Increased Fasting Serum Level of Arsenic Caused by Intake of Fish Meat Promotes a Potential Risk of Hypertension

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Research Article

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Increased fasting serum level of arsenic caused by intake of fish meat promotes a potential risk of hypertension

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Abstract

Despite identification of arsenic intake from well drinking water in developing countries as a crucial hazard for health, the health effects of diet-mediated intake of arsenic on health in developed countries have remained unclear. The Japanese diet, which is regarded as a healthy diet, includes a high intake of seafoods that contain high levels of arsenic. The associations among intake of Japanese food including 54 food items classified into 6 categories, arsenic exposure and hypertension were investigated in 2,709 adults in Japan. Logistic regression analysis including serum sodium and potassium levels as confounders indicated a positive association between fasting serum level of arsenic (fsl-As) and prevalence of hypertension. Seaweed, bone-edible small fish and fish meat in seafoods were strong contributors to the increased fsl-As among the food items examined. Fish meat intake was identified as the greatest contributor to prevalence of hypertension. Since 94% of arsenic has been reported to be caused by dietary intake in Japan, our results suggest that increased fsl-As caused by intake of fish meat could be a potential risk for hypertension. Considering the worldwide trend of increased fish meat intake, arsenic in fish meat might be a new global hazardous material.

Keywords: Arsenic, Japanese food, seafood, fish meat, prevalence of hypertension

Declarations:

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Conflicts of interest The authors declare that there is no conflict of interest.

Availability of data and material The data that support the findings of this study are not available for a while since data analysis for publications are ongoing.

Code availability Not applicable

Authors' contributions T.H. performed the data analysis. T.H., N.O. and M.K. wrote the manuscript. H.N., T.T., T.K. and K.W. collected samples and questionnaire from subjects. T.T., T.K., K.W. and M.K. developed the basic concept of this study. M.K. and N.O. conceived the associations between food intake and arsenic exposure. S.O., I.Y. and A.T. developed the methodology. S.O., H.N., I.Y. and A.T. analyzed human samples. M.K. provided the research foundation, supervised the work and revised the final version of the manuscript.

Ethics approval The manuscript in full has not been submitted or published anywhere. Ethics committee of Nagoya University Graduate School of Medicine approved the study (approval numbers: 2008-0618 and 2013-0070).

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication All of the authors have read and approved the paper for submission of publication.

1. Introduction

Hypertension, a silent killer, is widely known as a typical symptom of lifestyle-related diseases that reduce the health span in humans. Dietary habits are known to be strong risk factors for hypertension (Ndanuko et al., 2016). Since sodium (Na) derived from food intake might be one of the strongest inducers of hypertension (Adrogué and Madias, 2014; Grillo et al., 2019), worldwide campaigns to decrease the intake of foods with large amounts of Na are ongoing. In contrast, potassium (K), a homologous element of sodium, derived from food intake might be a factor that decreases the incidence of hypertension (Adrogué and Madias, 2014; Stone et al., 2016). Those studies indicate that there is a strong contribution of elements such as sodium and potassium via food intake to the prevalence of hypertension.

Arsenic (As) is known as a representative toxic element (Kato et al., 2020; Li et al., 2018; Yajima et al., 2017). Various arsenic-mediated health risks including risks for oncogenic, neurogenic and cutaneous disorders have been reported (Li et al., 2017; Yajima et al., 2018; Zhong et al., 2019). On the other hand, the contribution of arsenic to the prevalence of hypertension has remained unclear because of inconsistent results regarding the association between urinary arsenic level and prevalence of hypertension in previous human studies (Jones et al., 2011; Moon et al., 2013). Moreover, there have been very few studies on the association between serum arsenic level and prevalence of hypertension in humans. Since the serum level of arsenic is greatly affected by last-minute intake of foods (Mandal and Suzuki, 2002), serum level of arsenic might be inappropriate for assessment of arsenic-mediated health risks. However, previous studies indicated that fasting serum levels of arsenic in addition to other elements such as iron, cadmium and mercury are stable (Nguyen et al., 2017; Özel et al., 2019), suggesting that their fasting levels are close to the constitutive serum levels. Fasting serum level of arsenic may therefore be a good marker for assessing the arsenic-mediated health risks including the risk for hypertension in humans.

