Cut-off values of blood mercury concentration in relation to increased body mass index and waist circumference in Koreans

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ABSTRACT

Blood mercury (methyl-mercury) from environmental exposure may be related to inflammation in our body. We investigated the cut-off values of blood mercury concentration in relation to increased body mass index (BMI) and waist circumference. On the basis of data obtained from the Korea National Health and Nutrition Examination Survey (KNHANES, 2008–2012), 11,159 subjects (5543 males and 5616 females) were analyzed cross-sectionally. Partial correlation, linear regression, and analysis of covariance (according to the mercury quartile) tests were performed to evaluate the relationship between blood mercury and BMI or waist circumference. In addition, we determined the cut-off values of blood mercury concentration in relation to increased BMI and waist circumference in both genders. Mean values of blood mercury concentration were 5.07 ±0.07 µg/L in males and 3.59±0.04 µg/L in females. After log transformation of blood mercury, significant ($p<0.001$) correlation was found between blood mercury concentration and BMI or waist circumference. BMI and waist circumference showed a significant and gradual increase as mercury quartile increased in both genders. Blood mercury concentration was weakly but significantly ($p<0.001$) associated with BMI and waist circumference. Cut-off values of blood mercury concentration correlated with increased BMI and waist circumference were around 3.95 µg/L in males and 3.40 µg/L in females.

Significance of this study

What is already known on this subject?

- Excess blood mercury is a factor for inflammation in our body.
- Obesity can cause low grade inflammation.
- No published data are available in blood mercury cut-off values in relation to increased BMI and waist circumference.

What are the new findings?

- Excess blood mercury can be a factor for increased BMI and waist circumference.
- Cut-off values of blood mercury correlated with increased BMI and waist circumference were around 3.95 µg/L in males and 3.40 µg/L in females.

How might these results change the focus of research or clinical practice?

- Blood mercury should be considered in relation with inflammation in obese subjects.
- Physicians should be educated about the dangers surrounding increased blood mercury concentrations in obese patients.

INTRODUCTION

The prevalence of obesity has been increasing for several decades,[1 2] causing serious public health concerns. Obesity is known as a factor of type 2 diabetes,[3] metabolic syndrome,[3] cardiovascular diseases[4] and some cancers.[5] Policies for obesity control are important as an aspect of public health. Traditionally, causes of obesity are high calorie intake, including high fat or high carbohydrate but low physical activity,[6 7] that results in positive energy balance and consequent production of abnormal fat accumulated in the body. Recent studies have demonstrated that inflammation from excess adiposity after a high-fat diet was a risk factor for cardiovascular disease.[8] Inflammation is one of the causes of obesity,[9 10] including gut inflammation in dysbiosis[11] and inflammation due to heavy metal overload.[12] Of heavy metals, some studies have reported that abnormal blood mercury concentration might be associated with hypertension and coronary heart disease;[13] however, other studies have not.[14] One possible mechanism associated with heavy metal toxicity is through oxidative stress supported by a wide spectrum of nucleotide products typical of oxygen attack on DNA in cultured cells and animals.[15] In addition, blood mercury is associated with decreased nitric oxide production, causing endothelial dysfunction and atherosclerosis.[16] Possible links between toxins and obesity include inflammation, oxidative stress, mitochondrial injury, altered thyroid metabolism, and impairment of central appetite regulation.[17] Previous studies have suggested that heavy metals are potential risk factors for diabetes and obesity.[18 19]

Unfortunately, heavy metals in our body have long half-lives. The human body has no mechanism of active excretion for toxic heavy metals. Therefore, heavy metals will accumulate in the tissues of the body.[20] Consequently, their harmful effects such as oxidative stress and mitochondrial injury will be expected, increasing cardiovascular risk.

