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Impact of modernization on oxidative stress among indigenous populations in northern Laos

Yuki Mizuno[1] | Yohei Inaba[2] | Hiroaki Masuoka[3] | Mihoko Kibe[1] | Satoko Kosaka[4] | Kazumi Natsuhara[5] | Kazuhiro Hirayama[6] | Nouhak Inthavong[7] | Sengchanh Kounnavong[7] | Shinsuke Tomita[8] | Masahiro Umezaki[1]

[1]Department of Human Ecology, School of International Health, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

[2]Department of Environmental Health, National Institute of Public Health, Saitama, Japan

[3]RIKEN Center for Integrative Medical Sciences, Yokohama, Japan

[4]Department of Public Health and Nursing, Nagasaki University, Nagasaki, Japan

[5]Faculty of Nursing, Toho University, Tokyo, Japan

[6]Graduate School of Agricultural and Life Sciences, The University of Tokyo, Tokyo, Japan

[7]Lao Tropical and Public Health Institute, Ministry of Health, Vientiane, Laos

[8]Graduate School of Environmental Studies, Nagoya University, Nagoya, Japan

Correspondence
Yuki Mizuno, Department of Human Ecology, School of International Health, Graduate School of Medicine, The University of Tokyo, Medical Building No. 3 Annex, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan.
Email: mizuno@humeco.m.u-tokyo.ac.jp

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Abstract

Objectives: To explore the impact of modernization on oxidative stress during a momentous health transition process, we investigated differences in oxidative stress among the indigenous populations of villages in northern Laos with different levels of modernization.

Methods: We conducted a cross-sectional study of 380 adults in three villages with different levels of modernization. Three biomarkers related to oxidative stress were measured: urinary 8-hydroxy-2′-deoxyguanosine (8-OHdG) and 8-isoprostane concentrations (both measured by liquid chromatography–tandem mass spectrometry), and blood telomere length (measured with qPCR). We examined associations between village-level modernization and oxidative stress-related biomarkers in a multilevel analysis including a random effect and covariates.

Results: The geometric means of urinary 8-OHdG and 8-isoprostane concentrations were 2.92 and 0.700 μg/g creatinine, respectively, in our study population. Higher urinary 8-OHdG concentrations and shorter telomeres were observed in participants from the more modernized villages, whereas urinary 8-isoprostane concentrations did not differ significantly among villages.

Conclusions: Our findings imply that modernization-induced changes in lifestyle may increase oxidative DNA damage. Baseline levels of oxidative lipid damage are expected to be high in the indigenous populations of northern Laos. Assessments of oxidative stress may provide valuable insights into the mechanisms of health transition in specific populations.

KEYWORDS
8-isoprostane, 8-OHdG, modernization, northern Laos, oxidative stress

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1 | INTRODUCTION

According to the "health transition" theory (Riley, 2001), the disease burden shifts from communicable to non-communicable diseases (NCDs) when a population experiences modernization, which is defined as the process of adopting the technologies, lifestyles, and social norms of economically developed populations. Additionally, the health transition process varies among populations with similar degrees of modernization. For example, the prevalence of obesity in women differs greatly among countries with similar gross national products (Monteiro et al., 2004). The rates of cardiovascular disease-related mortality and cancer-related mortality are high in rural areas of Bangladesh, despite the absence of significant modernization (Ahsan Karar et al., 2009). This interpopulation variability in susceptibility to NCDs during modernization is typically explained by population-level differences in genetic traits, indigenous dietary habits, and/or physical activity patterns (Enas & Mehta, 1995; Hales & Barker, 1992; Lee et al., 2012; Nazroo, 1998; Popkin et al., 2009). In the present study, we hypothesized that oxidative stress, in addition to the factors mentioned above, plays a mediating role between modernization and health transition in northern Laos.

Oxidative stress comprises an imbalance between oxidation and antioxidant systems in the body (Yoshikawa & Naito, 2002). It is a known risk factor for NCDs (Maritim et al., 2003; Reuter et al., 2010; Siti et al., 2015). Recent studies have suggested that individuals' oxidative stress levels fluctuate according to chemical exposure, dietary composition, physical activity, and lifestyle factors such as smoking and alcohol consumption (Aseervatham et al., 2013), all of which can be affected by modernization. Importantly, some such changes (e.g., increased agrochemical exposure and animal protein consumption) may increase oxidative stress, while others (e.g., reduced smoking and improved nutritional status) may decrease oxidative stress. Therefore, the impact of modernization on oxidative stress is population-specific. A portion of the interpopulation variability in modernization-related susceptibility to NCDs during modernization may be explained by population-specific changes in oxidative stress that result from modernization.

In mountainous areas of northern Laos, where our study population resides, indigenous subsistence living was maintained until recent years because of the geographic remoteness of the areas. However, the people in these areas have begun to experience changes caused by modernization: swidden cultivation has been replaced by paddy cultivation; villagers collect wild edible plants less frequently than before, more people grow vegetable crops for money, and the consumption of animal meat and energy-dense Chinese-style food has gradually increased (Kibe et al., 2022). These changes have been driven primarily by economic investment from Chinese companies and rural development projects implemented by the Lao government (Thongmanivong & Fujita, 2006). Consequently, these areas are in the process of health transition. The percentage of deaths in Laos related to NCDs increased from 39.8% in 2000 to 65.3% in 2019 (World Health Organization, 2020). Similar trends are anticipated in mountainous areas of northern Laos.

