009

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ABSTRACT: Limited epidemiologic data is available regarding the cardiovascular effects of mercury exposure. The purpose of this study was to determine the relationship between mercury exposure from fish consumption and cardiovascular disease in a nationally representative sample of Korean adults using the Fourth Korea National Health and Nutrition Examination Survey (KNHANES IV 2008～2009). Survey logistic regression models accounting for the complex sampling were used to estimate the odds ratios (OR) adjusted for fish consumption frequency, age, education, individual annual income, household annual income, body mass index (BMI), waist circumference (WC), alcohol consumption status, and smoking status. The mean blood mercury level in the population was 5.44 μg/L. Trends toward increased blood mercury levels were seen for increased education level (P=0.0011), BMI (P<0.0001), WC (P<0.0001), and fish (i.e., anchovy) consumption frequency (P=0.0007). The unadjusted OR for hypertension in the highest blood mercury quartile was 1.450 [95% confidential interval (CI): 1.106～1.901] times higher than that of the lowest quartile. The fish consumption-adjusted OR for hypertension in the highest blood mercury quartile was 1.550 (95% CI: 1.131～2.123) times higher than that of the lowest quartile, and the OR for myocardial infarction or angina in the highest blood mercury quartile was 3.334 (95% CI: 1.338～8.308) times higher than that of the lowest quartile. No associations were observed between blood mercury levels and stroke. These findings suggest that mercury in the blood may be associated with an increased risk of hypertension and myocardial infarction or angina in the general Korean population.

Keywords: blood mercury levels, cardiovascular disease, KNHANES, fish consumption

INTRODUCTION

Mercury is a dangerous and highly reactive heavy metal with no known physiologic activity (1,2). Exposure to mercury may predispose people to atherosclerotic disease by promoting the production of free radicals or by inactivation of several antioxidant mechanisms through binding to thiol-containing molecules or selenium (2). Methylmercury, in particular, can promote lipid peroxidation (3). Recently, mercury has been reported to increase free radical production, oxidative stress, thrombosis, and vascular inflammation through the increase of tumor necrosis factor α and interleukin (4).

The risk of cardiovascular disease (CVD) is inversely related to the consumption of omega-3 fatty acids, eicosapentaenoic acid (EPA), and docosa hexaenoic acid (DHA) in fish (5). Fish consumption decreases low-density lipoprotein and total cholesterol levels and increases high-density lipoprotein cholesterol levels in blood (6). Epidemiological studies suggest that people who consume omega-3 fatty acids from fish and plants have a lower risk of coronary heart disease (CHD) (7). In patients with CHD, omega-3 fatty acid supplements reduced CVD events and slowed the progression of atherosclerosis (7). The American Heart Association (AHA) recommends that patients with CHD take 1 g/day of EPA and DHA from oily fish or omega-3 fatty acid supplements (7). The AHA also indicates that EPA and DHA supplements may be useful in patients with hypertriglyceridemia (7). Compared with statin consumption, EPA consumption reduced the risk of major coronary events in patients with hypercholesterolemia (8). However,

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despite their many benefits, some types of fish also contain significant levels of methylmercury, polychlorinated biphenyls, dioxins, and other environmental pollutants (9).

Most people are aware of the benefits of fish consumption, especially for children and women of child-bearing age, but there is a concern that consuming a large amount of fish may result in mercury poisoning (10). Children are particularly vulnerable to mercury exposure, which may lead to severe damage to the developing central nervous system, pulmonary injury, and nephritic injury (11). Prenatal mercury exposure is associated with reduced IQ and decreased performance in tests assessing memory, attention, language, and spatial cognition in children (12). Mercury is neurotoxic for humans and causes damage to the central nervous system and renal system (2,13). Methylmercury combines with the hemoglobin component of red blood cells in the portal vein, allowing it to accumulate in the central nervous system and cause neural disorders (14). Therefore, increased blood mercury levels may be a major health concern associated with fish consumption.

Although fish consumption decreases the risks of CVD, it is also a major cause of mercury exposure, which can increase the risks of CVD complications such as hypertension, stroke, and myocardial infarction or angina (4). Mercury accumulation in the human body is associated with accelerated carotid atherosclerosis progression (3). However, some studies have indicated that there is no association between mercury exposure and CVD. Yoshizawa indicated that blood mercury level was associated with fish consumption, but mercury exposure and CHD were not significantly correlated (15). Therefore, we investigated the relationship between mercury exposure, fish consumption, and CVD in a representative sample of Korean adults using the Fourth Korea National Health and Nutrition Examination Survey (KNHANES IV) from 2008 and 2009.

SUBJECTS AND METHODS

Subjects

This study was based on data sets obtained from the KNHANES IV 2007－2009, which was conducted by the Korea Centers for Disease Control and Prevention and the Korea Ministry of Health and Welfare. The KNHANES IV was a complex, stratified, multistage, probability-cluster survey of a representative sample of the noninstitutionalized civilian population of Korea. The survey employed stratified multistage probability sampling units based on geographical area, gender, and age, which were determined based on the household registries of the 2005 National Census Registry. For the KNHANES IV 2007－2009, the number of participants was 31,705 and the average participation rate was 74.8%. The survey consisted of the Health and Behavior Interview, Health Examination, and Nutrition Survey (16). As heavy metal measurements were not conducted in 2007, only the KNHANES 2008 and 2009 data sets were analyzed in the current study.