Japanese food, which was designated as a UNESCO's intangible cultural heritage in 2013, with low calories and low fat has been believed to be healthy food. As represented by sushi, which is a combination of seafood and rice, consumption of seafood containing large amounts of arsenic is a characteristic of Japanese food (Uneyama et al., 2007). Since consumption of seafood has been increasing worldwide due to the increasing popularity of Japanese food, investigation of the health effects of Japanese food is needed to predict food-mediated health effects of Japanese food. However, there has been no study showing an association between a dietary source of arsenic exposure and prevalence of hypertension.

In this study, we measured the fasting levels of serum arsenic in 2,709 adults in Japan. We then investigated the association between serum arsenic level and prevalence of hypertension. We finally identified a specific food that strongly affects the prevalence of hypertension among 54 food items classified into 6 food categories.

2. Methods

2.1. Study population

Subjects in this study were recruited from the second cross-sectional survey of the Japan Multi-Institutional Collaborative Cohort (J-MICC) Daiko Study (Hattori et al., 2016). A total of 2,808 participants aged 39-75 years were recruited from residents of Nagoya City in Japan. Subjects without serum samples (n = 99) were excluded from this study. After careful explanation of our protocol to all participants, informed consent was obtained in writing. The main study protocol was reviewed and approved by the Ethics Committees of Nagoya University Graduate School of Medicine (approval numbers: 2008-0618 and 2013-0070). This study was performed in accordance with relevant guidelines.

2.2. Collection and measurements of biological samples

The method for collecting biological samples was previously reported (Morita et al., 2011). All samples were stored at -80 °C in the Graduate School of Medicine, Nagoya University. Total arsenic concentrations in all serum samples that had been passed through a 0.45-μm filter were measured by an inductively coupled plasma mass spectrometer (ICP-MS; 7500cx, Agilent Technologies) following the method previously described (He et al., 2019; Li et al., 2017; Ohgami et al., 2016).

2.3. Questionnaire survey

The subjects were requested to complete a self-administered questionnaire that included questions on general characteristics, disease history, family history of hypertension, physical activity, and smoking and drinking habits. The participants answered the questions at home to ensure completeness, and accuracy and consistency, trained staff checked the questionnaires with participants face-to-face on the enrollment day.

A validated food-frequency questionnaire (FFQ) consisting of questions on a total of 54 items of food and beverages was used for surveying subjects' dietary habits in the past year. The frequencies of intake of rice, bread and noodles were divided into 6 categories: (1) rarely, (2) 1-3 times monthly, (3) 1 or 2 times weekly, (4) 3 or 4 times weekly, (5) 5 or 6 times weekly and (6) ≥1 time daily. The frequencies of intake of other foods were divided into 8 categories: (1) rarely, (2) 1 or 3 times monthly, (3) 1 or 2 times weekly, (4) 3 or 4 times weekly, (5) 5 or 6 times weekly, (6) once daily, (7) twice daily and (8) 3 times daily. Foods were classified into 6 categories: cereals/beans, livestock/dairy products, seafood, vegetables/fruits, confectionery and beverages. Each category was calculated by summing up all food intake daily in the same classification and was divided into low, medium and high intake groups by tri-sectional quantiles.

Intake of specific seafood items was also divided into low, medium and high intake groups. For fish meat, seaweed and bone-edible small fish, ≤2 times weekly, 3-6 times weekly, and ≥1 time daily were defined as low intake, medium intake and high intake, respectively. For intake of canned tuna, squid/octopus/shrimp/crab, shellfish and fish roe, ≤3 times monthly, 1 or 2 times weekly, and ≥5 times weekly were defined as low intake, medium intake and high intake, respectively. For fish-paste products, ≤2 times weekly, 3 or 4 times weekly, and ≥5 times weekly were defined as low intake, medium intake and high intake, respectively.

