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Cadmium Exposure and Renal Function Biomarkers: A 10-Year Follow-Up of Thailand's Tak Province Population

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Abstract: Cadmium (Cd) is a toxic heavy metal that has been recognized as significant to environmental health. Thailand's Tak Province, known for its historical mining and agricultural activities, has been identified as an area of high cadmium exposure. The objective of this investigation was to assess urinary cadmium (UCd), metallothionine in serum (B-MT-1), and kidney injured molecular-1 in urine (U-KIM-1). The target population and study area comprised individuals born between 1992–1999 in the zinc-mining areas of the Phatapadaeng, Mae Tao, and Mae Ku subdistricts of Mae Sot District, Tak Province, Thailand. The sample size was 122 participants and the criteria for inclusion were the individuals rechecked for UCd in 2016. The case definition included testing for UCd by ICP-MS, early renal dysfunction (U-KIM-1), amounts exceeding 0.20 µg/gCr, and environmental exposure to cadmium, indicated by B-MT-1 using the enzyme-linked immunosorbent assay (ELISA). Statistical analysis was performed using Pearson's product-moment correlation coefficient (r), chi-square (χ^2), and analysis of variance (ANOVA) at the 0.05 level of statistical significance to make inferences. The results indicate that 90.16% of the urine samples contained cadmium concentrations between 0.20 and 0.49 µg/gCr. The prevalence of MT-1 and KIM-1 in individuals aged 19–21 was 19.35% and 17.59%, respectively. We found that MT-1 was significantly higher among the residents of Phatadpadaeng, whereas KIM-1 was dominant among Mae Ku subdistrict participants. Females aged 15–18 and 19–21 had higher levels of MT-1 and KIM-1 compared to males in both age groups. The concentration of UCd was found to be higher among participants aged 15–18 and 19–21 years with UCd levels ranging between 0.20–0.49 µg/gCr-MT-1 and 0.50–0.80 µg/gCr-KIM-1. There was no correlation between age, gender, or region and MT-1 and KIM-1 detection. Menstruation is one of the risk factors for iron loss resulting in iron deficiency among teenage girls, and thus a source of cadmium bioavailability in the body. We, therefore, recommend that relevant authorities should focus on carrying out periodic surveillance among women aged 19 to 21 to identify those affected and subject them to treatment.

Keywords: urinary cadmium (UCd); renal dysfunction; serum-metallothionein-1 (MT-1); kidney injury molecule-1 (KIM-1); Thailand

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1. Introduction

Cadmium is found in nature as a naturally occurring element, and most of it is found in combination with lead and zinc as sulfide or sulfide oxide compounds. Zinc mines are one of the major sources of environmental and occupational health problems in Mae Sot District, Tak Province Thailand. Zinc is mined at two major locations in this area (longitude 98°59′–98°63′ E and latitude 16°67′–16°66′ N). The Pa De Zinc mine was a tunnel mine that opened from 1985 to 2013. Zinc deposits in the Doi Pa Deang and Phra Chedi mines are extracted using open-pit mining methods. This results in soil erosion, disturbance, and significant destruction of the environment. This explains why, in 1969–1975 and

1976–1983, the zinc mine was closed and the land was left to recover. Since 1999, the area has been surveyed for cadmium contamination in the environment due to past mining activities [1]. Because of the isomorphic substitution of chemical elements within their lattices, numerous minerals are characterized by complexities and variations in chemical composition. Eventually, the same type of mineral can exist in various forms, such as sulfides. Examples of associated minerals include pyrite (FeS_2), chalcopyrite ($CuFeS_2$), and sphalerite (ZnS) which contain lead (Pb) and cadmium (Cd) [2]. Therefore, when the zinc mine exposes these rocks and ores to acidic extraction, the elements in the rocks and ores dissolve, become a byproduct of refining minerals, and are released into the environment through agricultural irrigation.

The Pha De village is located close to the zinc mineral source. The years 2001–2003 were spent in the subdistrict of Mae Tao, which is downstream from the initial area. The office of Academic Research measured cadmium concentrations in the soil and rice of Mae Sot District, Tak Province. It was discovered that the cadmium content in the soil was 1800 times higher than the European Union's standard and that 95% of rice grains contained cadmium in greater concentrations than rice grown in other regions of Thailand [3,4]. It was discovered that the soil's cadmium contamination was 72 times greater than the EU standard. Additionally, elevated levels of cadmium were detected in rice and soy grown in the affected regions. From 2001 to 2004, it was discovered that agricultural fields receiving irrigation from two streams (Mae Tao and Mae Ku) contained substantially elevated levels of cadmium [3,5]. These waterways flowed through a zinc-rich region where a zinc mine had operated for nearly two decades. Approximately 69.2% of sediment samples from creeks exceeded the maximum allowable concentration of 3.0 mg/kg. Cadmium concentrations in creek samples collected prior to entering the zinc region were low, increased significantly after passing through this region, and decreased proportionally with distance. Approximately 85.0% of paddy soil samples irrigated by both streams had concentrations of cadmium that exceeded the allowable range. In 2004, an estimated 8,350,185.05 acres of rice fields were contaminated with cadmium, impacting 12 villages with a total population of 12,075 [6]. Similar to Cd pollution levels in the Mae Sot region, the International Water Management Institute (IWMI) reported that Cd levels in rice grains were 90% higher than the recommended safety levels [7]; this was in agreement with our findings and other published studies about Cd contamination in an agricultural field in the Mae Sot District, Tak Province, Northwestern Thailand [8,9]. The Cd concentration in unhusked rice (*Oryza sativa* L.) grains ranged from 0.04 to 1.75 mg Cd/kg, and more than half of the households' rice contained Cd levels higher than the CODEX-mandated critical level of 0.4 mg Cd/kg refined rice [10]. Cadmium is a toxic heavy metal that poses significant health hazards on a global scale. The accumulation of cadmium in the human body can cause cancer and have other negative effects on organs such as the kidneys, liver, and lungs [11–13].