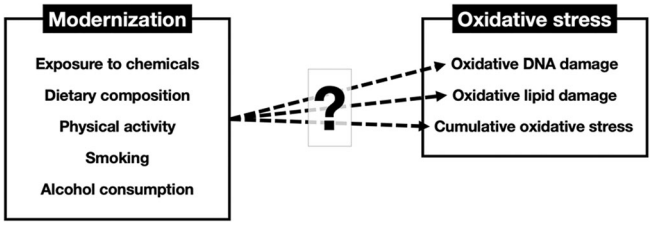

FIGURE 1 Conceptual diagram of this study.

Individual-level oxidative stress can be assessed by examining various biomarkers, each of which can reflect different aspects of oxidative stress. Urinary concentrations of 8-hydroxy-2′-deoxyguanosine (8-OHdG: oxidized deoxyguanosine) and 8-isoprostane (a prostaglandin-like compound formed from arachidonic acid peroxidation) are the most commonly used biomarkers of oxidative stress, reflecting oxidative damage to DNA (Graille et al., 2020a; Kasai, 1997; Kasai et al., 1984, 2008; Loft et al., 1992) and lipids (Davì et al., 2004; Graille et al., 2020b; Roberts II & Morrow, 2002), respectively. Additionally, blood telomere length is a recognized indicator of cumulative oxidative stress. Telomeres have a guanine-rich structure that is susceptible to reactive oxygen species (ROS) (Babizhayev, Savel'yeva, et al., 2011; Blackburn, 1991; Houben et al., 2008; O'Donovan et al., 2011; Wong et al., 2014), and they shorten with every cell division, attrition of which can be accelerated under oxidative stress.

Figure 1 shows the conceptual framework of the present study. We regarded the following variables as indicators of inter- and intra-village variations in the extent of modernization in northern Laos: chemical exposure, dietary intake, physical activity, and lifestyle (e.g., smoking and alcohol consumption). These variations in modernization-related variables might cause inter- and intra-population variations in oxidative DNA damage and lipid damage or cumulative oxidative stress.

The objective of the present study was to examine the associations between modernization and three oxidative-stress-related biomarkers (urinary 8-OHdG and 8-isoprostane concentrations, and telomere length in blood DNA) among the indigenous populations of northern Laos. This case study will provide further insights into changes in oxidative stress in ethnic minorities undergoing the health transition process.

2 | MATERIALS AND METHODS

2.1 | Study population and sampling

The characteristics of the study population have been described elsewhere (Mizuno et al., 2022). In brief, the study was conducted in three villages in Oudomxay Province, northern Laos: Nam Nyon (the least modernized), Na Savang (somewhat modernized), and Na Lae (the most modernized). Nam Nyon is in a remote mountainous area, where residents maintain a subsistence lifestyle through swidden cultivation and gathering wild plants; some households started paddy cultivation

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recently. Na Savang is in a flat basin, where irrigated wet rice farming is practiced. Access to a commercial center in Namo (district capital) is far easier from Na Savang than from Nam Nyon. Na Lae is a village near the provincial capital (Oudomxay), where people have a market-oriented lifestyle, purchasing most of their foods from markets and shops throughout the year. A total of 380 residents consented to participate in this study.

The study was conducted in August 2018 in Na Lae, and in March 2019 in Nam Nyon and Na Savang. Nam Nyon is an isolated village with a well-defined boundary. We asked the village leader to recruit participants from among all villagers who were aged ≥18 years in March 2019 ($n = 146$). The participation rate was approximately 74% (108/146). In contrast, Na Savang and Na Lae are larger villages with some satellite hamlets (the overall population of each village was approximately 1000). The village leaders used loudspeakers to recruit the participants, and it was unclear how many villagers were reached by loudspeaker announcements. The participants ($n = 150$ in Na Savang and $n = 83$ in Na Lae) were individuals who heard the announcement and visited the location of the survey. Therefore, the participation rates for these villages could not be calculated.

The participants were invited to each village's community center. The samples in Nam Nyon were collected in the dry season, when equipment for sampling could be transported by car. The samples in Na Savang were also collected in the dry season for comparison with samples collected in Nam Nyon. In both villages, there was considerable seasonality in dietary intake and physical activity. In contrast, in Na Lae, samples were collected in the rainy season. Our pilot study showed minimal seasonal changes in behavioral and dietary pattern among participants in Na Lae, presumably because Na Lae is located in the provincial capital; most of the participants worked in urban areas and purchased foods in local markets or shops throughout the year. Thus, we assumed that the samples collected in Na Lae in the rainy season were comparable with samples collected in the other two villages in the dry season.

We invited people from the villages to participate if they had neither a high fever nor diarrhea on the survey days. We interviewed the participants and recorded their sex, age, smoking status (smoker/non-smoker), and drinking habits (yes/no). Household IDs provided by the government of Laos were collected from all participants. Height was measured to the nearest millimeter using a mobile stadiometer (Holtain Ltd., Crosswell, UK), and body weight with minimum clothing was measured to the nearest 100 g using a digital scale (Tanita, Tokyo, Japan). We collected completed questionnaires, anthropometric data, and biological samples from 341 participants.

