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# Toenail mercury and dyslipidemia: Interaction with selenium

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ABSTRACT

*Background:* Although compelling evidences from in vivo and in vitro studies exist, limited studies have examined the association between chronic mercury exposure and dyslipidemia. Particularly, data are sparse regarding the influence of selenium on this association of mercury with dyslipidemia in humans.
*Purpose:* The purpose of the current study was to examine the associations of toenail mercury with dyslipidemia and its components, and to examine whether selenium in toenails modifies these associations.
*Methods:* We performed cross-sectional analyses using baseline data from a cohort in the Yeungnam area in South Korea, including 232 men and 269 women. Toenail mercury and selenium concentrations were quantified using neutron activation analysis, and fasting serum lipid measurements were obtained through the medical examination. Odds ratios of the prevalent hypercholesterolemia, hyper-LDL-cholesterolemia, hypo-HDL-cholesterolemia, hypertriglyceridemia, and dyslipidemia in correlation with mercury levels were calculated using multivariable logistic regression.
*Results:* The mean levels of toenail mercury were 0.47 μg/g for men and 0.34 μg/g for women. After adjustment for multiple confounding variables, participants in the highest tertile of toenail mercury levels had 4.08 (95% CI 1.09–15.32, $p$ for trend = 0.02) times higher risk of hyper-LDL-cholesterolemia, and 2.24 (95% CI 1.15–4.37, $p$ for trend = 0.004) times higher risk of dyslipidemia than those in the lowest tertile. Selenium is a significant effect-modifier for these associations; the highest tertile of toenail mercury were significantly associated with a higher risk of hypercholesterolemia (OR 5.25, 95% CI 1.04–26.38) and dyslipidemia (OR 2.98, 95% CI 1.16–7.66) compared to the lowest tertile at toenail selenium levels ≤0.685 μg/g, while these associations became weak and non-significant, showing OR 0.98 and 95% CI 0.25-3.80 for hypercholesterolemia and OR 1.99 and 95% CI 0.73–5.45 for dyslipidemia at toenail selenium levels >0.685 μg/g.
*Discussion:* We confirmed the beneficial effects of selenium against the harmful effects of mercury in humans with relatively high consumption of fish. Our finding has important implications in making dietary recommendations regarding optimal levels of fish and selenium intakes. Further studies are warranted to determine the appropriate level of fish consumption, considering both methylmercury and selenium exposure, in a larger prospective cohort or RCT.



## 1. Introduction

Mercury is a highly reactive heavy metal, which gets converted into methylmercury (MeHg) and accumulates along the food chain in the ocean. MeHg is significantly more toxic than other forms of mercury, and the toxic effects of MeHg are associated with decreased glutathione, increased oxidative stress and inflammation, and eventual development of obesity, hypertension, dyslipidemia, and coronary heart disease [1–7]. Marine species also contain selenium, an antioxidant that could dilute MeHg toxicity or elicit beneficial effects by itself [1,8–10]. Selenium is a component of glutathione peroxidase, a critical scavenger of lipid peroxides. High levels of MeHg exposure may increase the production of free radicals and reduce the bioavailability of selenium by binding it in an inactive form [11–14].

Although convincing evidences have been generated using in-vivo and in-vitro studies, limited epidemiological studies have examined the association between chronic exposure of mercury and dyslipidemia in community-based populations, while adjusting for multiple confounding factors. Studies have reported that high concentrations of mercury in blood or hair were observed with

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lower levels of high-density lipoprotein cholesterol (HDL-C) [15,16] and triglycerides (TG) [16–18]. However, most of the prior studies conducted on mercury concentrations in blood or hair, represent relatively short-term exposures or possible contamination by use of hair dyes or other hair products. In addition, there are convincing evidences from in-vivo and in-vitro studies that the association between mercury exposure and metabolic diseases may be modified by selenium. However, to our knowledge, few studies have been successful in showing the significant modifying effect of selenium on this association in epidemiological studies, and no study has been conducted in Asian populations whose consumption of fish and seafood are relatively high.

Therefore, we analyzed baseline data from the Trace Element Study of Korean Adults in the Yeungnam area (SELEN study), an ongoing cohort study of middle-aged adults living in urban and rural south-eastern areas of South Korea. The objectives of the current study were (1) to examine the associations of toenail mercury with lipid profiles (total cholesterol (TC), LDL cholesterol (LDL-C), HDL-C, TG), including dyslipidemia; and (2) to examine whether selenium in toenails can modify these associations.

## 2. Material and methods

### 2.1. Population and design

We analyzed baseline data from the SELEN cohort. The baseline survey collected extensive information on demographics, lifestyle, nutritional and health information through self-administered questionnaires. In this analysis, we included 232 men and 269 women with complete dataset on key information including toenail mercury and selenium levels as well as health information. All participants provided written consent and the study was approved by the Institutional Review Board of the Yeungnam University Medical Center (YUH-12-0468-O94).