The harmful effects of cadmium on animals and humans include lung, kidney, and bone diseases, as well as reproductive damage and cancer [11,14]. The involvement of metallothioneins in cadmium toxicity has been supported by developing research since 1957. MTs are low-molecular-weight cadmium-binding proteins observed in human and animal tissues, and it is believed that the binding of Cd to MTs affects cadmium's toxicity levels. Evidence was accumulated within the first two decades following the discovery of MTs concerning Cd binding to MTs in tissues in connection to Cd exposure. Several studies report that Cd binds to MT-1 in the liver. Cd ionizes and accumulates in the proximal tubule when the MT–Cd link is severed. Similar to wet weight, the connection between MT and Cd becomes important in the human liver and kidneys [15]. This study investigated the association between urinary metallothionein (U-MT) and UCd levels and observed a significant association between the two [16]. In patients with itai-itai disease, the U-MT value was elevated, which was related to the UCd value. MT-1 and Cd combine to form MT–Cd compounds, which are transported to the kidneys. Cd is normally eliminated from the body by decreasing its molecules to a size that allows them to pass through kidney

cells and be pumped out by urine, but this can only excrete 10% of the total Cd in the cell [17]. Cd has a half-life of between 10 and 30 years in the body, causing a prolonged overload of kidney operations that can lead to renal dysfunction, including glomerular capillary failure and a loss of filtration performance in the renal tubules. KIM-1 in the urine is a biomarker for early renal function impairments [11,18]. KIM-1 is a transmembrane glycoprotein exclusively found near the beginning of the proximal tubule in patients with renal impairment [19]. Similarly, the study investigated the relationship between UCd-KIM-1 and necrotic and apoptotic cell death in the proximal tubule, demonstrating a significant increase in U-KIM-1 after six weeks of Cd exposure [19,20]. While Cd in the body can damage proximal tubule epithelial cells, within 12 weeks of U-KIM-1 acting as a scavenger receptor in renal epithelial cell transfer to phagocytes, there is no evidence of necrotic cells. The presence of U-KIM-1 in the urine may indicate that a patient has renal failure. Another study investigated Cd-exposure cases in a polluted region of Mae Sot, Tak Province, Thailand, and they observed that U-KIM-1 was linked with urine UCd and BCd in Cd-exposed people [21].

Cd contamination has already occurred in Tak Province, Thailand, due to the zinc-extraction procedure (Figure 1). Thus, waste obtained from zinc-smelting operations in the aforementioned locations is discharged into the environment, enters the food chain, and accumulates in the bodies of community members for one-third of the half-life collection period of cadmium. Thus, it is believed that cadmium accumulation within the body could negatively impact the kidneys of residents who utilize KIM-1, a kidney substitute. At present, biomarkers of early loss of function in renal tubules and MT-1, which are biomarkers of local cadmium exposure and contamination, are used as part of the planning approach, as are the results of population classification performed by the gender and age of MT-1 and KIM-1 encounters, in order to avoid any adverse health effects among individuals. Regardless of age, this region's entire population has stores of Cd in their systems, which may affect their health and lead to renal illness in the future. The purposes are to evaluate the renal function of individuals in the Phatadpadaeng, Mae Tao, and Mae Ku subdistricts that have been exposed to Cd pollution. The results of this study are to be used as a database by health agencies in order for them to plan solutions to health problems for at-risk groups inhabiting the area. These solutions may include health promotion policies to reduce the amount of cadmium taken into the bodies of people who live in at-risk areas in the future.

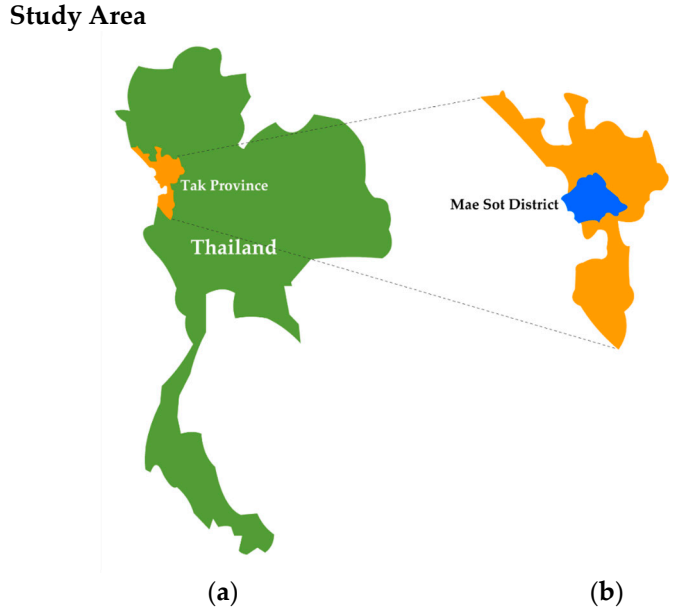

Figure 1. Map of Thailand showing Tak Province (**a**) and Mae Sot district, where the Padaeng zinc mine is located (**b**).