We obtained written informed consent from each participant before the survey. This study was approved by the research ethics committee of the Graduate School of Medicine, University of Tokyo (approval number: 12033-(3)) and the National Ethics Committee for Health Research (NECHR), Ministry of Health, Lao PDR (approval number: 2018.22.MP). The procedures used in this study conformed to the tenets of the Declaration of Helsinki.

2.2 | Sample collection and analysis

Urine samples were collected in each village; after collection, the samples were frozen in an ordinary freezer (−15°C) and then transported to a deep freezer (−80°C) in the laboratory of the Laos Tropical and Public Health Institute in Vientiane. The samples were finally transported with sufficient numbers of ice packs to the laboratory at the University of Tokyo and stored at −80°C until analysis of 8-OHdG and 8-isoprostane. The urine samples never experienced a freeze–thaw cycle after collection. Dried blood spot samples were kept at room temperature during transportation from the village to the laboratory at the University of Tokyo, then stored at −80°C until analysis of telomere length. Urinary 8-OHdG and 8-isoprostane concentrations were measured during the period between November 2019 and July 2020, and telomere length was measured during the period between January and February 2020. Thus, all measurements were completed within 2 years from the time of sample collection, which ensured the reliability of the measured values was not compromised because of long-term storage (Matsumoto et al., 2008).

We measured urinary 8-OHdG and 8-isoprostane concentrations using liquid chromatography–tandem mass spectrometry (LC–MS/MS) following solid-phase extraction (Inaba et al., 2011; Oba et al., 2019). Urine was processed with a C18 solid-phase extraction cartridge (YMC Co., Ltd., Kyoto, Japan) for both 8-OHdG and 8-isoprostane. For 8-isoprostane only, further extraction followed using ENVI-Carb™ cartridges (Merck KGaA, Darmstadt, Germany). For LC–MS/MS we used a Xevo TQ-S spectrometer (Waters, Milford, MA, USA) with C18 columns in multiple-reaction-monitoring (MRM) mode. Electrospray ionization was positive for 8-OHdG and negative for 8-isoprostane. MassLynx software (Waters, Milford, MA, USA) was used to generate the chromatogram, detect peaks, calculate the area of a peak, generate calibration curves, and calculate concentrations of analytes. The limits of quantitation were 0.05 and 0.1 μg/L for 8-OHdG and 8-isoprostane, respectively; the detection rate was 100% for both. To adjust for the dilution effect, urine specific gravity and urinary creatinine concentration were measured (Mizuno et al., 2022).

We used urine specific gravity rather than urinary creatinine to adjust for urinary dilution, because it has been suggested that use of urine specific gravity is more appropriate than adjustment for creatinine in populations with large interindividual variations in muscle mass and meat intake (Suwazono et al., 2005), as was the case in our study population. We also calculated creatinine-adjusted concentrations to allow comparison of our results with those of previous studies.

We also measured telomere length in DNA. Chromosomal DNA was extracted from six DBS punches (3 mm in diameter) using a QIAamp DNA Investigator Kit (Qiagen, Hilden, Germany) in accordance with the manufacturer's protocol. Telomere length was measured by the quantitative polymerase chain reaction (qPCR) method (Cawthon, 2002; Mizuno, et al., 2021) using tel1-tel2 and 36B4u-36B4d primer sets on a LightCycler Nano instrument (Roche, Penzberg, Germany). This method provides the ratio of telomere repeat copy number (T) to single-copy gene number (S) (i.e., the T/S ratio).

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TABLE 1 Characteristics of the study participants by villages.

	All ($n = 341$)	Nam Nyon ($n = 108$)	Na Savang ($n = 150$)	Na Lae ($n = 83$)	p for difference among village
Number of households	210	43	97	70	–
Sex[a]					
Male	134 (39)	50 (46)	60 (40)	24 (29)	0.05[b]
Female	207 (61)	58 (54)	90 (60)	59 (71)	
Age (years)[c]	40 ± 11	35 ± 12	43 ± 11	43 ± 10	<0.001[d]
Smoking[a]					
Smoker	85 (25)	44 (41)	29 (19)	12 (14)	<0.001[b]
Non-smoker	256 (75)	64 (59)	121 (81)	71 (86)	
Drinking[a]					
Yes	169 (50)	50 (46)	71 (47)	48 (58)	0.22[b]
No	172 (50)	58 (54)	79 (53)	35 (42)	
Body mass index (kg/m^2)[c]	23.1 ± 3.7	22.3 ± 3.5	22.9 ± 3.4	24.6 ± 3.9	<0.001[e]
Underweight[a,f]	20 (6)	13 (12)	6 (4)	1 (1)	
Normal[a,f]	228 (67)	73 (68)	107 (71)	48 (58)	
Overweight[a,f]	72 (21)	18 (17)	30 (20)	24 (29)	
Obesity[a,f]	21 (6)	4 (4)	7 (5)	10 (12)	

[a]*n* (%).
[b]Chi-square test.
[c]Mean ± standard deviation.
[d]Kruskal–Wallis test.
[e]One-way analysis of variance.
[f]Underweight: BMI < 18.5; normal: 18.5 ≤ BMI < 25; overweight: 25 ≤ BMI < 30; obesity: 30 ≤ BMI.