2.4. Health examination and assessment of other covariates

Blood pressure was measured twice in a seated position with a standard automated blood pressure measurement monitor (HEM-1000, Omron, Japan). All of the subjects rested for 5 minutes before the first measurement and for 2 minutes before the second measurement (Morita et al., 2011). According to previous studies (Ghosh et al., 2016; Wu et al., 2018), hypertension was defined by one of the following conditions: (1) previous diagnosis of hypertension, (2) systolic blood pressure ≥ 140 mmHg, (3) diastolic blood pressure ≥ 90 mmHg, and (4) currently taking anti-hypertension medicine. Body measurements (height and body weight) were performed by trained staff in health checkups, and body mass index (BMI) was calculated after adjustment for wearing clothes. Information on physical activities during leisure time was obtained in 3 categories: light activity (walking, golf, etc.), moderate activity (jogging, swimming, etc.) and heavy activity (football, marathons, etc.). All activities were reported in frequency and average time per week. Metabolic equivalents (METs) for light, moderate and heavy activities are 3.3, 4.0 and 8.0, respectively, as previously reported (Nishida et al., 2020). METs-hours-per week were calculated to assess physical activity by summing up the multiplications of time spent in each activity.

2.5. Statistical analysis

All analyses were conducted by SPSS (Statistical Package for the Social Sciences) software version 25.0 (SPSS Inc., Chicago, IL, USA). All statistical tests were 2-sided, and $p < 0.05$ was considered to be significant. Values are presented as means ± standard deviations (SDs) and as medians (interquartile ranges) for normal and abnormal distributions, respectively, and as numbers (percentages) for categorical variables. Binary logistic regression was used to investigate the associations between food intake and serum arsenic levels and we considered several variables for inclusion in the final covariates-adjusted model: gender, age, BMI, and smoking and drinking (current or not current) habits as shown previously (Al Hossain et al., 2019). For categorical variables, the lowest group was considered as a reference.

3. **Results**

3.1. Characteristics of subjects.

The subjects of this study were 2709 adults (26.7% males and 73.3% females) in Japan, and the basic characteristics of the subjects are shown in Table 1. The mean age of the subjects was 58.9 years [standard deviation (SD): 9.8 years], and the median of arsenic concentrations in fasting serum was 0.7 [interquartile range (IQR): 2.3] μg/L. Of the 2709 subjects, 697 (25.7%) were diagnosed as having hypertension. Analysis of the median food intake frequencies showed that the highest and lowest intake levels were for beverages and confectionery, respectively. The median intake frequency of seafood was more than once per day.

3.2. Association between serum arsenic level and hypertension.

The association between fasting serum levels of arsenic and prevalence of hypertension is shown in Fig. 1. The cut-off value in serum was determined by the receiver operating characteristic (ROC) curve to be 1.7 μg/L. In the original model, a significant positive association was found between arsenic in fasting serum and hypertension [odd ratios (ORs) with 95% confidence interval (CI): 1.612 (1.348, 1.928), $p < 0.001$]. The significant association remained after adjustment for lifestyle-related factors and family history of hypertension [OR=1.385 (1.137, 1.688), $p = 0.001$] and after adjustment for sodium and potassium levels in fasting serum [OR=1.391 (1.140, 1.698), $p = 0.001$].

3.3. Associations between food intake and serum arsenic level.

The relationships between 6 food categories and fasting serum level of arsenic were investigated by using a covariate-adjusted model (Fig. 2). There was a significant positive association between high intake of seafood and high level of serum arsenic [OR = 1.909 (1.490, 2.447), $p < 0.001$]. In contrast, high intake of livestock/dairy products was negatively associated with serum level of arsenic [OR = 0.644 (0.512, 0.811), $p < 0.001$]. The relative contribution of each food category to arsenic level is shown in Table 2. The contribution of seafood intake to serum level of arsenic was highest (25.3%) among the food categories, followed by livestock/dairy products (9.6%) and vegetables/fruits (4.9%), and the contribution of confectionery intake was the smallest (0.3%). The relative contribution of intake of cereals/beans was not high but was same as the contribution of beverage intake (1.8%) to serum level of arsenic.