Within the KNHANES 2008 and the KNHANES 2009, ten subjects were randomly selected, according to gender and age group (20～29, 30～39, 40～49, 50～59, and 60 years and older), from each of 200 primary sampling units, yielding a total of 2,000 subjects in each year (i.e., a total of 4,000 subjects). The blood of these 4,000 subjects was tested for heavy metals. This study examined the 3,800 representative participants who completed the Health and Behavior Interview, Health Examination, and Nutrition Survey and whose blood was analyzed for heavy metals.

Blood mercury determination

We obtained the heavy metal data sets as a part of the Health Examination from the KNHANES IV (16). The heavy metal analyses were carried out by NEODIN Medical Institute (Seoul, Korea), a laboratory certified by the Korean Ministry of Health and Welfare (Sejong, Korea). To assess the heavy metal concentration in whole blood, 6 mL blood samples were drawn into EDTA tubes and mixed with the anticoagulant for 10 min using a roller mixer to prevent clotting. The blood mercury level was measured by a gold amalgamation method with DMA-80 equipment (Milestone, Sorisole, Bergamo, Italy) (16). Whole blood metals control (Bio-Rad, Hercules, CA, USA) and blood metals control [German External Quality Assessment Scheme (G-EQUAS), Erlangen, Germany] were used as internal quality assurance and control samples, respectively. The coefficients of variation were 0.85～1.94% for the whole blood metals and 1.54～4.57% for the blood metals control. The external quality assurance and control program of the NEODIN Medical Institute (Seoul, Korea) was approved by the G-EQUAS. The detection limit for blood mercury was 0.05 μg/L.

General characteristics, fish consumption, and cardiovascular diseases

Socio-demographic factors (i.e., age, gender, education, individual annual income, household annual income, alcohol consumption status, and smoking status) were collected using a self-reported questionnaire from the Health and Behavior Interview of the KNHANES IV. In this study, the subjects were divided into five age groups: 20～29, 30～39, 40～49, 50～59, and ≥60 years old. Education levels were divided into three groups: less than high school diploma, high school diploma, and some college education. Individual annual income and household annual income were categorized into four groups: low, low to medium, medium to high, and high. Alcohol consumption was divided into three categories: none, moderate, and heavy. Smoking status was categorized as never, former, and current.

Anthropometric measurements including waist circumference (WC) and body mass index (BMI) were conducted during the Health Examination Survey. BMI was divided into <18.5, 18.5~22.9, 23~24.9, and ≥25 kg/m^2. WC was categorized into <80 cm or ≥80 cm for females and <90 cm or ≥90 cm for males. The CVD items that were focused on in this study were hypertension, stroke, and myocardial infarction or angina (12). Disease status was collected from the self-reported questionnaire of the Health and Behavior Interview, with participants answering 'Yes' or 'No' as to whether they had CVD.

The fish consumption frequency was reported in the Nutrition Survey of the KNHANES IV. Subjects completed a simple food frequency questionnaire that only asked about consumption frequency, without concern for the consumption amount. The questionnaire listed the seven fish and shellfish that are consumed most frequently in Korea: mackerel, tuna, yellow corvina, pollack, anchovy, seafood paste, squid, clam, and pickled seafood. On the questionnaire, fish consumption frequency was categorized as follows: rare, 6~11 times/year, 1 time/month, 2~3 times/month, 1 time/week, 2~3 times/week, 4~6 times/week, 1 time/day, 2 times/day, and 3 times/day (16). However, because the number of respondents who indicated that they consumed fish "6~11 times/year" or "over 1 time/day" was limited, the categories on the questionnaire were combined into the following categories for the present study: rare, ≤1 time/month, 2~4 times/month, and ≥1 time/week (12).

Statistical analysis

The statistical analysis was performed using SAS version 9.2.3 (SAS Institute Inc., Cary, NC, USA). The KNHANES IV had a complex sampling design, and thus the data in this study were analyzed using the SAS procedure (16). For all analyses, survey sample weights were used to produce estimates that were representative of the non-institutionalized, civilian Korean population. Subjects were separated by gender. Histogram and Q-Q plots were used to determine whether the variables were normally distributed. A survey *t*-test as used to test the difference in blood mercury levels between genders. Within each gender, the Rao-Scott chi square test was used to confirm differences in blood mercury levels by age, education level, individual annual income, household annual income, BMI, WC, alcohol consumption status, and smoking status. Cochran-Armitage trend tests were performed to determine the trend between blood mercury levels and each variable.

Logistic regression models were used to calculate an odds ratio (OR) for the prevalence of CVD by blood mercury quartile. The results are presented as the OR and corresponding 95% confidence interval (CI). An OR with a 95% CI that did not include the value of 1.0 in its range was considered statistically significant. The blood mercury concentration of the lowest blood mercury quartile (Q1) was ≤3 μg/L, the second quartile (Q2) was 3.01~4.31 μg/L, the third (Q3) was 4.32~6.33 μg/L, and the highest blood mercury level quartile, Q4, was >6.33 μg/L. This study examined the unadjusted ORs, the fish consumption frequency-adjusted ORs, and the fish consumption frequency and general characteristics (i.e., age, education level, individual annual income, household annual income, BMI, WC, alcohol consumption status, and smoking status)-adjusted ORs for hypertension, stroke, and myocardial infarction or angina.