2.3 | Statistical analysis

Urinary 8-OHdG and 8-isoprostane concentrations were adjusted for specific gravity and logarithmically transformed to approximate a normal distribution. We investigated differences among the villages in sex, smoking status, and drinking habits using the chi-square test; differences in age using the Kruskal-Wallis test; and differences in body mass index (BMI) using one-way analysis of variance (ANOVA). Following these bivariate analyses, we performed a multilevel analysis with household as a random effect to examine the associations between the modernization level of the villages and oxidative stress-related biomarkers after adjusting for covariates (sex, age, smoking status, drinking habits, and BMI). The least squares means of oxidative stress-related biomarkers were also calculated; Dunnett's test was performed for multiple comparisons of biomarkers among the three villages, using Nam Nyon as the reference village (Nam Nyon vs. Na Savang/Na Lae). All analyses were performed using R software (version 4.1.0; R Development Core Team, Vienna, Austria).

3 | RESULTS

Table 1 shows the participants' characteristics. The study population comprised 108 participants from 43 households in Nam Nyon, 150 participants from 97 households in Na Savang, and 83 participants from 70 households in Na Lae. In Nam Nyon, the least modernized village, the participants tended to be younger and had lower BMI values than those in more modernized villages ($p < 0.01$). There was also a higher proportion of smokers in Nam Nyon than in the other villages ($p < 0.001$).

Table 2 shows the geometric means (GMs) and geometric standard deviations (GSDs) for the specific gravity-adjusted urinary 8-OHdG and 8-isoprostane concentrations, and the arithmetic means (AMs) and standard deviations (SDs) of telomere length. The unadjusted and creatinine-adjusted urinary 8-OHdG and 8-isoprostane concentrations are shown in Tables S1 and S2.

Table 3 shows the associations between the modernization level of villages and urinary 8-OHdG and 8-isoprostane concentrations and telomere length. In the multilevel analysis, the lowest urinary 8-OHdG concentration and the longest telomeres were observed in the least modernized village (Nam Nyon). Urinary 8-isoprostane concentrations did not differ by village. Males had lower urinary 8-isoprostane concentrations than females, and smokers had higher urinary 8-isoprostane concentrations than non-smokers. BMI values were negatively associated with urinary 8-OHdG concentration and positively associated with urinary 8-isoprostane concentration (see Figure 2 and Table S3 for a comparison of the least squares means of oxidative stress-related biomarkers among the villages). The results did not change when using creatinine-adjusted oxidative stress-related biomarkers (Table S3).

Figure 3 shows scatterplots of telomere length and urinary 8-OHdG and 8-isoprostane concentrations. Telomere length was negatively correlated with urinary 8-OHdG concentration ($r = -0.15$, 95% confidence interval $= -0.25, -0.04$), but not significantly

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TABLE 2 Urinary 8-OHdG and 8-isoprostane concentrations and telomere length of the study participants by villages.

	All ($n = 341$)		Nam Nyon ($n = 108$)		Na Savang ($n = 150$)		Na Lae ($n = 83$)	
	GM	(GSD)	GM	(GSD)	GM	(GSD)	GM	(GSD)
8-OHdG[a]	3.89	(1.77)	3.27	(1.63)	4.23	(1.80)	4.18	(1.80)
8-isoprostane[a]	0.934	(1.58)	0.941	(1.47)	0.908	(1.63)	0.973	(1.64)
	AM	(SD)	AM	(SD)	AM	(SD)	AM	(SD)
Telomere length[b]	0.80	(0.11)	0.84	(0.12)	0.79	(0.11)	0.76	(0.10)

Abbreviations: 8-OHdG, 8-hydroxy-2′-deoxyguanosine; AM, arithmetic mean; GM, geometric mean; GSD, geometric standard deviation; SD, standard deviation.
[a]Specific gravity-adjusted urinary concentration (μg/L).
[b]T/S ratio determined by the qPCR method.

TABLE 3 Associations between village and oxidative stress-related biomarkers: results of multiple linear regression analyses ($n = 341$).

		8-OHdG (μg/L)[a]		8-isoprostane (μg/L)[a]		Telomere length[b]	
Fixed effects		**Coef.**	**(95% CI)**	**Coef.**	**(95% CI)**	**Coef.**	**(95% CI)**
Village (ref. = Nam Nyon)	Na Savang	0.26	(0.10, 0.41)**	−0.04	(−0.17, 0.08)	−0.052	(−0.085, −0.019)**
	Na Lae	0.31	(0.13, 0.48)***	−0.01	(−0.16, 0.14)	−0.085	(−0.122, −0.047)***
Sex (ref. = Female)	Male	0.08	(−0.09, 0.26)	−0.15	(−0.29, 0.00)*	−0.018	(−0.052, 0.016)
Age (years)		0.00	(0.00,0.01)	0.00	(0.00, 0.01)	−0.001	(−0.002, 0.000)
Smoking status (ref. = Non-smoker)	Smoker	−0.05	(−0.25, 0.15)	0.20	(0.04, 0.37)*	−0.002	(−0.041, 0.036)
Drinking habit (ref. = No)	Yes	−0.03	(−0.16, 0.10)	0.02	(−0.08, 0.13)	−0.003	(−0.029, 0.022)
Body mass index (kg/m^2)		−0.03	(−0.05, −0.01)*	0.01	(0.00, 0.03)*	0.001	(−0.003, 0.004)
Random effect		Var.	ICC (%)	Var.	ICC (%)	Var.	ICC (%)
Household-level		0.01	2.79	0.02	8.28	0.003	25.00
Individual-level		0.29		0.19		0.009	

Note: *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.
Abbreviations: 8-OHdG, 8-hydroxy-2′-deoxyguanosine; CI, confidence interval; ICC, intra-class correlation.
[a]Specific gravity-adjusted and log-transformed.
[b]T/S ratio determined by the qPCR method.

correlated with urinary 8-isoprostane concentration ($r = -0.01$, 95% confidence interval = −0.12, 0.10).