3.4. Associations among seafood intake, serum arsenic level and hypertension.

Based on the contribution of seafood to increased serum level of arsenic, the associations between seafood items and fasting serum level of arsenic were investigated by using a covariate-adjusted model (Fig. 3). Analysis of 8 kinds of seafoods indicated that intake of fish meat [medium: OR = 1.387 (1.156, 1.663), $p < 0.001$; high: OR = 1.855 (1.197, 2.877), $p = 0.006$], intake of bone-edible small fish [high: OR = 1.656 (1.084, 2.530), $p = 0.020$], intake of seaweed [OR = 1.413 (1.050, 1.901), $p = 0.022$] and intake of squid/octopus/shrimp/crab [medium: OR = 1.303 (1.058, 1.605), $p = 0.013$] were associated with a high level of serum arsenic. In contrast, intake of canned tuna [high: OR = 0.408 (0.219, 0.761), $p = 0.005$] was negatively associated with serum level of arsenic.

Based on the contribution of 3 specific seafood items (seaweed, bone-edible small fish and fish meat) to serum level of arsenic, the associations between seafood items and prevalence of hypertension were further investigated by using the covariate-adjusted model (Fig. 4). There was a significant association of prevalence of hypertension with intake of fish meat [high: OR = 1.703 (1.045, 2.775), $p = 0.033$] but not with intake of seaweed or intake of bone-edible small fish.

4. **Discussion**

This study demonstrated a novel association between fasting serum level of arsenic and prevalence of hypertension in 2,709 adults in Japan. Our results partially correspond to the results of a previous study showing a positive association between fasting serum level of arsenic and levels of systolic and diastolic blood pressure but not prevalence of hypertension (Gao et al., 2018). These results suggest that an increased fasting serum level of arsenic is a risk factor for hypertension as was previously reported for sodium and potassium (Ekmekcioglu et al., 2016; Radhika et al., 2007; Strazzullo et al., 2001). In previous animal studies, exposure to arsenic has been shown to suppress aortic vasodilation caused by inhibition of endothelial nitric oxide synthase (Lee et al., 2003) and to induce hypertension in rats (Sarath et al., 2014).

In this study, we tried to find the source of serum arsenic. Well drinking water contaminated with arsenic has been shown to be a major source of arsenic in humans in developing countries including Bangladesh (Kato et al., 2013), Vietnam (Ilmiawati et al., 2016) and Afghanistan (Kato et al., 2016). However, drinking water provided as tap water in Japan has been estimated to be a minor (less than 2%) source of exposure to arsenic (Ohno et al., 2010). Since 94% of arsenic was shown to be derived from the diet in Japan (Ohno et al., 2010), the contribution of each Japanese food to fasting serum level of arsenic was further investigated. Seafood was identified as the main contributor to the serum level of arsenic among the foods that were classified into 6 categories according to a previous study (Nanri et al., 2016). Correspondingly, it was estimated by the pseudo R Square test that there was more than 25% contribution of seafood to the serum arsenic level among all of the confounders including food intake. Further analysis focusing on 8 items of seafood showed that seaweed, bone-edible small fish and fish meat are associated with an increase in fasting serum arsenic level. These results suggest that intake of seafood, especially seaweed, bone-edible small fish and fish meat, could be a major source of increase in the fasting serum level of arsenic. The results of our study conducted in Japan correspond to the results of previous studies showing that seafood is a major source of exposure to arsenic in Mediterranean areas and other European countries (Filippini et al., 2018; Miklavčič et al., 2013).