RESULTS

General characteristics of study population

The study population consisted of 3,800 subjects (males=1,895 and females=1,905). The average age of the participants was 41.60±0.22 years, and the mean BMI and WC were 23.47±0.07 kg/m^2 and 80.68±0.34 cm, respectively. The mean±SE for blood mercury levels grouped by general characteristics and gender are listed in Table 1. The blood mercury levels of individuals less than a high school diploma were higher than the blood mercury levels of individuals with a high school diploma and individuals with some college education (P=0.0011). Blood mercury levels significantly increased with BMI (P<0.0001) and WC (P<0.0001). The blood mercury levels of males with a WC of ≥90 cm and females with a WC of ≥80 cm were 7.92 μg/L and 4.58 μg/L, respectively, which is higher than the blood mercury level of males with a WC of <90 cm (blood mercury level: 5.86 μg/L) and females with a WC of <80 cm (blood mercury level: 3.98 μg/L). There were no significant trends between blood mercury level and age, individual annual income, household annual income, alcohol consumption status, or smoking status. The blood mercury levels had significant differences between male and female in education level (P<0.0001), household annual income (P<0.0001), BMI (P<0.0001), waist circumference (P<0.0001), alcohol consumption status (P<0.0001), and smoking status (P<0.0001).

Blood mercury concentrations by fish consumption

Table 2 shows blood mercury levels separated by gender and according to consumption frequency of the following types of marine life: mackerel, tuna, yellow fish, pol-

Table 1. Blood mercury levels (mg/L) by general subject characteristics, KNHANES IV 2008−2009

Variables	Total (n=3,800)			Males (n=1,895)			Females (n=1,905)			P value[3]
	N	% wt[1]	Mercury (SE)[2]	N	% wt	Mercury (SE)	N	% wt	Mercury (SE)	
Overall	3,800		5.44 (0.09)	1,895		6.37 (0.13)	1,905		4.22 (0.07)	<0.0001
Age (years)										
20~29	763	16.26	4.43 (0.12)	382	15.42	4.92 (0.17)	381	17.50	3.73 (0.10)	
30~39	780	19.92	5.31 (0.12)	394	20.53	6.28 (0.18)	386	18.00	3.94 (0.10)	
40~49	753	22.09	6.32 (0.22)	379	22.62	7.44 (0.33)	374	21.30	4.80 (0.18)	
50~59	745	22.77	6.37 (0.22)	369	23.45	7.73 (0.36)	376	21.75	4.64 (0.14)	
≥60	759	18.99	5.12 (0.16)	371	17.00	6.06 (0.25)	388	20.47	4.17 (0.16)	
P value for trend			0.9920			0.8056			0.9987	0.2768
Education level										
Less than high school diploma	1,225	32.22	5.53 (0.19)	497	25.46	6.67 (0.34)	728	40.82	4.57 (0.15)	
High school diploma	1,127	28.87	5.29 (0.12)	546	27.51	6.14 (0.19)	581	30.90	4.29 (0.09)	
Some college education	1,448	38.92	5.50 (0.12)	852	46.04	6.38 (0.17)	596	28.30	3.86 (0.09)	
P value for trend			0.0011			0.0216			0.0145	<0.0001
Individual annual income										
Low	970	22.63	4.81 (0.12)	481	21.14	5.37 (0.19)	489	24.86	4.06 (0.12)	
Low to medium	945	24.32	5.34 (0.15)	466	23.90	6.17 (0.22)	479	24.95	4.27 (0.15)	
Medium to high	947	25.26	5.44 (0.19)	448	24.63	6.54 (0.31)	499	26.19	4.15 (0.12)	
High	938	27.81	6.18 (0.18)	500	30.34	7.32 (0.27)	438	24.02	4.43 (0.12)	
P value for trend			0.4928			0.9773			0.0524	0.0051
Household annual income										
Low	670	15.51	4.77 (0.19)	303	12.89	5.29 (0.31)	367	19.43	4.16 (0.13)	
Low to medium	973	23.53	5.01 (0.11)	471	22.47	5.70 (0.16)	502	25.12	4.16 (0.13)	
Medium to high	1,077	28.78	5.37 (0.18)	538	29.22	6.31 (0.27)	539	28.11	4.13 (0.11)	
High	1,080	32.20	6.20 (0.17)	583	35.44	7.37 (0.26)	497	27.36	4.42 (0.11)	
P value for trend			0.3086			0.9864			0.0015	<0.0001
BMI (kg/m^2)										
<18.5	192	3.34	3.53 (1.79)	72	2.33	3.71 (0.25)	120	4.84	3.39 (0.20)	
18.5~22.9	1,455	33.88	4.79 (0.10)	621	27.90	5.45 (0.17)	834	42.82	4.16 (0.10)	
23~24.9	950	26.27	5.53 (0.21)	537	29.15	6.30 (0.29)	413	21.97	4.18 (0.12)	
≥25	1,202	36.53	6.49 (0.17)	664	40.64	7.57 (0.25)	538	30.38	4.55 (0.14)	
P value for trend			<0.0001			<0.0001			0.038	<0.0001
Waist circumference (cm)										
<80 (female) or <90 (male)	2,497	62.21	5.15 (0.08)	1,404	68.13	5.86 (0.12)	1,093	53.37	3.98 (0.08)	
≥80 (female) or ≥90 (male)	1,302	37.80	6.10 (0.19)	490	31.87	7.92 (0.36)	812	46.64	4.58 (0.12)	
P value for trend			<0.0001			0.1586			0.3663	<0.0001
Alcohol consumption status										
None	1,275	29.68	4.74 (0.11)	501	23.63	5.71 (0.23)	774	33.73	3.97 (0.08)	
Moderate	1,734	46.05	5.42 (0.12)	885	46.98	6.24 (0.18)	849	44.66	4.24 (0.09)	
Heavy	791	24.28	6.46 (0.23)	509	29.41	7.16 (0.30)	282	16.63	4.79 (0.24)	
P value for trend			0.8038			0.4063				<0.0001
Smoking status										
Never	2,045	46.21	4.58 (0.08)	378	18.21	5.67 (0.21)	1,667	87.98	4.23 (0.08)	
Former	981	29.94	6.15 (0.17)	855	45.58	6.38 (0.19)	126	6.59	4.30 (0.18)	
Current	774	23.87	6.45 (0.21)	662	36.21	6.81 (0.23)	112	5.44	4.07 (0.25)	
P value for trend			0.0594			0.0006			0.305	<0.0001