2. Materials and Methods

2.1. Population

In Thailand's northern Tak Province, the study population was located in the Mae Sot district, which is close to a zinc-mining facility. In 2009, 849 individuals' urine samples were analyzed for cadmium. In 2016, the same 441 participants were evaluated (as in Figure 2). We also determined the early diagnosis of renal failure by KIM-1.

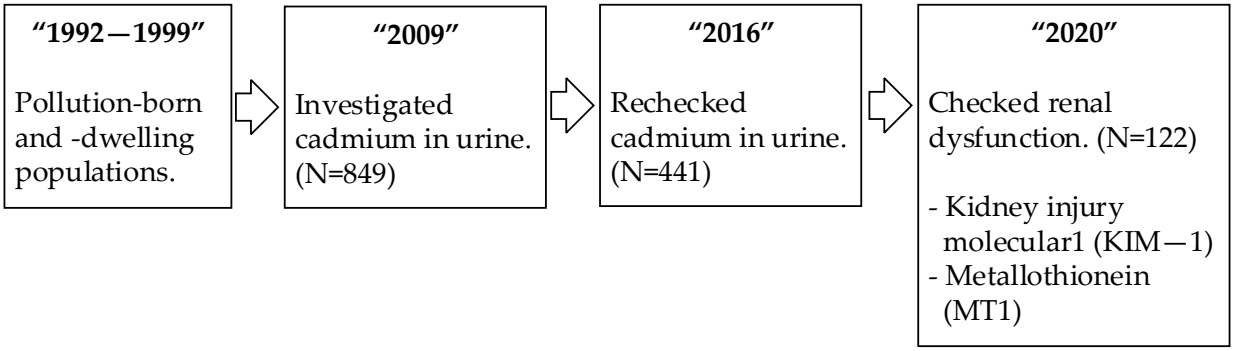

Figure 2. Overview of time span, subjects, and processes.

Inclusion Criteria

1. Residing in the subdistricts of Phatadpadaeng, Mae Tao, and Mae Ku, covering 12 villages in the Tak Province.
2. This study's population was identified as individuals born between the years 1992 and 1999.
3. UCd values of at least 0.20 μg/gCr were measured in 2009 and subsequently confirmed in 2016 [22].
4. Both males and females.

2.2. Sampling and Processing of Samples

Plastic containers were immersed overnight in deionized water after being rinsed with distilled water. After oven drying the cleaned polyethylene containers, they were soaked in diluted nitric acid and subsequently dried again. All polyethylene (PE) tube containers were covered and stored in a box until they were required for use. In the present study, morning urine and blood samples were obtained from 122 participants using sterile, plastic containers. The nitric acid concentration was applied to blood samples (1 mL). All urine and blood samples were kept at −20 °C.

2.3. Cadmium Urine Detection

Urine samples were centrifuged for 10 min at 3000 rpm and then stored at −20 °C until further examination. Ir and Rh standard solutions were produced at a concentration of 5 g/L. In a cleaned polypropylene tube, standard solutions of Ir and Rh (g/L) were diluted with 900 L of deionized water (DI 18 M). A total of 100 L of urine was placed into the same polypropylene tube and spun at 3000 rpm for 10 min. The Cd content of the urine samples was determined by dividing the clear solutions into clean, 20 mL polypropylene tubes and measuring the Cd content of the urine samples. ICP-MS was utilized to determine the Cd concentration in the urine samples.

2.4. Creatinine Concentration

Using Jaffe's reaction, the creatinine content of the urine was biochemically analyzed. Urinary creatinine was measured using the Roche/Hitachi Cobas c system, Bangkok, Thailand, with reagents potassium hydroxide R1 (80 mmol/L), phosphate R1 (12 mmol/L), and picric acid SR 50 (4.4 mmol/L) at pH > 13. The ratio of diluted urine to distilled water was 1:25 (urine sample:distilled water). Prior to analyzing the samples, the automated

systems were calibrated using a standard material (c.f.a.s., Cat. No. 759350). Using precinorm U Cat. No. 171743 and precipath U Cat. No. 171778, the quality of the sample was evaluated using Thailand's branch of Roche diagnostics.

2.5. Urinary KIM-1 Determination

Nunc-Maxisorp EIA with 72 g/mL trapping antibody was diluted to 0.4 g/mL in PBS with 100 L of each well, sealed, and incubated for 24 h at room temperature (DY1750, R&D, Minneapolis, MN, USA, filtered, 0.2 m) for 2 h at room temperature. A total of 100 mL of the recombinant human KIM-1 standard (0–2000 pg/mL), control, and urine samples were pipetted into the appropriate wells coated with adhesive strip and shaken in an orbital shaker at 400 rpm for 2 h at room temperature. After washing, it was treated with 100 mL of biotinylated goat anti-human KIM-1 antibody diluted to 400 ng/mL. Fresh adhesive strips were applied to the plate and incubated at room temperature for 2 h at 400 rpm. Each well received 100 mL of diluted streptavidin–HRP after washing again. Use a new adhesive strip, which was stirred at 400 rpm, and incubate at room temperature for 20 min after the washing step. Each well received 100 mL of the substrate solution, sealed, stirred at 400 rpm, and incubated at room temperature for 7 min. The absorbance level at 450 nm was recorded by a plate reader (BioTek Elx800, Shanghai, China).