Our hypothesis is that higher blood mercury (methylmercury) concentration is significantly correlated with higher body mass index (BMI) and waist circumference in the general population. Therefore, the aim of this study was to evaluate the correlation between blood mercury concentration and BMI and waist circumference. In addition, we aimed to determine the cut-off values of blood mercury concentration that have the highest sensitivity and specificity for predicting increase of BMI and waist circumference.

MATERIALS AND METHODS

Data of study subjects

The Korea National Health and Nutrition Examination Survey (KNHANES) is a nationwide cross-sectional health survey. Participants are representatives of the Korean population. KNHANES results have external validity. The study was based on data obtained from the fourth to fifth year of KNHANES (2008–2012). KNHANES data included blood mercury concentration. From an initial total of 20,829 males and 24,982 females, we selected subjects who completed personal interviews and self-questionnaires about demographic characteristics, diet and health-related variables, physical examination and blood sampling. A total of 15,286 males and 19,366 females had missing values in general characteristics or blood mercury concentration. Finally, a total of 11,159 subjects (5543 males and 5616 females) were included in this study, including 1000 males and 1006 females in 2008, 996 males and 995 females in 2009, 1164 males and 1191 females in 2010, 1188 males and 1207 females in 2011, and 1195 males and 1217 females in 2012. All participants provided written informed consents before the survey.

Measurement

Physical examinations were performed by a trained examiner following a standardized procedure. Body weight and height were measured in light indoor clothing without shoes to the nearest 0.1 kg and 0.1 cm, respectively. BMI was calculated as weight (kg) divided by height (m^2). Waist circumference was measured at the level of mid-distance between the bottom of the rib cage and the top of the iliac crest. Blood samples were collected from the antecubital vein of each participant after fasting overnight. Blood samples were properly processed, refrigerated at 2–8°C, and shipped to the Central Testing Institute (NeoDin Medical Institute, Seoul, South Korea). Total cholesterol, triglyceride, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol levels were measured using a Hitachi 7600-110 chemistry analyzer (Hitachi, Tokyo, Japan). Fasting plasma glucose concentrations were measured using an automated analyzer with an enzymatic assay (Pureauto S GLU: Daiichi, Tokyo, Japan). Blood mercury (methyl-mercury) was checked by the standard method using PerkinElmerA Analyst60 or by the atomic absorption method using Ammonium Phosphate and TritonX-10 as substrates. The CV% range of serum mercury was 0.7–38.9 μg/L. Nutrient intakes including total calorie and calcium intakes were assessed with a 24 h dietary recall questionnaire administered by a trained dietician. Results were calculated using the Food Composition Table developed by the National Rural Resources Development Institute (7th revision).

Lifestyle questionnaires

Current smokers were defined as those who were currently smoking and had smoked more than five packs of cigarettes during their life. Ex-smokers were defined as those who had smoked in the past but had quit smoking. Non-smokers were defined as those who had no history of smoking. Regular alcohol drinkers were those who drank alcohol more than once per month. All others were considered as non-drinkers. Physical activity was assessed by a questionnaire and categorized as 'yes' or 'no'. A 'yes' indicated 30 min of moderate physical activity three or more times in the last week in which the subject was tired compared to ordinary levels. Sleep time per day and total education years were also evaluated. The menarche age was determined by a health questionnaire administered by a trained examiner. Women were classified into women in menopausal status and women with hormone replacement therapy.

Statistics

Complex sample analysis was used for KNHANES data for weighting all values following the guidance on statistics from the Korea Centers for Disease Control and Prevention.[21] For general characteristics, we used a simple descriptive analysis. After log-transformation of blood mercury and confirmation of its normal distribution, partial correlation analysis was conducted to evaluate the relationship between blood mercury and BMI and waist circumference in both genders after adjusting for age, education, occupation, alcohol intake, smoking status, moderate physical activity, sleep time and daily total energy intake. For women, oral contraceptive intake, hormone replacement therapy and menopause were also adjusted. To evaluate the relationship between blood mercury levels and BMI and waist circumference, linear regression analysis was conducted. In addition, we divided blood mercury concentration into quartiles and conducted an analysis of covariance test after adjusting for age, education, occupation, alcohol intake, smoking status, moderate physical activity, sleep time, and daily total energy intake, fish consumption and hematocrit. In case of women, oral contraceptive intake, hormone replacement therapy, and menopause were also adjusted for. Receiver operating characteristic (ROC) curves and cut-off values for blood mercury concentrations associated with increased BMI (>25 kg/m^2) and waist circumference (>90 cm for males and >85 cm for females) were run using published procedures.[22,23] Data were analyzed using SPSS V.19.0 (SPSS Inc., Chicago, Illinois, USA). p Values were used to assess the significance of all analysis. Statistical significance was considered when the p value was less than 0.05.