[1]Weighted percentages.
[2]Values are mean (standard error).
[3]*P* value for the within-gender differences in frequency of each variable from the Rao-Scott chi-square test and for the difference in blood mercury levels between genders from the survey *t*-test.

Table 2. Blood mercury levels (μg/L) by fish consumption and gender, KNHANES IV 2008−2009

Variables	Total (n=3,270)			Males (n=1,548)			Females (n=1,722)			*P* value[3]
	N	% wt[1]	Mercury (SE)[2]	N	% wt	Mercury (SE)	N	% wt	Mercury (SE)	
Mackerel										
Rare	633	16.83	4.73 (0.20)	279	14.78	5.45 (0.34)	354	19.54	3.92 (0.16)	
<1 time/month	653	19.53	5.07 (0.16)	316	19.65	5.79 (0.26)	337	19.38	4.23 (0.18)	
2∼4 times/month	1,582	49.53	5.55 (0.12)	759	50.74	6.59 (0.19)	823	47.93	4.30 (0.10)	
≥1 time/week	402	14.13	6.13 (0.31)	194	14.85	7.39 (0.54)	208	13.17	4.67 (0.16)	
P value for trend			0.0983			0.2636			0.1286	0.0048
Tuna										
Rare	1,474	45.95	5.45 (0.15)	679	45.12	6.52 (6.26)	795	47.04	4.33 (0.10)	
<1 time/month	58	18.08	5.37 (0.19)	299	18.91	6.05 (0.28)	288	16.99	4.40 (0.20)	
2∼4 times/month	1,012	29.41	5.20 (0.12)	476	29.41	6.15 (0.21)	536	29.40	4.05 (0.11)	
≥1 time/week	197	6.58	5.94 (0.41)	94	6.58	7.09 (0.66)	103	6.58	4.58 (0.26)	
P value for trend			0.09			0.2696			0.141	<0.0001
Yellow corvina										
Rare	1,079	30.30	4.89 (0.13)	528	30.54	5.65 (0.21)	551	29.99	3.93 (0.11)	
<1 time/month	768	24.58	5.53 (0.20)	383	26.43	6.53 (0.32)	385	22.14	4.19 (0.14)	
2∼4 times/month	1,161	36.37	5.64 (0.14)	519	34.84	6.71 (0.23)	642	38.40	4.52 (0.13)	
≥1 time/week	262	8.76	5.94 (0.30)	118	8.21	7.30 (0.52)	144	9.50	4.64 (0.24)	
P value for trend			0.5283			0.4645			0.6991	<0.0001
Pollack										
Rare	1,092	29.75	4.72 (0.11)	477	27.28	5.56 (0.19)	615	33.02	3.85 (0.09)	
<1 time/month	901	27.61	5.47 (0.15)	419	28.09	6.61 (0.26)	482	26.98	4.23 (0.16)	
2∼4 times/month	1,128	36.43	5.73 (0.14)	577	37.41	6.49 (0.22)	551	35.14	4.71 (0.13)	
≥1 time/week	149	6.23	7.10 (0.83)	75	7.25	8.78 (1.37)	74	4.88	4.80 (0.32)	
P value for trend			0.9931			0.99			0.8516	0.0067
Anchovy										
Rare	414	11.51	5.09 (0.25)	207	11.84	5.86 (0.40)	207	11.08	3.95 (0.16)	
<1 time/month	388	10.56	4.78 (0.19)	192	11.15	5.65 (0.29)	196	9.77	3.70 (0.16)	
2∼4 times/month	1,181	36.49	5.51 (0.15)	566	36.36	6.38 (0.24)	615	26.65	4.45 (0.14)	
≥1 time/week	1,287	41.46	5.53 (0.17)	583	40.67	6.69 (0.29)	704	42.51	4.34 (0.11)	
P value for trend			0.0007			0.1811			0.0003	<0.0001
Squid										
Rare	1,189	34.55	5.25 (0.14)	543	32.84	6.30 (0.25)	646	36.82	4.14 (0.11)	
<1 time/month	754	23.47	5.42 (0.17)	349	23.95	6.61 (0.31)	405	22.85	4.07 (0.13)	
2∼4 times/month	1,072	32.68	5.31 (0.13)	524	33.16	6.06 (0.20)	548	32.05	4.37 (0.14)	
≥1 time/week	255	9.31	5.98 (0.38)	132	10.07	6.81 (0.62)	123	8.30	4.86 (0.27)	
P value for trend			0.2278			0.4644			0.2761	<0.0001
Clam										
Rare	1,231	34.10	4.92 (0.13)	524	30.37	5.90 (0.23)	707	39.05	4.00 (0.11)	
<1 time/month	777	26.08	5.73 (0.23)	404	29.11	6.69 (0.38)	373	22.06	4.37 (0.15)	
2∼4 times/month	1,043	32.52	5.49 (0.13)	520	34.07	6.43 (0.20)	523	30.47	4.26 (0.10)	
≥1 time/week	219	7.32	5.88 (0.28)	100	6.47	6.40 (0.37)	119	8.44	5.33 (0.40)	
P value for trend			0.0751			0.2622			0.09	0.0032