2.6. The Detection of MT-1

MT was diluted from 1 to 100 ng/mL in 50 mM of Tris-25 mM HCl, or 100 L of plasma was incubated overnight at 4 °C on microtiter plates. The wells were washed 3 times with 40 mM of Tris-33 mM HCl, 154 mM of NaCl, and 0.05% (*w*/*v*) Triton X-100 (Sigma-Aldrich, ref. no. X100, Wesel, Germany), blocked for 1 h at 25 °C with 3% (*w*/*v*) gelatin (Bio-Rad, ref. no. 170-6537, Hercules, CA, USA) in 40 mM of Tris-20 mM HCl, 154 mM of NaCl, and 0.05% Triton X-100 (300 L). A 1:20 dilution of a primary monoclonal mouse metallothionein clone E-9 antibody (Dako, ref. NoM0639, Glostrup, Denmark) was added to 1% (*w*/*v*) gelatin in 40 mM of Tris-33 mM HCl with 154 mM of NaCl and 0.05 percent Triton X-100 (100 L). Wells were washed three times with 40 mM of Tris-33 mM HCl, 154 mM of NaCl, and 0.5% (*w*/*v*) Triton X-100. The secondary biotinylated polyclonal goat anti-mouse IgG antibody (Dako, ref. NoE0433, Denmark) was added to a buffer containing 1% (*w*/*v*) gelatin in 40 mM of Tris-33 mM HCl with 154 mM of NaCl and 0.05% Triton X-100 (100 L) at 1:400 and then incubated. Following 3 washes, the wells were incubated for 1 h at 25 °C with HRP-Avidin (Dako, ref. NoP0347, Denmark) diluted at 1:800 in 1% (*w*/*v*) gelatin in 40 mM of Tris-33 mM HCl, 154 mM of NaCl, and 0.1% Triton X-100 (100 L). A total of 50 L of 3 M HCl halted coloring. A total of 490 nm ELISA readers recorded absorbance (STAT-FAX 2100, Analco, GBG, Atlanta, GA, USA). The MT-I and MT-II samples had 140 pg/well ELISA sensitivity.

2.7. Analytical Statistics

1. Descriptive statistics: the frequencies, percentages, and means were calculated.
2. Statistical analyses, such as Pearson's product correlation (*r*) (Table 1), chi-square (χ^2), independent *t*-test, and analysis of variance (ANOVA) at statistical significance at the 0.05 level, were performed.

Table 1. Guidelines for interpreting Pearson's correlation coefficient.

Strength of Association	Coefficient (*r*)	
	Positive	Negative
Small	0.1 to 0.3	−0.1 to −0.3
Medium	0.3 to 0.5	−0.3 to −0.5
Large	0.5 to 1.0	−0.5 to −1.0

The Results

Table 2 displays the urine cadmium levels of participants by age group. It was discovered that among the urine samples, 90.16% had cadmium concentrations of 0.20–0.49 μg/gCr, and 9.84% had cadmium concentrations of 0.50–0.89 μg/gCr.

Table 2. The urine cadmium levels of participants by age group (N = 122).

Age Group (Years Old)	Cd Levels in Urine (μg/gCr)	
	0.20–0.49	**0.50–0.89**
15–18	55	5
19–21	55	7
Total	110	12
%	90.16	9.84

The proportion of participants in whom MT1 was found in serum, broken down by gender and age, is displayed in Figure 3. The proportion was 13.82% for males between the ages of 15 and 18 and 19.35% for males between the ages of 19 and 21, whereas the percentages for women aged between 15 and 18 years and 19 and 21 years were 10.49% and 14.92%, respectively.

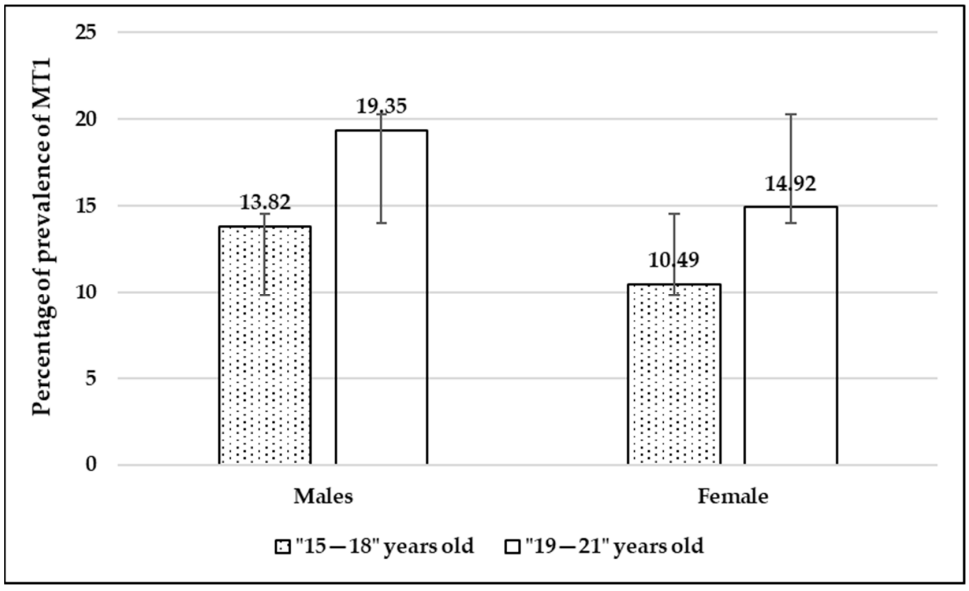

Figure 3. Percentages of MT1 detected in serum by gender and age (N = 122). Males: detected (N = 31) and none detected (N = 23); females: detected (N = 38) and none detected (N = 30).

