論文の内容の要旨

論文題目

**Oxidative stress in indigenous populations under modernization:**
**Investigation of the determinants and the consequences in Northern Laos**
**（近代化の途上にあるラオス北部少数民族集団の酸化ストレス：**
**その決定要因および健康影響）**

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## General introduction

The progress of health transition possibly differed among populations even with similar extent of modernization. The impact of modernization on oxidative stress is thought to be population-specific; the inter-population variation in NCDs susceptibility under modernization can be explained by focusing on population-specific oxidative stress changes due to modernization. In mountainous areas of Northern Laos, the people in the areas have recently experienced various changes due to modernization; thus, the health transition was expected to progress drastically in the areas. I hypothesized that the study about oxidative stress in rural populations might provide further insight into the roles of population specific oxidative stress among them under the health transition progress; therefore, I conducted a case study in indigenous populations of Northern Laos, to investigate the determinants and consequences of oxidative stress under modernization, with paying special attention to following points:

1) Impact of modernization on trace element exposure.
2) Impact of modernization on oxidative stress.
3) Determinants of oxidative stress.

## Chapter 1: Impact of modernization on trace element exposure

**Objectives:** The impacts of modernization on toxic heavy metal exposure and essential trace element intake in indigenous populations of subsistence societies are unknown. I assessed urinary trace element concentrations in indigenous populations of Northern Laos and examined associations with levels of modernization.

**Methods:** A cross-sectional study was conducted comprising 380 residents of three villages in Northern Laos with different levels of modernization. I surveyed general characteristics and measured the weight and height of 341 participants. Arsenic, cadmium, lead, and selenium concentrations were measured in spot urine samples by inductively coupled plasma mass spectrometry. I examined associations between urinary trace element concentrations and variables related to modernization (village, roofing material, possessions index [total number of possessions], and body mass index) using multilevel analyses with household as a random effect, after adjusting for sex, age, and smoking status.

**Results:** Urinary concentrations of arsenic and cadmium were high, while those of lead and selenium were low in comparison to previous reports of populations in non-contaminated regions or without excess/deficiency. I observed associations between urinary trace element concentrations and village-level modernization: lead and selenium concentrations were higher in more modernized villages and cadmium concentration was highest in the least modernized village. Urinary arsenic concentration was not predicted by the modernization level of a village, although it was lowest in the least modernized village. In addition, urinary selenium concentration was higher in participants inhabiting more modernized houses.

**Conclusion:** Modernization of villages may impact toxic heavy metal exposure and selenium intake in indigenous populations of Northern Laos.

**Chapter 2: Impact of modernization on oxidative stress**

**Objectives:** To clarify the impact of modernization on oxidative stress in ethnic minorities under the drastic health transition process, I investigated difference in oxidative stress among indigenous populations of villages with different levels of modernization in Northern Laos.

**Methods:** Three oxidative stress-related biomarkers were measured: urinary 8-hydroxy-2′-deoxyguanosine (8-OHdG) and 8-isoprostane concentrations were measured by a liquid chromatography-tandem mass spectrometer; blood telomere length was measured by a qPCR. I examined associations between village-level modernization and the oxidative stress-related biomarkers in multilevel analyses considering a random effect and covariates.

**Results:** This study population had lower 8-OHdG and higher 8-isoprostane concentrations in urine in comparisons with previous values reported in healthy adult populations. Higher urinary 8-OHdG concentration and shorter telomere were observed in the participants of more modernized villages, whereas there was no significant difference in urinary 8-isoprostane concentration.

**Conclusion:** Our findings suggested that modernization-induced changes in lifestyle might increase oxidative DNA damage, while oxidative lipid damage was originally high in ethnic minorities of Northern Laos. Oxidative stress might be important factor to clarify the mechanisms of the population-specific health transition.

**Chapter 3: Determinants of oxidative stress**

**Objectives:** Determinants of oxidative stress may partly be population-specific, but studies that investigated them were limited in rural populations. I investigated the determinants of inter-individual variations in several oxidative stress-related biomarkers with paying special attention to changes in trace element exposure an dietary pattern under modernization in indigenous populations of Northern Laos.

**Methods:** I examined associations of urinary arsenic, cadmium, and selenium concentrations, their interaction terms (arsenic or cadmium × selenium), and wild plant food score (a principal component score summarized food consumption frequencies), with oxidative stress-related biomarkers in multilevel analyses considering a random effect and covariates. Associations between oxidative stress-related biomarkers and blood pressure were tested.

**Results:** Urinary arsenic and selenium concentrations were positively associated with urinary 8-OHdG concentration, while the interaction term between urinary arsenic and selenium concentrations was negatively associated with that. Urinary cadmium concentration was positively associated with urinary 8-isoprostane concentration, and the interaction term between urinary cadmium and selenium concentrations was negatively associated with that. Wild plant food score was positively associated with telomere length. Any oxidative stress-related biomarkers were not associated with blood pressure.

**Conclusion:** Our findings suggested that arsenic and cadmium exposure could cause oxidative DNA and lipid damage, respectively, in indigenous populations of Northern

Laos. Individual differences in each of oxidative-related biomarkers might be determined by population-specific changes in environmental factors under modernization.

**General conclusion:**

This case study in Northern Laos clarified the impact of modernization on oxidative stress in ethnic minorities under the drastic health transition progress. Oxidative DNA damage was low in the least modernized village but has increased in more modernized villages by arsenic exposure through consuming wet-grown rice in paddy farming. Oxidative lipid damage might have been originally prevalent because of cadmium exposure from consumption of dry-grown rice in swidden farming. The people in more modernized villages consumed more Se from animal-based foods, protecting oxidative stress induced by arsenic and cadmium exposures. The decrease in wild plant food consumption was expected to shorten telomere. These findings proposed that relationships between oxidative stress-related biomarkers and various determinants among the peoples under modernization were more complex than expected. It was suggested that population-specific experiences of modernization might influence the progress of health transition, and oxidative stress could be a notable intermediate variable.