[1]Weighted percentages.
[2]Values are mean (standard error).
[3]*P* value for the within-gender differences in frequency of each variable from the Rao-Scott chi-square test.

Table 3. Blood mercury levels (μg/L) by fish consumption and age, KNHANES IV 2008−2009

Variables	20~29 y (n=615)			30~39 y (n=666)			40~49 y (n=648)			50~59 y (n=650)			≥60 y (n=691)			P value[3]
	N	% wt[1]	Mercury (SE)[2]	N	% wt	Mercury (SE)	N	% wt	Mercury (SE)	N	% wt	Mercury (SE)	N	% wt	Mercury (SE)	
Mackerel																
Rare	122	18.75	4.72 (0.18)	83	10.17	3.97 (0.23)	90	12.89	5.88 (0.62)	112	14.42	5.54 (0.36)	226	28.57	4.36 (0.22)	<0.0001
<1 time/month	142	23.00	5.15 (0.16)	130	19.60	5.22 (0.42)	113	18.00	6.20 (0.41)	141	19.20	5.43 (0.27)	127	18.86	4.75 (0.34)	
2~4 times/month	286	46.51	5.61 (0.11)	370	57.09	5.53 (0.17)	348	55.21	6.33 (0.24)	307	46.82	6.38 (0.29)	271	41.71	5.71 (0.27)	
≥1 time/week	65	11.74	6.29 (0.38)	83	13.14	5.37 (0.28)	97	13.89	5.98 (0.37)	90	19.56	8.63 (1.30)	67	10.86	5.53 (0.45)	
Tuna																
Rare	116	17.74	4.24 (0.20)	174	24.70	4.91 (0.19)	256	39.61	6.19 (0.27)	405	62.36	6.20 (0.35)	523	75.02	5.13 (0.17)	<0.0001
<1 time/month	135	21.49	4.36 (0.26)	169	27.21	5.54 (0.37)	123	48.44	5.90 (0.38)	90	13.94	6.35 (0.39)	70	11.28	5.46 (0.60)	
2~4 times/month	291	47.29	4.47 (0.16)	276	39.01	5.03 (0.16)	228	35.24	6.25 (0.28)	129	19.44	6.77 (0.53)	88	12.16	4.88 (0.28)	
≥1 time/week	73	13.48	4.48 (0.33)	47	9.08	6.75 (0.61)	41	6.72	6.64 (1.21)	26	4.27	7.48 (1.12)	10	1.54	4.22 (0.91)	
Yellow corvina																
Rare	237	36.06	4.85 (0.13)	184	25.90	4.85 (0.30)	178	25.33	5.68 (0.34)	204	27.37	5.18 (0.25)	276	38.78	4.92 (0.24)	<0.0001
<1 time/month	165	28.52	5.61 (0.22)	181	27.93	5.51 (0.26)	141	22.73	6.50 (0.42)	155	26.06	6.55 (0.80)	126	18.77	5.40 (0.42)	
2~4 times/month	177	28.92	5.79 (0.13)	255	39.09	5.38 (0.18)	283	44.58	6.37 (0.26)	231	36.26	6.97 (0.36)	125	30.73	5.14 (0.23)	
≥1 time/week	36	6.51	6.10 (0.29)	46	7.08	0.23 (0.37)	46	7.38	6.25 (0.69)	60	10.31	7.70 (0.64)	74	11.71	5.22 (0.42)	
Pollack																
Rare	271	40.62	4.71 (0.10)	220	29.82	4.74 (0.18)	166	23.97	5.92 (0.35)	192	23.85	4.97 (0.22)	243	34.58	5.15 (0.26)	0.0004
<1 time/month	167	28.48	5.64 (0.15)	191	29.83	5.59 (0.35)	183	28.13	6.36 (0.35)	181	27.48	6.32 (0.30)	179	24.46	4.73 (0.21)	
2~4 times/month	156	27.73	5.86 (0.13)	235	36.93	5.42 (0.18)	255	40.42	6.24 (0.24)	243	38.39	6.83 (0.34)	239	35.96	5.33 (0.29)	
≥1 time/week	21	3.37	6.71 (0.98)	20	3.43	5.89 (0.61)	44	7.48	6.20 (1.02)	34	10.27	10.30 (3.35)	30	5.00	5.41 (0.92)	
Anchovy																
Rare	90	13.86	5.17 (0.23)	53	8.27	5.09 (0.41)	54	8.43	6.43 (0.72)	80	10.17	5.57 (0.37)	137	17.60	4.72 (0.30)	<0.0001
<1 time/month	85	13.85	4.71 (0.18)	92	11.84	4.59 (0.23)	60	7.71	5.10 (0.51)	71	9.79	5.38 (0.50)	80	10.78	4.78 (0.32)	
2~4 times/month	237	40.33	5.67 (0.13)	291	43.73	5.37 (0.18)	272	43.65	6.43 (0.30)	185	28.67	7.00 (0.42)	196	28.08	4.91 (0.25)	
≥1 time/week	203	31.96	5.57 (0.16)	230	36.16	5.41 (0.28)	262	40.21	6.14 (0.26)	314	51.36	6.52 (0.44)	278	43.54	5.51 (0.27)	
Squid																
Rare	125	19.13	5.38 (0.14)	154	21.98	4.96 (0.25)	190	27.27	5.95 (0.33)	290	41.06	5.88 (0.23)	430	58.21	4.89 (0.17)	<0.0001
<1 time/month	128	18.46	5.54 (0.18)	151	23.32	5.25 (0.39)	176	29.80	6.91 (0.38)	165	23.97	6.32 (0.38)	134	20.03	5.04 (0.37)	
2~4 times/month	277	45.87	5.30 (0.11)	298	44.47	5.35 (0.18)	228	34.37	5.94 (0.29)	162	24.87	6.37 (0.38)	107	18.82	6.07 (0.46)	
≥1 time/week	85	16.53	6.07 (0.49)	63	10.22	5.51 (0.29)	54	8.56	5.75 (0.51)	33	10.09	10.98 (3.51)	20	2.94	5.06 (0.55)	
Clam																
Rare	188	27.75	4.89 (0.12)	202	25.80	4.42 (0.16)	204	28.29	5.50 (0.31)	263	36.16	5.68 (0.26)	374	50.49	4.84 (0.20)	<0.0001
<1 time/month	145	24.71	5.83 (0.24)	173	28.09	5.78 (0.36)	162	26.42	6.77 (0.39)	160	25.57	6.90 (0.80)	137	21.96	5.23 (0.37)	
2~4 times/month	233	39.09	5.55 (0.12)	240	37.09	5.42 (0.19)	235	37.31	6.30 (0.29)	186	28.28	6.51 (0.34)	149	23.03	5.65 (0.33)	
≥1 time/week	49	8.45	6.11 (0.26)	51	9.01	5.88 (0.43)	47	7.98	6.60 (0.54)	41	6.98	7.89 (0.77)	31	4.52	5.00 (0.46)	