The percentage of participants in whom KIM-1 was discovered in urine samples, divided according to gender and age, is presented in Figure 4. The percentage was 11.81% in males aged between 15 and 18 years, whereas it increased to 17.59% in males between the ages of 19 and 21 years. The percentage was 13.51% in women between the ages of 15 and 18 years and 15.31% in women between the ages of 19 and 21 years.

Table 3 compares the serum levels of MT-1 and KIM-1 in the urine samples. The mean MT-1 concentration in both males and females was 7939.32 pg/mL. At the 0.05 significance level, females (8377.93 pg/mL) had substantially higher levels than males (7500.71 pg/mL). In both males and females, the average concentration of KIM-1 was 699.67 pg/mL. Females (756.34 pg/mL) were observed to have significantly higher levels than males (643.00 pg/mL) at a significance level of 0.05 ($p < 0.05$).

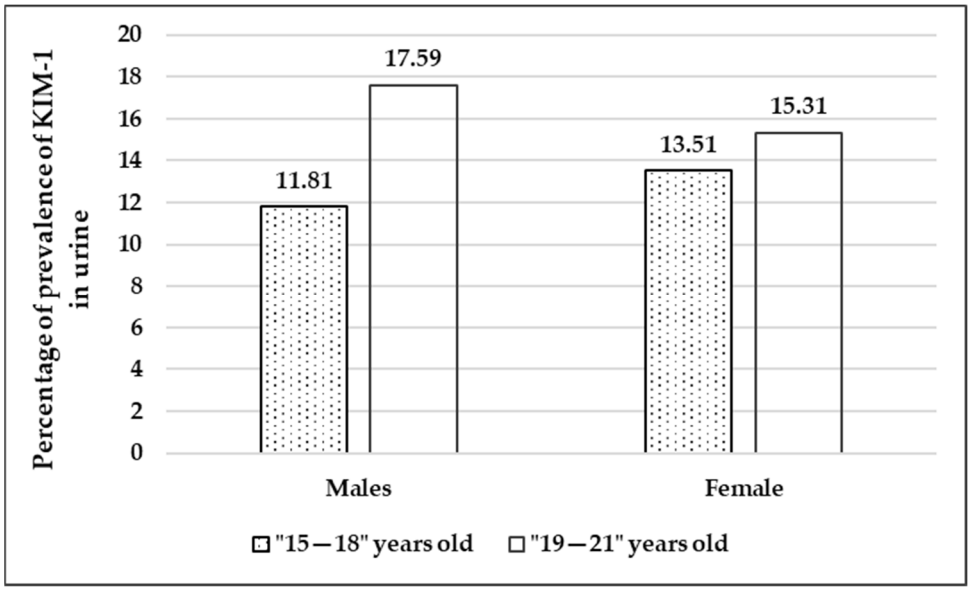

Figure 4. The proportion and prevalence of KIM-1 in urine investigations based on the gender and age of the participants (N = 122). Males: detected (N = 36) and none detected (N = 18); females: detected (N = 37) and none detected (N = 31).

Table 3. The MT-1 levels present in serum (N = 69) and KIM-1 levels present in urine (N = 73) by gender.

Genders	Biomarkers of Environmental Exposure			
	MT-1 (pg/mL)		KIM-1 (pg/mL)	
	N	Quantity	N	Quantity
Male	31	7500.71	36	643.00
Female	38	8377.93 *	37	756.34 *
Total	69	$\overline{X}$ = 7939.32	73	$\overline{X}$ = 699.67

* Significance level of 0.05.

MT-1 in serum: Phatadpadaeng presented the highest concentration of MT-1 in serum ($\overline{X}$ = 11,040.62 pg/mL), followed by the Mae Tao ($\overline{X}$ = 8013.75 pg/mL) and Mae Ku ($\overline{X}$ = 7281.44 pg/mL) subdistricts. When the statistical results were examined, it was discovered that the three subdistricts differed significantly at the 0.05 level ($p < 0.05$) as shown in Table 4.

Table 4. Comparison of the area-based mean levels of MT-1 in serum and KIM-1 in urine.

Genders	Biomarkers of Environmental Exposure			
	MT-1 (pg/mL)		KIM-1 (pg/mL)	
	N	Quantity	N	Quantity
Phatadpadaeng	20	11,040.62 *	22	635.37
Mae Tao	30	8013.75	28	691.39
Mae Ku	19	7281.44	23	721.29 *
Total	69	$\overline{X}$ = 8689.45	73	$\overline{X}$ = 682.68

* Significance level of 0.05.

KIM-1 in urine: The mean concentration of KIM-1 in urine samples across the three subdistricts was 682.68 pg/mL. Mae Ku subdistrict samples contained the highest concentration of KIM-1 in the urine ($\overline{X}$ = 721.29 pg/mL), followed by the Mae Tao ($\overline{X}$ = 691.39 pg/mL) and Phatadpadaeng ($\overline{X}$ = 635.37 pg/mL) subdistricts. The statistical analysis revealed that

the three subdistricts were substantially different at the 0.05 level ($p < 0.05$) as shown in Table 4.