### 2.2. Assessment of toenail mercury and selenium levels

Toenail clippings from all 10 toes of each participant were obtained and tendered to the SELEN investigators. Collected toenail clippings were carefully inspected by trained technicians, and shipped to the University of Missouri Research Reactor (USA) to quantify the levels of mercury and selenium using neutron activation analysis (NAA). Details on the analytical methods and validation of these measures using NAA at University of Missouri Research Reactor have been published previously [19–22]. Briefly, toenail clippings were washed in a sonicator with deionized water, and assayed in random order by trained laboratory personnel blinded to participants' identification information.

Toenail mercury and selenium levels are known to reflect long-term exposures over approximately 1 year [3,19,23–25], compared to blood mercury and selenium levels [8,9,18]. Mercury and selenium are also stored in hair and fingernails, but these markers can be contaminated by the use of anti-dandruff shampoos [25,26].

### 2.3. Assessment of dietary and lifestyle information

Dietary information was estimated using a validated 146-item semi-quantitative food frequency questionnaire (FFQ), specifically developed for this population [27]. The FFQ listed 21 fish and seafood items most frequently consumed by the study population including: mackerel, anchovy, salmon, eel, tuna (fresh and canned), pollack/cod, yellow corvina/flounder, hair tail, rock fish/yellow tail/skate ray, file fish/monk fish/naked sand lance, puffer, sea bream, squid/octopus, shellfish, whelk/gastropods/urban/marsh snail, oyster/abalone, warty sea squirt, crab, shrimp, fish paste and seafood processing byproducts (salted seafood). In addition, intake levels of whale and shark containing relatively high mercury were also obtained from the FFQ. Frequency of consumption of items on the FFQ were rated on a Likert-type scale ranging from "rarely" to "3 times a day", and the portion size of each food item was categorized into: small (0.5 times reference), medium (reference), and large (1.5 or 2 times of reference). Daily fish intake levels were quantified as follows: the frequency per food item was converted into times per day using median values, which was then multiplied by the reported portion size.

Demographic and lifestyle information was obtained through a self-reported questionnaire. Smoking status was categorized as never, former, or current smoker, and alcohol consumption status was categorized as drinker and non-drinker. Monthly household income was categorized into 5 groups from the lowest group representing "less than 3,000,000 Korean won" to the highest group which represented "more than or equal to 6,000,000 Korean won". Educational levels were categorized as high school graduation or less and college graduation or more. Physical activity levels were quantified as the metabolic equivalents (METs)-h/week [28].

### 2.4. Assessment of anthropometry and lipid measurements

Anthropometric and serum lipid measurements were obtained from the results of the medical- examination, which is legally required for all Korean workers and their dependents through the Korea National Health Insurance Service (KNHIS). Study participants went through the medical-checkups 6–12 months after completing the baseline survey and toenail clipping collections.They were also requested to send a copy of their medical-checkup results to SELEN investigators, and all collected information was carefully inspected by two independent technicians.

According to KNHIS guidelines, all anthropometric and medical examinations were conducted at the medical clinics regulated by KNHIS [29]. Participants were required to fast for 12 h before their examinations. Anthropometric measures including height, weight and waist circumference were measured by a trained nurse, and BMI was calculated as the weight in kilograms divided by square of the height in meters. The serum concentrations of TG and cholesterol were measured at qualified clinical laboratories with standard quality assurance and control protocols in place. Based on recommendations of the 2001 National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) [30], dyslipidemia was defined as the presence of one or more of the following: 1) hypercholesterolemia (TC levels $\geq$240 mg/dL or the use of lipid lowering drugs); 2) hypo-HDL-cholesterolemia (HDL-C levels < 40 mg/dL); 3) hyper-LDL-cholesterolemia (LDL-C levels $\geq$160 mg/dL or the use of lipid lowering drugs); or 4) hypertriglyceridemia (TG levels $\geq$200 mg/dL).

### 2.5. Statistical analysis

Participants were classified into gender-specific tertiles of toenail mercury levels. Chi-square statistic was computed to compare categorical variables with tertiles of toenail mercury. Age adjusted mean values were estimated and compared with tertiles of toenail mercury using generalized linear regression. Potential confounding factors were determined with literature review and preliminary analyses. To minimize and account for the potential confounding factors, we evaluated three covariate models using unconditional logistic regression: Model 1) adjusted for age; Model 2) additionally adjusted for lifestyle factors, including monthly household income, smoking status, alcohol intake, and physical activity levels; and Model 3) further adjusted for BMI. Potential effect modification was assessed by gender, smoking, alcohol consumption, physical activity and selenium levels, using multiplicative terms