4 | DISCUSSION

This study compared three oxidative stress-related biomarkers among three villages in northern Laos with different levels of modernization. We found the lowest urinary 8-OHdG concentration and the longest telomeres in the least modernized village (Nam Nyon), but urinary 8-isoprostane concentrations did not differ according to village.

4.1 | Urinary 8-OHdG and 8-isoprostane concentrations among indigenous populations in northern Laos

For evaluation of the urinary 8-OHdG and 8-isoprostane concentrations observed in the present study, we collected the results of comparable studies conducted in apparently healthy adults because previous studies that reported urinary 8-OHdG and 8-isoprostane concentrations could generally be grouped into two categories: studies that were conducted in "general" populations in a community setting and studies conducted in hospitals that targeted patients with diagnosed diseases. Because the present study was conducted in villages in northern Laos, we sought to compare the results with non-hospital or "general" populations in other regions. Notably, general populations may include some individuals with NCDs; this is a natural characteristic of contemporary human populations. However, we excluded studies from our comparison if they involved the recruitment of patients with specific diseases in hospitals. Studies that used immunological assays (e.g., the enzyme-linked immunosorbent assay [ELISA]) for measurements of 8-OHdG and 8-isoprostane were also excluded from the comparison because these measures are considerably less accurate and not comparable with the results obtained by chromatography methods (e.g., LC with MS or electrochemical detection) (Barregard et al., 2013; Klawitter et al., 2011). After application of the two exclusion criteria mentioned above, eight studies in Asia and the USA remained eligible for inclusion in the comparison.

Table 4 compares the urinary 8-OHdG and 8-isoprostane concentrations observed in this study with the concentration reported in

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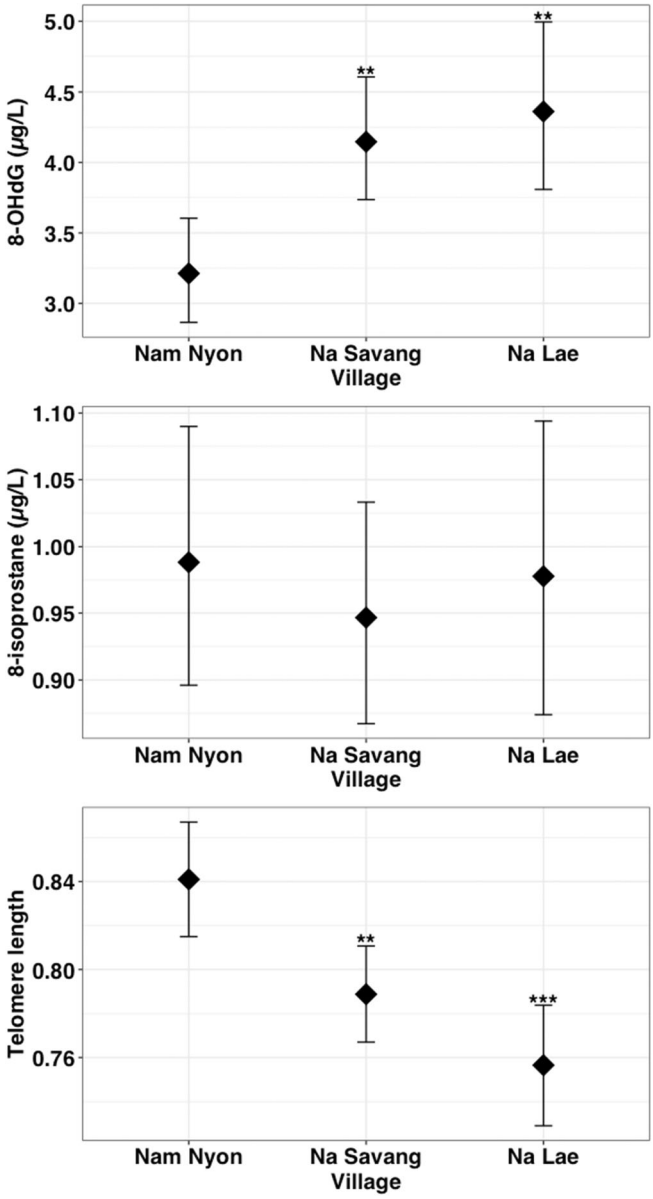

FIGURE 2 The least squares means of urinary 8-OHdG and 8-isoprostane concentrations (specific gravity-adjusted) and telomere length in each village. The least squares means were analyzed using multilevel models adjusted for sex, age, smoking status, drinking habits, and body mass index. Household ID was included as a random effect. Closed squares represent the least squares means, and error bars indicate the 95% confidence interval. Telomere length is determined by the qPCR method (i.e., T/S ratio). Differences between villages were examined by Dunnett's test (Nam Nyon vs. Na Savang/Na Lae). $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$. 8-OHdG, 8-hydroxy-2′-deoxyguanosine.

previous studies (Il'yasova et al., 2018; Kim et al., 2011; Nakano et al., 2003; Pan et al., 2008, 2018; Shimanoe et al., 2018; Wong et al., 2008; Yuan et al., 2018). The mean urinary 8-OHdG concentration was lower in the present study than in previous studies, whereas the mean urinary 8-isoprostane concentration was higher in the present study than in previous studies. Our study population might exhibit lower oxidative DNA damage and higher oxidative lipid damage compared with the previously reported values for apparently healthy adults, although these findings might be biased because of the small number and high heterogeneity of included studies ($n = 8$).