The average concentration of MT-1 in the serum is presented in Figure 5, disaggregated by age group and gender. It was discovered to occur more frequently in females between the ages of 19 and 21 years than in males between the ages of 15 and 18 years, although it was more prevalent in males between the ages of 19 and 21 years and was higher than those in the age range of 15 to 18 years. When the statistical data were analyzed, it was discovered that the mean values of MT-1 in the serum of the 19–21-year-old groups of males and females were significantly different from those in the 15–18-year-old groups at the level of 0.05. This was the case when comparing the two age groups.

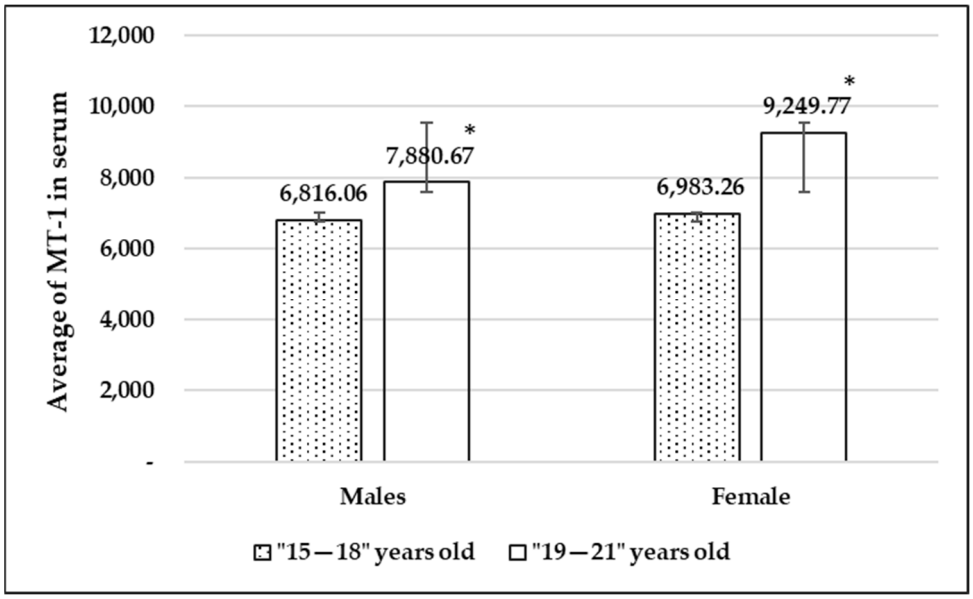

Figure 5. Average MT-1 concentrations in serum samples were categorized by age group and gender (N = 69). * Significance level of 0.05. Note: $\overline{X}$ of MT-1 by sex: male = 7272.32 pg/mL; female = 7954.62 pg/mL.

The mean values of KIM-1 in the urine samples were divided into groups based on age and gender and are presented in Figure 6. The overall mean values for females were observed to be significantly higher than those of the males. When taking into account the age groups, the values for males in the 19–21-year-old age group were greater than those in the 15–18-year-old age group, whereas the values for females in the 19–21-year-old age group were higher than those in the 15–18-year-old age group. When the statistical data were analyzed, we discovered that the level of KIM-1 in the urine samples obtained from participants aged 19–21 years, both men and females, was substantially different from the level of KIM-1 in the urine of those aged 15–18 years at the level of 0.05.

Figure 7 displays an average of the MT-1 concentration in the serum samples, broken down by UCd and age group. When comparing the 15–18- to the 19–21-year-old group, the total mean value for the 19–21-year-old group was considerably higher than that for the 15–18-year-old group. It was determined that the MT-1 concentrations of participants with mean urine cadmium concentrations of 0.20–0.49 μg/gCr in the 15–18- and 19–21-year-old age groups were higher than those of participants with UCd concentrations of 0.50–0.89 μg/gCr. This was the situation when the data were categorized according to age group. When the statistical results were analyzed, it was observed that the mean MT-1 in the serum samples of the participants in the 15–18- and 19–21-year-old age groups with UCd concentrations of 0.20–0.49 μg/gCr were significantly different from those with UCd concentrations of 0.50–0.89 μg/gCr at the 0.05 significance level.

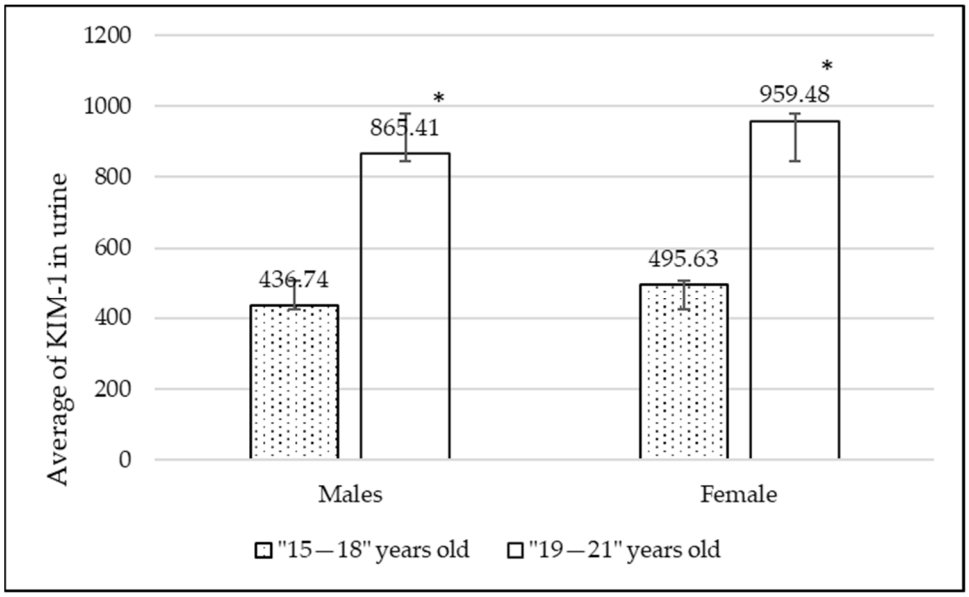

Figure 6. The average of KIM-1 in urine was classified by age group and gender (N = 73). * Significance level of 0.05. Note: $\overline{X}$ of KIM-1 by gender: male = 620.45 pg/mL; female = 694.36 pg/mL.