RESULTS

General characteristics

A total of 11 159 subjects' data were analyzed in this study. General characteristics of subjects were summarized in

Table 1 General characteristics of subjects used in this study

	Male (n=5543)	Female (n=5616)
Age (years)	36.6±0.2	38.9±0.2
BMI (kg/m^2)	23.1±0.1	22.4±0.1
WC (cm)	79.6±0.2	74.4±0.1
TC (mg/dL)	182.5±0.5	184.9±0.4
TG (mg/dL)	144.9±1.4	109.0±0.8
HDLC (mg/dL)	49.7±0.2	55.2±0.2
LDLC (mg/dL)	122.5±2.1	123.1±2.3
FBS (mg/dL)	97.2±0.2	94.5±0.2
Blood mercury (μg/L)	5.07±0.07	3.59±0.04
Energy (kcal/day)	2288.6±11.2	1650.1±6.9
Sleep time (hours)	7.0±0.1	6.9±0.1
Smoking		
Yes	44.9 (0.6)	6.3 (0.3)
Alcohol		
Yes	73.5 (0.5)	40.2 (0.5)
Physical activity		
Yes	11.7 (0.4)	10.0 (0.3)
Education (years)		
≤6	26.9 (0.4)	36.2 (0.5)
7–9	12.6 (0.3)	11.8 (0.3)
10–12	33.4 (0.5)	30.0 (0.4)
>12	27.1 (0.5)	22.0 (0.5)

Values were presented as mean±SE after data weighting.
Blood mercury, methyl-mercury; BMI, body mass index; Energy, total daily energy intake; FBS, fasting blood sugar; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; WC, waist circumference.

table 1. Mean concentration of blood mercury was 5.07±0.07 μg/L in males and 3.59±0.04 μg/L in females. Mean BMI was 23.1±0.1 kg/m^2 for males and 22.4±0.1 kg/m^2 for females. Mean waist circumference was 79.6±0.2 cm for males and 74.4±0.1 cm for females.

Correlation between blood mercury concentration and BMI or waist circumference

To evaluate the relationship between blood mercury concentration and BMI or waist circumference, we conducted partial correlation analysis (table 2). After log transformation of blood mercury, significant (p<0.001) association was noted between blood mercury and BMI or waist circumference (BMI: r=0.176 in males, 0.107 in females; waist circumference: r=0.173 in males, 0.120 in females) after adjusting for relevant variables.

Table 2 Partial correlation between blood mercury concentration and BMI or waist circumference

	Ln (Hg)	p Value
Male		
BMI	0.176	<0.001
WC	0.173	<0.001
Female		
BMI	0.107	<0.001
WC	0.120	<0.001

p Values were obtained from analysis of partial correlation test after adjusting for age, education, occupation, alcohol intake, smoking status, moderate physical activity, sleep time, daily total energy intake, oral contraceptive intake, hormone replacement therapy, and menopause in case of women.
BMI, body mass index; Ln (Hg), natural logarithm of blood mercury; WC, waist circumference.

Table 3 Linear regression of blood mercury and BMI or waist circumference

	β	t	R^2	p Value
Male				
BMI (kg/m^2)	0.14	15.05	0.04	<0.001
WC (cm)	0.49	18.23	0.06	<0.001
Female				
BMI (kg/m^2)	0.22	11.71	0.02	<0.001
WC (cm)	0.77	14.65	0.04	<0.001

BMI, body mass index; WC, waist circumference.