4.2 | Associations of modernization level with urinary 8-OHdG and 8-isoprostane concentrations and telomere length

The comparison of oxidative stress-related biomarkers among the villages found that higher urinary 8-OHdG concentrations and shorter telomeres were observed in the more modernized villages, whereas urinary 8-isoprostane concentrations did not differ by village.

The participants in this study had urinary 8-OHdG concentrations that were below the range reported in previous studies. We suspect that some of the lifestyle changes related to modernization might lead to the exacerbation of oxidative DNA damage (Aseervatham et al., 2013; Banerjee et al., 2001; Longo & Fontana, 2010; Macho-González et al., 2020). Conversely, the urinary 8-isoprostane concentrations in our participants were at the high end of the range of values reported in previous studies. Oxidative lipid damage may have historically been high in the indigenous populations of northern Laos, presumably because of certain characteristics of their indigenous lifestyle (Aseervatham et al., 2013; Nasca et al., 2010; Sakano et al., 2009). This damage might not have been exacerbated by modernization-induced lifestyle changes. Previous studies have also used urinary 8-OHdG and 8-isoprostane concentrations as biomarkers of oxidative stress, but there has been limited research concerning differences in determinants of urinary 8-OHdG and 8-isoprostane concentrations (Gao et al., 2017; Kordas et al., 2018; Lai et al., 2016; Sakano et al., 2009; Xie et al., 2019). The origin of the differential responses of urinary 8-OHdG and 8-isoprostane concentrations to modernization remains unclear.

Because 8-OHdG is excreted into the urine during the course of base-excision repair of oxidative DNA damage (David et al., 2007), urinary 8-OHdG concentrations can reflect both oxidative DNA damage and its repair (Cooke et al., 2005; Il'yasova et al., 2012; Wilson et al., 2011). Modernization-related lifestyle changes are expected to increase the capacity for DNA repair. For example, zinc intake is higher among people in more modernized villages because the people in these villages consume larger amounts of animal-based foods, which include abundant zinc (Salter, 2018; York & Gossard, 2004). Zinc is an essential component of enzymes involved in the repair of oxidative DNA damage (e.g., 8-oxoguanine glycosylase) (McAfee et al., 2010; York & Gossard, 2004). Accordingly, higher urinary 8-OHdG concentrations in more modernized villages might be the results of modernization-induced oxidative stress, as well as modernization-enhanced DNA repair capacity. Further studies are needed to more fully characterize the modernization-related lifestyle changes associated with oxidative DNA damage and improvements in DNA repair capacity.

Telomere length is regarded as a biomarker of cumulative oxidative DNA damage (Babizhayev, Savel'yeva, et al., 2011; Barnes et al., 2019), and differences in telomere length among the villages were consistent with differences in urinary 8-OHdG concentrations. Indeed, telomere length and urinary 8-OHdG concentration were negatively correlated.

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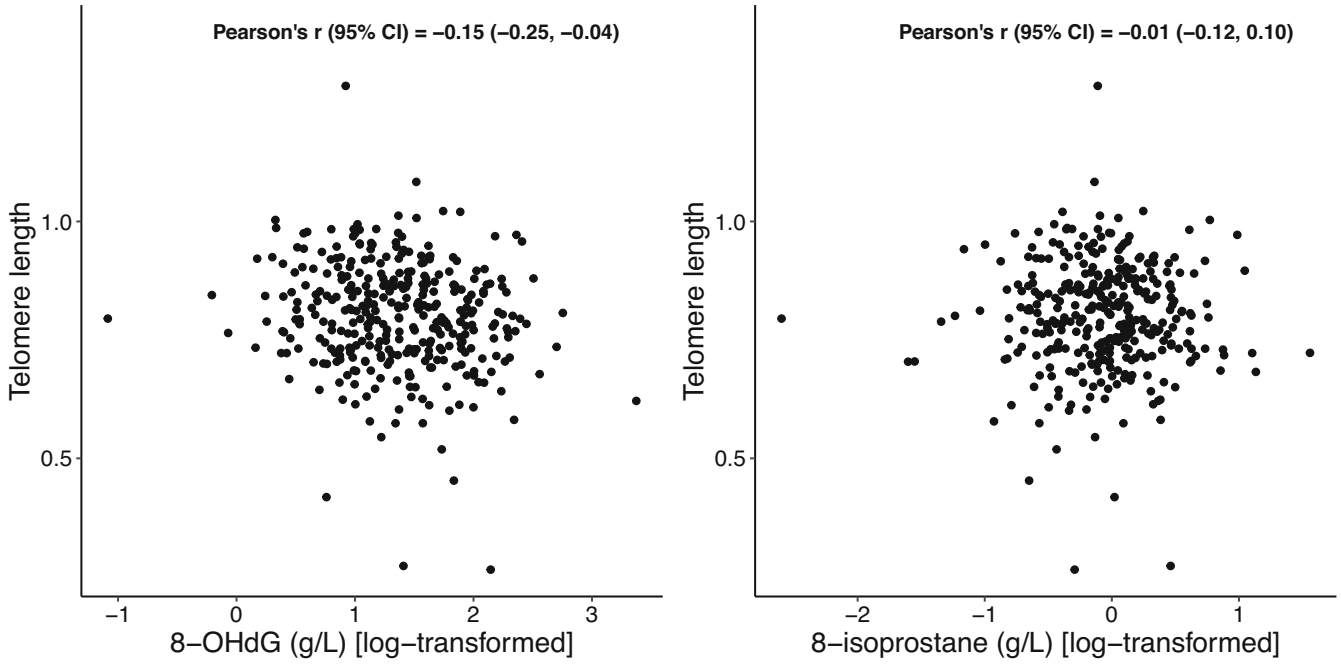