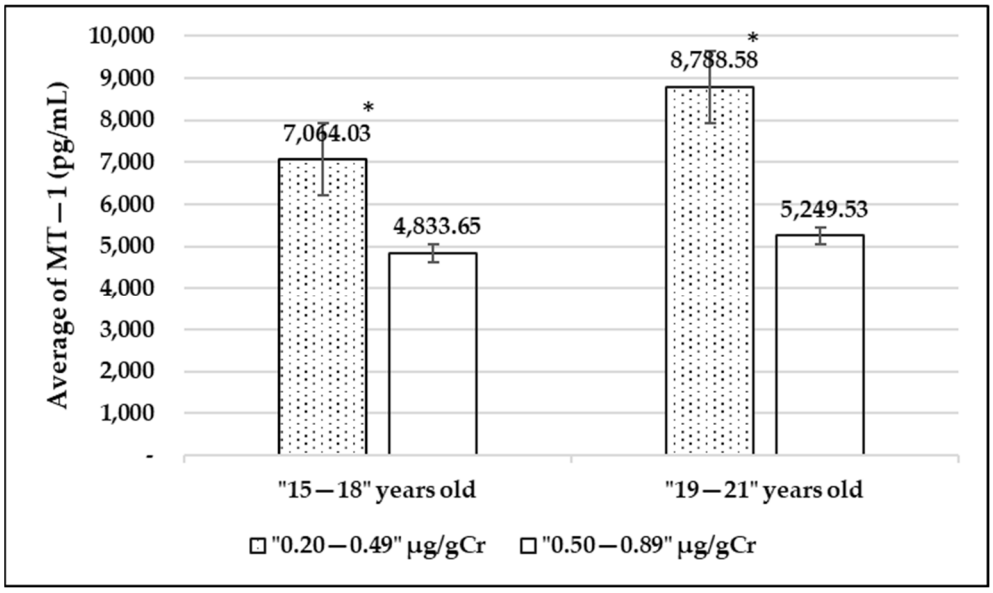

Figure 7. Average MT-1 concentration in serum as a function of age group and UCd concentration (N = 69). * Significance level of 0.05. Note: MT-1 by UCd: male = 6108.15 pg/mL; female = 6843.27 pg/mL.

Figure 8 presents the average concentration of KIM-1 in urine, divided by UCd and age group. When comparing the 19–21- to the 15–18-year-old group, it was observed that the 19–21-year-old group's total mean value was significantly higher than that of the 15–18-year-old group. It was revealed that, in the 15–18- and 19–21-year-old age groups, those with UCd concentrations of 0.5–0.89 μg/gCr had higher KIM-1 concentrations than did those with UCd concentrations between 0.20 and 0.49 μg/gCr. This was the result when the data were separated according to age group. When the statistical results were evaluated, it was observed that the mean KIM-1 concentration in the urine of participants in the 15–18- and 19–21-year-old age groups with UCd concentrations of 0.2–0.49 μg/gCr did not differ significantly from those with 0.5–0.89 μg/gCr concentrations.

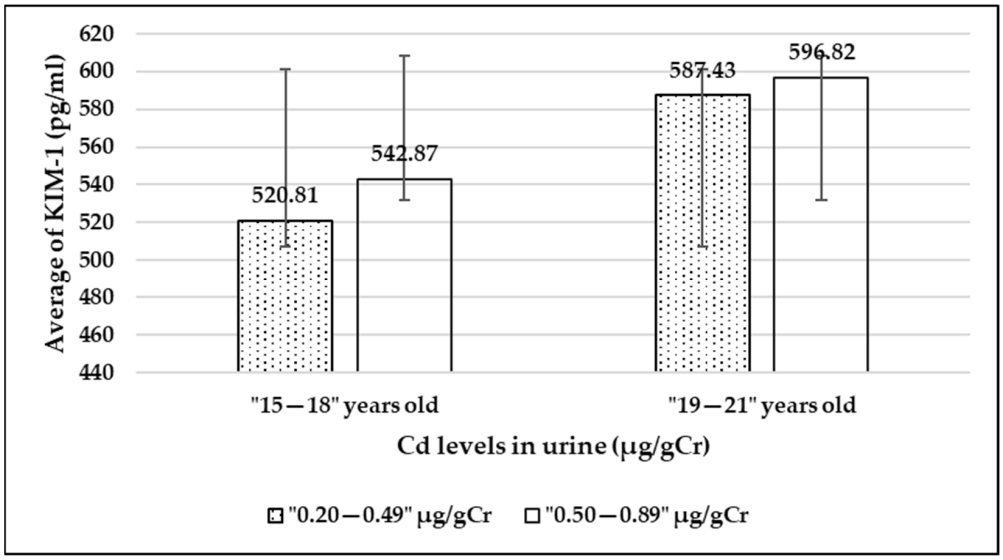

Figure 8. The contents of KIM-1 in urine are classified by the levels of cadmium in urine (μg/gCr) and genders (N = 73). Note: $\overline{X}$ of KIM-1 by 15–18 years with cadmium in urine: 0.20–0.49 μg/gCr = 531.84 pg/mL; 19–21 years with cadmium in urine: 0.50–0.89 μg/gCr = 592.16 pg/mL.