[1]Weighted percentages.
[2]Values are mean (standard error).
[3]*P* value for the differences between fish consumption frequency and age from the chi-square test.

Table 4. Odds ratio (95% CIs) for cardiovascular diseases associated with blood mercury levels

Cardiovascular disease	Blood mercury level quartile	Unadjusted[1)]	Adjusted for fish consumption[2)]	Adjusted for all characteristics and fish consumption[3)]
Hypertension	Q1	1	1	1
	Q2	0.800 (0.580～1.103)	0.867 (0.616～1.219)	0.853 (0.583～1.248)
	Q3	1.027 (0.777～1.356)	1.245 (0.917～1.690)	1.184 (0.830～1.689)
	Q4	1.450 (1.106～1.901)	1.550 (1.131～2.123)	1.221 (0.845～1.764)
Stroke	Q1	1	1	1
	Q2	0.716 (0.322～1.596)	0.644 (0.285～1.457)	0.708 (0.302～1.662)
	Q3	0.380 (0.149～0.974)	0.393 (0.141～1.095)	0.418 (0.150～1.165)
	Q4	1.023 (0.515～2.036)	1.030 (0.504～2.105)	0.986 (0.468～2.079)
Myocardial infarction or angina	Q1	1	1	1
	Q2	1.048 (0.388～2.829)	1.158 (0.393～3.408)	1.083 (0.370～3.171)
	Q3	2.138 (0.883～5.172)	2.585 (1.005～6.650)	2.265 (0.896～5.727)
	Q4	2.293 (0.961～5.469)	3.334 (1.338～8.308)	2.740 (0.978～7.675)

[1)]Not adjusted.
[2)]Adjusted for fish (i.e., mackerel, tuna, yellow fish, pollack, anchovy, squid, and clam) consumption frequency.
[3)]Adjusted for age, education level (less than high school diploma, high school diploma, and some college education), BMI (<18.5 kg/m^2, 18.5～24.9 kg/m^2, and ≥25 kg/m^2), alcohol consumption frequency (none, moderate, and heavy), smoking status (never, former, and current), and waist circumference (male: <90 cm and ≥90 cm, female: <80 cm and ≥80 cm).

lack, anchovy, squid, and clam. Blood mercury levels significantly increased with increasing anchovy consumption frequency (P=0.0007). Elevated blood mercury levels were also observed with increased mackerel, tuna, yellow fish, pollack, squid, and clam consumption, but these increases were not significant.