FIGURE 3 Correlations between telomere length and urinary 8-OHdG and 8-isoprostane concentrations ($n = 341$). Telomere length is the T/S ratio determined by the qPCR method. Urinary 8-OHdG and 8-isoprostane concentrations were adjusted for specific gravity and logarithmically transformed. 8-OHdG, 8-hydroxy-2′-deoxyguanosine; CI, confidence interval.

TABLE 4 Comparisons of urinary 8-OHdG and 8-isoprostane concentrations between the present and previous studies conducted in "general" populations in community setting.

	Location	*n*	Age (years)[a]	BMI (kg/m^2)[a]	Concentration (μg/g creatinine)		Reference
					GM	AM	
8-OHdG	Laos	341	40	23.1	2.92	3.48	This study
	Japan	6517	60.3	22.7	3.9		Shimanoe et al. (2018)
	Japan	2507	51[b]	NA		4.52	Nakano et al. (2003)
	China	185 (non-smokers)	40.4	24.4	5.5		Pan et al. (2008)
	Taiwan	125 (males, non-smokers)	34.1	22.8	4.1		Pan et al. (2018)
	Taiwan	129	51.7	24.6		4.3	Wong et al. (2008)
	Korea	102 (females, non-smokers)	55	24.1		6.5	Kim et al. (2011)
8-isoprostane	Laos	341	40	23.1	0.700	0.780	This study
	China	610 (males)	57.1	22.1	0.402		Yuan et al. (2018)
	USA	143	38.0	25.2		0.209	Il'yasova et al. (2018)
	USA	75	37.9	25.1		0.211	Il'yasova et al. (2018)

Note: Previous studies were searched for the most recent systematic reviews of the two biomarkers (Graille et al., 2020a, 2020b). We excluded a subset of the previous studies because those studies involved very limited number of study populations.
Abbreviations: 8-OHdG, 8-hydroxy-2′-deoxyguanosine; AM, arithmetic mean; BMI, body mass index; GM, geometric mean.
[a]AM of age/BMI in study populations.
[b]Median.

Some recent studies have shown that differences in telomere length in adults are determined primarily by telomere length at birth (Benetos et al., 2013, 2019; Cui et al., 2016) and that telomere length can be inherited (Broer et al., 2013; Kim et al., 2020). Thus, the differences in telomere length among the villages in the present study may reflect the influences of indigenous population-specific oxidative stress and modernization-induced oxidative stress.

4.3 | Oxidative stress-related biomarkers and risks for NCDs

Elevated oxidative stress has been observed among patients with NCDs, including cardiovascular diseases, diabetes, and cancer (Davì et al., 2004; Patrignani & Tacconelli, 2005; Rizvi et al., 2015; Wu et al., 2004). Here, we discuss the potential risk of an elevated urinary

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8-OHdG concentration in more modernized villages and the historically high urinary 8-isoprostane concentration in the study villages. Only studies that used chromatography methods for the measurement of urinary 8-OHdG and 8-isoprostane concentrations were considered in our review of these topics because absolute values from the ELISA method are not comparable (Barregard et al., 2013; Klawitter et al., 2011).

Because the urinary concentration of 8-OHdG is presumed to reflect oxidative DNA damage, some studies have investigated the impact of elevated urinary 8-OHdG concentration on carcinogenic diseases. For example, a follow-up study of middle-aged adults in Taiwan (mean age of 58 years at baseline) showed that individuals who had a higher baseline urinary 8-OHdG concentration (>6.26 μg/g creatinine) exhibited a greater risk of bladder cancer (hazard ratio = 5.1), compared with individuals who had a lower baseline urinary 8-OHdG concentration (≤6.26 μg/g creatinine) (Tsai et al., 2021). A case–control study in Taiwan showed that the odds ratio of renal cell carcinoma was 1.6 for a 1 μg/g creatinine increase in the urinary 8-OHdG concentration among middle-aged individuals whose mean urinary 8-OHdG concentrations were 4.81 (patients) and 3.68 (controls) μg/g creatinine (Huang et al., 2012). In studies that showed an association between urinary 8-OHdG concentration and carcinogenic diseases, the range of urinary 8-OHdG concentrations among participants was higher than the values observed in the present study (mean creatinine-adjusted urinary 8-OHdG concentrations: 2.60 μg/g creatinine in Nam Nyon, 4.02 μg/g creatinine in Na Savang, and 3.65 μg/g creatinine in Na Lae). The exception was a study conducted in Saudi Arabia that reported higher odds of diabetes among participants with urinary 8-OHdG concentrations in the range of 2.48–5.20 μg/L than among participants with urinary 8-OHdG concentrations below 1.36 μg/L (Li et al., 2019). The urinary 8-OHdG concentrations observed in the present study were comparable with the concentration among participants who exhibited higher odds of diabetes in Saudi Arabia (see Tables S1 and S2 for the unadjusted urinary 8-OHdG concentrations observed in the present study). In summary, the modernization-induced elevation of oxidative DNA damage in the study villages may not have reached the level associated with increased risks of carcinogenic diseases, but it has the potential to increase the risk of diabetes in the indigenous populations of northern Laos.