Intake of arsenic from well drinking water has been shown to be an important health risk for people in developing countries (Kato et al., 2020; Kumasaka et al., 2013; Li et al., 2017; Yajima et al., 2018; Yajima et al., 2015). The aim of our study was to elucidate the health risk of arsenic from dietary intake in Japan. A significant association between intake of fish meat and prevalence of hypertension was found in our study. Our results suggest that intake of fish meat is a potential risk for hypertension through increasing the fasting serum level of arsenic. In contrast, intake of seafoods to prevent hypertension was recommended in a previous study (Filippini et al., 2018). Fish consumption per capita in Japan (around 60 kg/year) is the highest in the world (Guillen et al., 2019). Almost half of the participants in our study had a high frequency of fish meat intake (more than 3 times per week). Considering that the level of arsenic in fish meat is higher than the levels in other tissues including the intestine, gills and mouthpieces (Shah et al., 2009), the dietary habit of a high frequency of fish meat intake in Japan may result in the arsenic-mediated hypertension in this study. On the other hand, a salty diet including intake of soy sauce that is used when eating raw fish meat (sashimi) may have a limited effect on the prevalence of hypertension because the positive association between fish meat intake and prevalence of hypertension was maintained after adding information about serum levels of sodium and potassium as confounding factors.

According to the Food and Agriculture Organization (FAO) of the United Nations, the rate of global fish consumption has been increasing and outpacing the rate of world population growth and the rate of consumption of meat from all other animals for the past six decades (FAO, 2020). Thus, arsenic exposure via intake of fish meat is not limited to Japan. Further investigation with a global perspective is needed to assess the health effects of arsenic via intake of fish meat.

5. Conclusion

Individual associations between arsenic levels and intake of food items such as fish meat, shellfish and seaweed have been reported (Filippini et al., 2018). An association between fasting serum level of arsenic and blood pressure has also been reported (Gao et al., 2018). Since exposure to arsenic mainly originates from the diet in Japan (Ohno et al., 2010), individual associations should be comprehensively considered for evaluation of the effect of arsenic exposure via food intake on the prevalence of hypertension. However, there is no direct evidence for associations among food intake, arsenic exposure and prevalence of hypertension. This study demonstrated for the first time that an increased fasting serum level of arsenic caused by intake of fish meat is a potential risk for hypertension. Due to the rapid increase in worldwide consumption of seafood, the effects of arsenic exposure caused by intake of seafood on human health should be addressed.

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Table 1. Basic characteristics of the subjects

Variables	Values
Number of subjects †	2709 (100)
Arsenic levels in fasting serum (μg/L) ‡	0.7 (0 - 2.2)
Age (years) *	58.9 ± 9.8
Male (%) †	724 (26.7)
Body mass index (kg/m^2) *	21.6 ± 3.2
Physical activity (METs/W) †	8.7 (0.9 -18.3)
Current smoker (%) †	193 (7.2)
Current drinker (%) †	1383 (51.1)
Family history of hypertension (%) †	1324 (48.9)
Hypertension †	697 (25.7)
Food intake frequency (times/daily) ‡	
Cereal/beans	4.1 (3.4 - 4.8)
Livestock/dairy products	4.2 (3.1 - 5.3)
Seafood	1.3 (0.8 - 1.8)
Vegetables/fruits	4.5 (3.0 - 6.3)
Confectionery	0.1 (0.1 - 0.4)
Beverages	7.0 (4.7 - 8.9)

† Number (Percentage)

‡ Median (25th - 75th)

* Means ± SD.

Table 2. Pseudo R Square (%) in logistic regression model

Variables		Serum arsenic levels
Food category		
	Seafood	**25.25**
	Livestock/dairy	9.63
	Vegetables/fruits	4.94
	Cereals/bean	1.82
	Beverage	1.82
	Confectionery	0.25
Confounders		
	Age	33.07
	Drinking	0.12
	Smoking	0.07
	BMI	1.82
	Gender	0.60
	Redundancy	20.61