Anthropometrics difference according to variations in blood mercury concentration

To evaluate the linear relationship of blood mercury and BMI or waist circumference, linear regression analysis was performed. A weak but significant (p<0.001) association between BMI or waist circumference and blood mercury concentration was found. R^2 of waist circumference was higher than BMI in both sexes (table 3).

After blood mercury concentration had been log-transformed, we divided it into quartile (table 4). BMI and waist circumference showed a significant and gradual increase as blood mercury quartile increased in both genders. In males, the difference of BMI and waist circumference increased 4.9 kg/m^2 and 9.7 cm, respectively, when the highest blood mercury quartile was compared to the lowest blood mercury quartile. In females, the difference of mean BMI and waist circumference increased 2.0 kg/m^2 and 9.9 cm, respectively.

Table 4 BMI or waist circumference by blood mercury quartile after log transformation

Ln (Blood mercury)	BMI (kg/m^2)	WC (cm)
Male (n=5543)		
Q1 (0.363–1.023)	22.6 (1.6)	75.6 (4.3)
Q2 (1.024–1.463)	23.6 (1.4)	77.9 (3.6)
Q3 (1.464–1.896)	25.4 (1.5)	80.3 (3.9)
Q4 (>1.897)	27.5 (1.4)	85.3 (3.5)
p Value	<0.001	<0.001
Female (n=5616)		
Q1 (0.370–0.761)	21.4 (1.6)	66.7 (4.5)
Q2 (0.762–1.120)	22.1 (1.4)	69.6 (3.7)
Q3 (1.121–1.498)	23.2 (1.3)	70.3 (3.4)
Q4 (>1.499)	23.4 (1.2)	76.6 (3.2)
p Value	<0.001	<0.001

Values were presented as log–transformed mean (range). p Values were obtained from analysis of covariance test after adjusting for age, education, occupation, alcohol intake, smoking status, moderate physical activity, sleep time, daily total energy intake, fish consumption, hematocrit, oral contraceptive intake, hormone replacement therapy, and menopause in case of women.
BMI, body mass index; WC, waist circumference.

Table 5 AUC and its cut-off values for blood mercury concentration according to the increase in BMI or waist circumference in both genders

	AUC (95% CI)	Hg (μg/L)	Sensitivity	1-Specificity	p Value
Male					
BMI (kg/m^2) ≥25	0.623 (0.608 to 0.639)	3.949	0.678	0.498	<0.001
WC (cm) ≥90	0.618 (0.601 to 0.636)	3.944	0.685	0.522	<0.001
Female					
BMI (kg/m^2) ≥25	0.584 (0.567 to 0.601)	3.403	0.520	0.391	<0.001
WC (cm) ≥85	0.601 (0.583 to 0.619)	3.557	0.522	0.364	<0.001

Hg represented blood mercury concentration correspondent to the cut-off values.
AUC, area under curve; BMI, body mass index; WC, waist circumference.

AUC cut-off values of blood mercury concentration associated with increased BMI and waist circumference in both genders

The area under curve (AUC) values associated with increased BMI and waist circumference in males were 0.623 (95% CIs 0.608 to 0.639) and 0.618 (95% CI 0.601 to 0.636), respectively. Cut-off values of blood mercury concentration corresponding to AUC associated with increased BMI and waist circumference were 3.949 μg/L and 3.944 μg/L, respectively. In females, AUC values associated with increased BMI and waist circumference were 0.584 (95% CI 0.567 to 0.610) and 0.601 (95% CI 0.583 to 0.619), respectively. Cut-off values of blood mercury concentration corresponding to AUC associated with increased BMI and waist circumference were 3.403 μg/L and 3.557 μg/L, respectively (table 5).