The urinary 8-isoprostane concentration reflects oxidative lipid damage; thus, an elevated concentration can be associated with the onset of cardiovascular diseases through the acceleration of plaque formation (Davies & Roberts, 2011; Zhong et al., 2019). A cohort study among middle-aged women in the Netherlands showed that the odds of cardiovascular disease was 1.8-fold higher for the participants in the group with the highest quartile of urinary 8-isoprostane concentration than for participants in groups with the lowest three quartiles (mean urinary 8-isoprostane concentrations were 0.27 [<60 years] and 0.24 [≥60 years] μg/g creatinine) (Roest et al., 2008). A case–control study in Germany revealed higher odds for coronary heart disease among individuals with urinary 8-isoprostane concentrations of 0.251–0.407 μg/g than among individuals with urinary 8-isoprostane concentrations below 0.251 μg/g creatinine (Schwedhelm et al., 2004). Because the urinary 8-isoprostane concentrations observed in the present study were higher than the concentrations reported in the previous studies, we suspect that historically high urinary concentrations of 8-isoprostane in the study villages in northern Laos led to an increased risk of cardiovascular diseases among these indigenous populations. This historically high urinary concentration of 8-isoprostane in the study villages merits further exploration.

4.4 | Limitations

First, our recruitment process in Na Savang and Na Lae did not allow an investigation of representativeness among the participants in each village. People concerned about non-communicable diseases may have been more likely to participate in the study. Such bias might have caused the observed levels of oxidative stress markers to be slightly higher than the true values in Na Savang and Na Lae. Second, most participants had not undergone any screening for NCDs, partly because of the poor medical system in the study villages. However, we assumed that the prevalence of NCDs was low in the study villages because these villages were among the most remote areas in Laos. The prevalence of NCDs is increasing trend in Laos (World Health Organization, 2020); accordingly, the prevalence of NCDs may have been higher in the most modernized village (i.e., Na Lae) than in the least modernized village (Nam Nyon). However, if the prevalence of NCDs differed among villages, the difference would have been reflected in the oxidative stress indicators evaluated in the present study.

5 | CONCLUSIONS

To the best of our knowledge, this is the first study to investigate the association between modernization and oxidative stress in indigenous populations during the momentous health transition process. We performed simultaneous evaluations of three oxidative stress-related biomarkers that would respectively reflect oxidative DNA damage, lipid damage, and cumulative oxidative stress. Furthermore, urinary 8-OHdG and 8-isoprostane concentrations were measured by LC–MS/MS. This method provides far more reliable values than ELISA, particularly in low concentration ranges.

This comparative study of three villages in northern Laos explored the impact of modernization on oxidative stress in indigenous populations during the health transition process. Urinary 8-OHdG concentrations were low, whereas urinary 8-isoprostane concentrations were high, in comparison with values previously reported in apparently healthy adults. Oxidative DNA damage was higher in more modernized villages, but oxidative lipid damage did not differ by village. Modernization may have distinct effects on oxidative DNA damage and lipid damage.

AUTHOR CONTRIBUTIONS

Yuki Mizuno: Conceptualization (lead); data curation (lead); formal analysis (lead); funding acquisition (supporting); investigation (equal);

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methodology (lead); validation (lead); writing – original draft (lead); writing – review and editing (lead). **Yohei Inaba:** Methodology (lead); resources (lead); validation (lead); writing – review and editing (supporting). **Hiroaki Masuoka:** Investigation (equal); writing – review and editing (supporting). **Mihoko Kibe:** Investigation (equal); writing – review and editing (supporting). **Satoko Kosaka:** Investigation (equal); writing – review and editing (supporting). **Kazumi Natsuhara:** Investigation (equal); writing – review and editing (supporting). **Kazuhiro Hirayama:** Investigation (equal); writing – review and editing (supporting). **Nouhak Inthavong:** Data curation (lead); investigation (equal); project administration (equal); writing – review and editing (supporting). **Sengchanh Kounnavong:** Project administration (equal); writing – review and editing (supporting). **Shinsuke Tomita:** Conceptualization (supporting); data curation (lead); funding acquisition (lead); investigation (equal); project administration (equal); writing – review and editing (supporting). **Masahiro Umezaki:** Conceptualization (lead); funding acquisition (lead); investigation (equal); project administration (equal); supervision (lead); writing – original draft (supporting); writing – review and editing (supporting).

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Because the population size of each target village was small, individuals could be identified by sex, age, and village name. To ensure participant privacy, we have chosen not to publicly share the full dataset. For further comparative studies, we are able to provide a dataset that includes age, sex and the three oxidative stress markers, which are available in the supplementary material of this article.

ORCID

Yuki Mizuno https://orcid.org/0000-0002-7383-4706

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