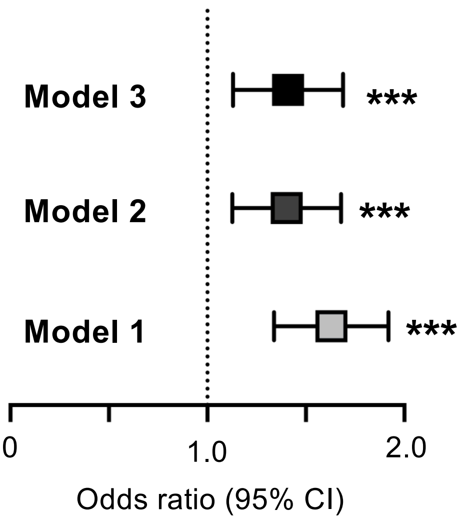

Figure. 1. Associations between serum levels of arsenic and hypertension. Associations between fasting serum level of arsenic and prevalence of hypertension analyzed by logistic regression are shown. **Model 1** is a model without any adjustments, **model 2** was adjusted with age, BMI, smoking, drinking, family history of hypertension and physical activity during leisure time, and **model 3** was adjusted with fasting serum levels of sodium and potassium in addition to the covariates in model 2. *** $P < 0.001$.

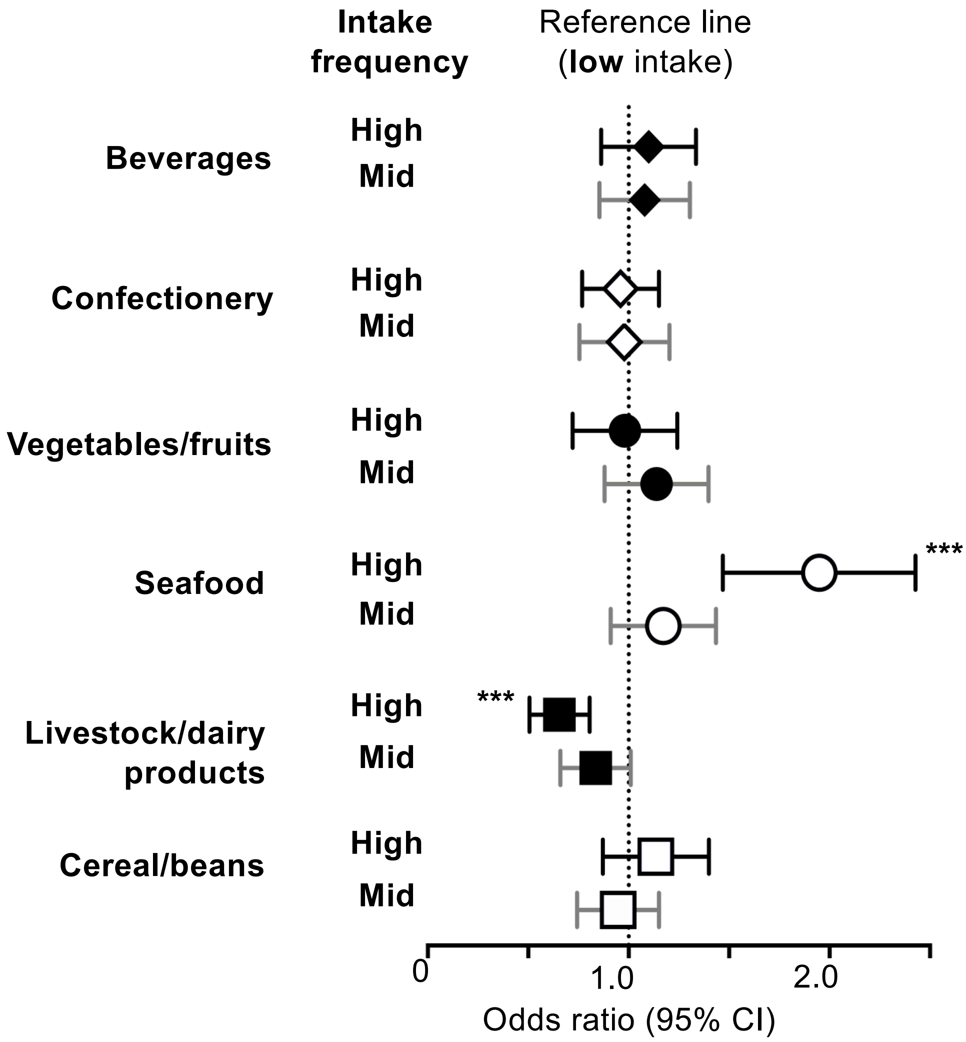

Figure. 2. Associations between frequencies of food intake and serum level of arsenic. Associations between frequencies of intake of cereal/beans, livestock/dairy products, seafood, vegetables/fruits, confectionery and beverages and fasting serum levels of arsenic analyzed by logistic regression are shown. Models were adjusted with age, gender, BMI, smoking and drinking besides food intake. Mid, medium intake; High, high intake; ** $P < 0.01$; *** $P < 0.001$.