Fish consumption was significantly affected by age group (Table 3). The tuna consumption frequency of subjects in their 20s was higher than the tuna consumption frequency of subjects in their 50s and ≥60 years old. Over 40% of the subjects in their 20s and 30s reported that they consumed squid 2～4 times/month, but 41% and 58% of subjects in their 50s and ≥60 years old, respectively, reported that they rarely consumed squid.

Cardiovascular disease odds ratios by blood mercy level

Table 4 shows the hypertension, stroke, and myocardial infarction or angina ORs for different blood mercury quartiles in the general population. The unadjusted hypertension OR in Q4 was 1.45 times (95% CI: 1.106～1.901) higher than that of Q1. The fish consumption-adjusted OR for hypertension in Q4 was 1.550 times (1.131～2.213) higher than that of Q1 and the fish consumption-adjusted OR for myocardial infarction or angina in Q4 was 3.334 times (1.338～8.308) higher than that of Q1. There were no associations between blood mercury concentrations and the fish consumption and general characteristic-adjusted ORs for hypertension, stroke, and myocardial infarction or angina.

DISCUSSION

This study examined the 2008 and 2009 KNHANES IV for associations between blood mercury levels, socio-demographic factors, and fish consumption frequency and CVD ORs for different blood mercury levels in Korean adults aged ≥20 years. The results of the present study indicated that blood mercury was increased by education level, BMI, WC, and fish (i.e., anchovy) consumption frequency and was associated with increased risk of hypertension and myocardial infarction or angina.

Most studies have reported that blood mercury levels increased with age. In the National Health and Nutrition Examination Survey (NHANES) 1999－2000, Mahaffey et al. (17) reported that blood mercury levels were higher in 40～49 year-old individuals than those 16～19 years old. The percentage of subjects with blood mercury levels >5.8 μg/L, equivalent to the current reference dose (18), was 2.4% in 16～19 year-olds and 8.8% in 40～49 year-olds. In our study, blood mercury levels increased with age, but the trend was not statistically significant. The mean blood mercury concentration was lowest in individuals in their 20s. In the current study, the percentage of subjects with blood mercury levels >5.8 μg/L was 18.1% in 20- to 29-year-olds, 28.9% in 30- to 39-year-olds, 37.2% in 40- to 49-year-olds, 38.2% in 50～59 year-olds, and 26.8% in those greater than 60 years of age (data not shown). These results indicate that the prevalence of mercury exposure in the Korean population is much higher than the prevalence of mercury exposure in the US population.

In the current study, blood mercury levels were influenced by higher education (P=0.0011), BMI (P<0.0001), and WC (P<0.0001). According to the study conducted by Kim and Lee (19), blood mercury levels increased with higher education levels in the KNHANES 2005. The NHANES 1999－2000, which examined a US population, showed that individuals with more than a high school education had higher blood mercury levels than individuals with a high school education and individuals with less than a high school education (17), which is in line with the results of the current study. Because mercury in the body tends to accumulate in adipose tissue, blood mercury concentrations may be associated with obesity indicators such as BMI and WC. You et al. (20) reported that the blood mercury level of elderly Koreans living in coastal areas was 5.22 μg/L in individuals with BMIs <18.5 kg/m^2, 7.44 μg/L for those with BMIs of 18.5∼25 kg/m^2, and 8.90 μg/L in individuals with BMIs >25 kg/m^2. In addition, the blood mercury level of elderly participants with a WC <90 cm was 7.84 μg/L, whereas the blood mercury level of those with a WC ≥90 cm was 9.35 μg/L. In our study, blood mercury levels were also significantly increased by rising BMI and WC, indicating a positive relationship between blood mercury concentrations and obesity indices.

Fish consumption is a major cause of mercury exposure, which has many adverse effects for humans (21). Thus, in the US, the Institute of Medicine recommends that pregnant women restrict consumption of fish that contain high levels of mercury (e.g., predatory fish, shark, tuna, and swordfish) to one meal every two weeks (22). Lincoln et al. (21) reported that hair mercury concentrations were higher in those who consume fish ≥1 time per day (n=6) than in those who consumed fish ≤1 time per month (n=23). In NHANES 1999−2004, blood mercury levels increased with increasing fish and shellfish consumption frequency (23). Similar studies reported that the geometric mean of blood mercury levels was almost four times higher among women who consumed three or more servings of fish over a period of 30 days than among women who ate no fish in the same period (24).

In the current study, blood mercury levels tended to increase with increasing fish consumption frequency, and the levels were particularly increased by anchovy consumption (P=0.0007). The mercury content of seafood varies by species. The mercury contents of mackerel, yellow corvine, pollack, and squid, which are frequently consumed by Koreans (25), are much higher than the mercury level of anchovies (26). However, the number of participants indicating that they consumed anchovies 2∼4 times/month and ≥1 time/week was 1,181 and 1,287, respectively, which was much higher than the consumption frequency reported for the other fish species. Thus, there seems to be a significant trend between blood mercury concentration and anchovy consumption.

Fish contains omega-3 fatty acids such as EPA and DHA that contribute to the reduction of CVD risk (5). Thus, fish consumption is a well-known strategy for preventing CVD. However, some fish contain significant amounts of mercury, and consuming them can result in the accumulation of mercury in the human body.