DISCUSSION

This study examined blood mercury concentration in relation to increased BMI and waist circumference using KNHNES data assessed between 2008 and 2012. There was a positive and significant association between blood mercury concentration and BMI or waist circumference. The cut-off values of blood mercury concentration for increased BMI and waist circumference in males were around 3.95 μg/L and 3.40 μg/L, respectively, in females.

Several studies have shown that blood heavy metals are significantly associated with metabolic syndrome after adjustment for multiple parameters.[13 17 24 25] Other studies have also shown that higher urine mercury concentrations are associated with serum cholesterol concentration and cardiovascular disease.[26 27] Hair sampled mercury concentrations were found to affect cardiac autonomic activity.[28 29] In this study, subjects who had blood mercury concentration around 3.95 μg/L and 3.40 μg/L showed significantly higher BMI and waist circumference in males and females after adjusting for relevant confounders.

The mechanism between obesity and blood mercury (methyl-mercury) concentration remains unclear, although a possible relationship between dysregulation of lipid and glucose metabolism has been suggested.[30] Effects of mercury toxin on our body include oxidative stress, increased free radical production, abnormal platelet aggregation and interfering normal metabolism. Mercury could increase vascular inflammation and increase the risk of cardiovascular disease.[13] Systemic inflammation can also affect the accumulation of abnormal adipocytes as well as diverse types of immune cells such as T cells and macrophages that have similar roles in pathways such as complement activation and inflammatory cytokine production.[31] Therefore, elevated blood mercury concentration might cause an increase in systemic inflammation associated with obesity. In this study, we measured BMI and waist circumference associated with obesity. Consequently, we found that higher blood mercury concentration was associated with increased BMI and waist circumference. Although linear regression analysis results and AUC values were not remarkably significant, higher blood mercury concentration could be associated with increased BMI and waist circumference. Higher blood mercury concentration has been suggested to be linked to increased risk of cardiovascular disease and metabolic syndrome.[24 30]

Mean concentration of blood mercury has gradually increased in Korean adults. It might be partially related to increased obesity and waist circumference that contribute to increased risk of cardiovascular disease.[32] The National Institute of Environmental Research in Korea announced that blood mercury concentrations of Koreans were higher than those in other countries in 2012.[21 33] In the 2009–2011 examination of 6000 Korean men and women, the average blood mercury concentration was 3.08 μg/L, which was more than three times higher than those in the USA (0.94 μg/L), Germany (0.58 μg/L), and Canada (0.69 μg/L). In this study, cut-off values of blood mercury were approximately 3.95 μg/L in men and 3.40 μg/L in women in relation to increased BMI and waist circumference. On the basis of these values, about 55.9% of men and 43.5% of women were above the cut-off values. Thus, these cut-off values exceeded the average blood mercury concentration of Koreans. Mean blood mercury concentration was higher in males than in females (5.07 μg/L vs 3.59 μg/L). This result is inconsistent with reports of prior studies.[24 34] Occupational environments, fish consumption,[35] and frequency of smoking might be the causes of elevated blood mercury concentration.

Our study had several limitations. First, this study had a cross-sectional design. Second, urine mercury concentration was a better marker than blood samples, but data of KNHANES were based on blood samplings. In addition, personal history of fish consumption and occupational exposure are important to blood mercury concentration. However, we could not adjust for these confounders.[21] Nonetheless, this study was based on large samples of

KNHANES. Therefore, it can represent the general Korean population. In addition, this is the first study to document the cut-off values of blood mercury concentration in relation to increased BMI and waist circumference.

In conclusion, higher blood mercury concentration is significantly associated with higher BMI and waist circumference. Cut-off values of blood mercury concentration in relation to increased BMI and waist circumference were around 3.95 μg/L in males and 3.40 μg/L in females, which may mean that the increase in BMI and waist circumference is associated with those cut-off values. Large prospective studies are needed to investigate the exact relationship between blood mercury concentration and increased BMI or waist circumference.

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