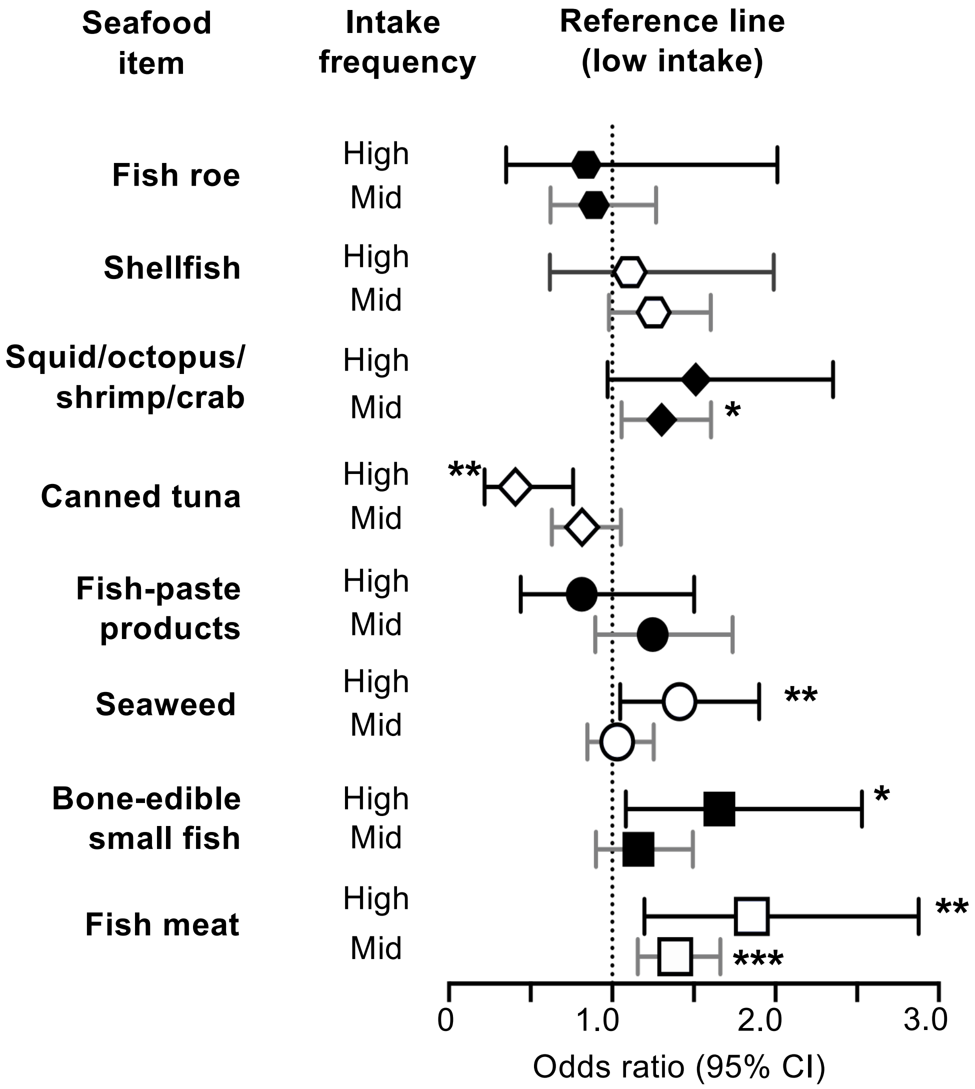

Figure. 3. Associations between frequencies of intake of seafood items and serum levels of arsenic. Associations between frequencies of intake of 8 kinds of seafood items and fasting serum levels of arsenic analyzed by logistic regression are shown. Models were adjusted with age, gender, BMI, smoking and drinking besides seafood intake. Mid, medium intake; High, high intake; * *P* < 0.05; ** *P* < 0.01; *** *P* < 0.001.