Recently, Mozaffarian et al. (27) indicated that chronic mercury exposure in adults can cause adverse health effects such as stroke, myocardial infarction, and acute coronary events. Mercury stimulates the proliferation of vascular smooth muscle cells and inactivates paraoxonase, an extracellular antioxidative enzyme related to high-density lipoprotein, which can lead to CHD and myocardial infarction risk (4). In addition, mercury in blood increases oxidative stress, inflammation, thrombosis, and immune dysfunction (4). Therefore, higher mercury levels in the body may be associated with increased risk of CVDs such as hypertension, stroke, and CHD (28). The cohort study in Finland showed that hair mercury levels were associated with risk of cardiovascular outcomes (28). In addition, Guallar et al. found that toenail mercury levels were significantly associated with myocardial infarction risk (2), and a study from the Faroe Islands (29) reported that methylmercury exposure was significantly associated with increased blood pressure and intima-media thickness.

According to the study conducted by Yorifuji et al. (30), the prevalence ORs for past and current hypertension outcomes were 1.6 times (95% CI: 1.2∼2.1) and 1.4 times (95% CI: 1.1∼1.9) higher than average in Minamata, Japan, an area known to have high mercury exposure. The blood mercury levels of Cree adults (Canada) who consumed large quantities of fish were associated with CVD risk factors such as heart rate variability (31). In the Kuopio Ischemic Heart Disease Risk Factor Cohort Study (n=1,871), males with high blood mercury levels had a 1.6 times higher risk of acute coronary events, a 1.68 times higher risk of CVD, and a 1.56 times higher risk of CHD (32). In addition, the results of the Kuopio Ischemic Heart Disease Risk Factor Cohort Study indicated that blood mercury concentrations influenced the prevalence of hypertension and myocardial infarction or angina (32). Fillion et al. (33) indicated that increased hair mercury levels were associated with elevated systolic blood pressure, even after adjusting for age, sex, BMI, smoking status, and community.

In our study, blood mercury levels influenced the ORs for hypertension and myocardial infarction or angina. The ORs between Q1 and Q2 did not differ for the CVD items in this study, although the ORs of Q3 and Q4 were much higher than those of Q1 and Q2, especially for the risk of myocardial infarction or angina. The unadjusted OR for hypertension in Q4 was 1.450 times (95% CI: 1.106∼1.901) higher than that of Q1. The fish consumption-adjusted OR for hypertension of Q4 was 1.550 times (95% CI: 1.131∼2.123) higher than Q1 and the fish consumption-adjusted OR for myocardial infarction or angina was 3.334 times (95% CI: 1.338∼8.308) higher than Q1. The results of this study did not reveal an association between blood mercury levels and stroke.

Nevertheless, higher blood mercury levels may increase the risk of hypertension and myocardial infarction or angina in the Korean population. However, the Kazuko study reported that there was no association between mercury exposure and the risk of CHD (15). In addition, a nested case-control study of 40- to 75-year-old individuals reported that toenail mercury level is significantly associated with fish consumption, but toenail mercury levels were not significantly associated with the risk for CHD, coronary artery surgery, nonfatal myocardial infarction, or fatal CHD (15).

Fish containing omega-3 fatty acids are well known to have cardio-protective benefits (22), but fish consumption is also a major cause of mercury exposure. In the current study, blood mercury concentrations increased with fish consumption; the higher the blood mercury levels, the greater the ORs for hypertension and myocardial infarction or angina. Thus, high blood mercury levels from frequent fish consumption may increase CVD risk. Approximately 30% of the Korean adults in this study had blood mercury concentrations greater than 5.8 μg/L, the US Environmental Protection Agency reference blood level (18). Therefore, to prevent mercury exposure and help reduce the risk of CVD, fish intake guidelines should be provided in Korea.

Our study has some limitations. First, as the KNHANES IV from 2008 and 2009 was a cross-sectional study, a causal relationship between heavy metals and CVD cannot be determined. Second, the heavy metal exposure status was evaluated only by blood sample tests, not by measuring heavy metal levels in bone or soft tissue samples. Therefore, the results may not accurately reflect the relationship between CVD and mercury exposure. Third, CVD is defined as a prevalence status. It is not clear whether CVD should be regarded as a single disease entity. Forth, this study did not include all species of fish. Therefore, fish consumption may not affect CVD. Korea is bordered by seas on 3 sides, and blood mercury levels and fish consumption may vary by the geographic location of the subjects included in the KNHANES IV. Thus, further research is needed to compare blood mercury levels and fish consumption by region. Despite these limitations, our study results are meaningful because they show a significant association between blood mercury level and CVD.

All subjects in this study underwent accurate heavy metal analyses with strict quality controls. After adjusting for fish consumption, significant associations between blood mercury level and hypertension and between blood mercury level and myocardial infarction or angina were identified. Furthermore, because previous studies have already showed that blood mercury is closely related to high CVD risk, the results of the present study should be useful regardless of the debate regarding the definition of CVD. The AHA reports that some fish contain significant levels of methylmercury (7). Thus, our finding that blood mercury exposure is a risk factor for CVD, especially hypertension and myocardial infarction or angina, is meaningful.

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AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

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