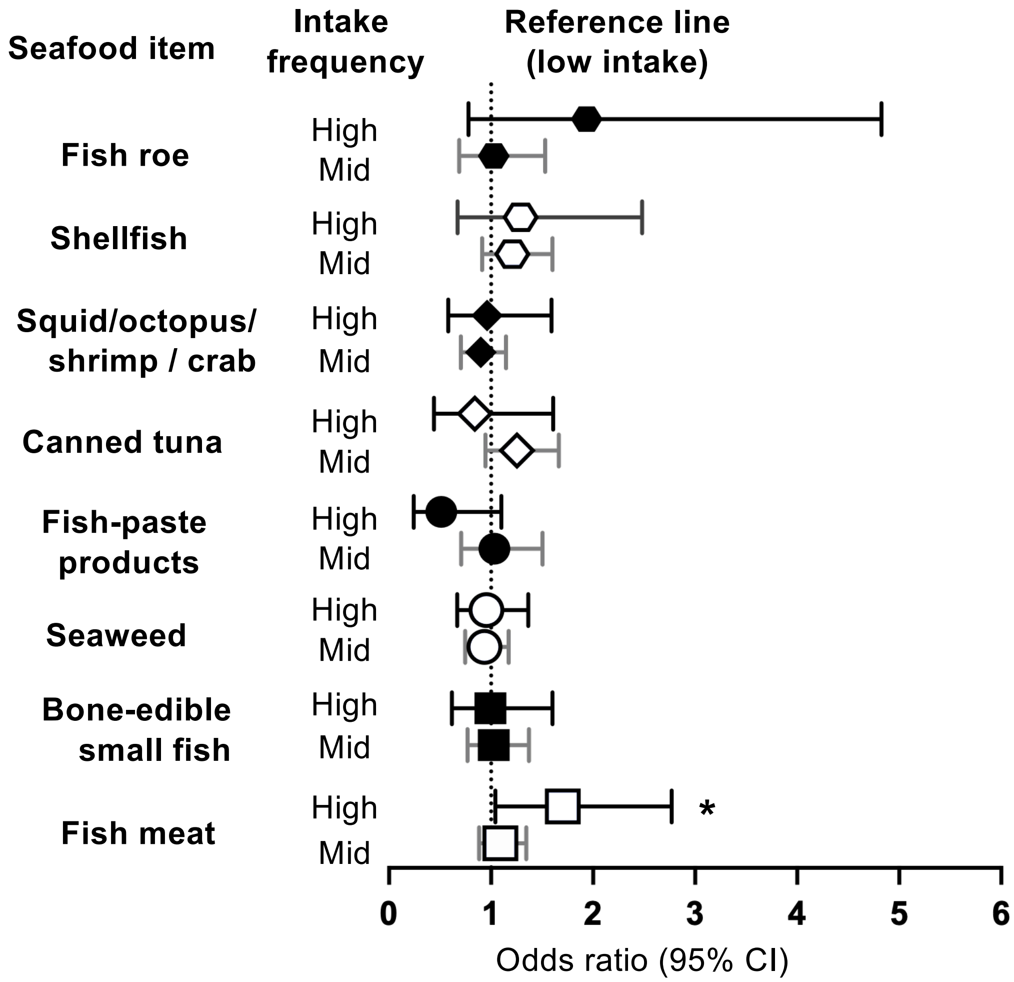

Figure. 4. Associations between frequencies of intake seafood items and hypertension. Associations between frequencies of intake of 8 kinds of seafood items and prevalence of hypertension analyzed by logistic regression are shown. Models were adjusted with age, gender, BMI, smoking, drinking, family history of hypertension, physical activity, and ratios of sodium and potassium in fasting serum besides intake of seafood items. Mid, medium intake; High, high intake; * *P* < 0.05; ** *P* < 0.01; *** *P* < 0.001.