2.8. The Effects of Age and Cadmium in Urine on Serum MT-1 and Urinary KIM-1

Table 5 shows that MT-1 in serum and KIM-1 in urine were both at a medium level in terms of age, but KIM-1 in both was at a high level. Cadmium was also at a medium level in the urine, while KIM-1 was at a high level in both. The influence of age and cadmium levels in urine on serum and urine levels of MT-1 and KIM-1 was explored, and it was discovered that age has a negative association with MT-1 in serum and that the two are significantly different ($p < 0.05$). KIM-1 was negatively associated with age, although it was adversely associated with cadmium in urine. KIM-1, on the other hand, was found to be inextricably connected to age and cadmium levels in urine ($p < 0.05$).

Table 5. The interaction of age and cadmium content in urine on MT-1 and KIM-1 levels in serum and urine (N = 122).

Parameters	Contents of MT-1 in Serum		Contents of KIM-1 in Urine	
	r	Results	*r*	Results
Ages (Years old)	−0.315 *	Medium	−0.350 *	Medium
Cd in urine (μg/gCr)	−0.674 *	High	−0.485 *	Medium

* Correlation with a significance level of 0.05.

2.9. The Relation of Age, Gender, and Areas of the Prevalence of MT-1 in Serum and KIM-1

Table 6 illustrates the association between the prevalence of MT-1 in the serum and KIM-1 in the urine based on the individual's age. There was no relationship found between age and the predominance of either MT-1 or KIM-1 ($p > 0.05$).

Table 6. The prevalence of KIM-1 in urine and MT-1 in serum as a function of age (N = 122).

Ages (Years Old)	N	Prevalence of MT-1 in Serum		χ^2	Prevalence of KIM-1 in Urine		χ^2
		Detected	None Detected		Detected	None Detected	
15–18	60	34	26	0.434	37	23	0.721
19–21	62	35	27		36	26	
Total	122	69	53		73	49	

Table 7 presents the results of a correlation between the prevalence of MT-1 in the serum and KIM-1 in the urine, segmented according to gender. There was no statistically significant correlation between gender and the prevalence rate of either MT-1 or KIM-1 ($p > 0.05$).

Table 7. The prevalence of KIM-1 in urine and MT-1 in serum as a function of gender (N = 122).

Genders	N	Prevalence of MT-1 in Serum		χ^2	Prevalence of KIM-1 in Urine		χ^2
		Detected	None Detected		Detected	None Detected	
Male	54	31	23	0.443	36	18	0.445
Female	68	38	30		37	31	
Total	122	69	53		73	49	

Table 8 illustrates the correlation between the prevalence of MT-1 in the serum and KIM-1 in the urine based on the location of the participants. There was no correlation between the prevalence of MT-1 and KIM-1 and the location ($p > 0.05$).

Table 8. The prevalence of KIM-1 in urine and MT-1 in serum as a function of location (N = 122).

Areas	N	Prevalence of MT-1 in Serum		χ^2	Prevalence of KIM-1 in Urine		χ^2
		Detected	None Detected		Detected	None Detected	
Phatadpadaeng	32	20	12	0.436	22	10	0.438
Mae Tao	47	30	17		28	19	
Mae Ku	43	19	24		23	20	
Total	122	69	53		73	49	

3. Discussion

Researchers evaluated three assumptions in this study: (1) adolescents aged 15–18 and 19–21 years had different levels of cadmium in their urine; (2) residents of Prathadpadeang, Mae Tao, and Mae Ku subdistricts had different levels of MT-1 in their serum and KIM-1 in their urine; and (3) male and female adolescents aged 15–18 and 19–21 years had different levels of MT-1 in their serum and KIM-1 in their urine. Thus, the discussion is separated into three sections:

1. The 19–21-year-old age group had the highest concentration of UCd between 0.20 and 0.49 g/gCr.

Cadmium enters the bloodstream when absorbed by the body. It travels with red blood cells (RBCs) (metallothionein) and liver albumin through the bloodstream (plasma). MT-1 forms a compound in the form of MT–Cd and is transported [12]. The quantity increases with age and continues to increase for a long period of time after being consumed. It has a half-life of between 10 and 30 years, causing the kidneys to work harder as time progresses. Half of the body's cadmium is deposited in the liver and kidneys [11,12]. Half of the body's cadmium content is deposited in the liver and kidneys. Cadmium is eliminated from the body at a rate that is 10% lower than its absorption rate, resulting in its accumulation in the body, particularly in the liver and kidneys. Cadmium is also excreted via the hair, skin, and milk, but to a smaller degree. This also depends on the period of time for which cadmium remains in the body and the total body burden of the individual. In the cadmium-contaminated regions of Tak Province, the data indicate that UCd levels increase with age. Cadmium can be eliminated from the human body by decreasing its molecular size to the point where it can pass through the filter in the renal unit cell and be excreted in the urine. Approximately 0.005% of the body's total Cd content is excreted daily in the urine [15]. These variables may contribute to renal illness and the failure of filtration organs, including the glomerulus [5]. This may be the result of a substantial reduction in

Cd accumulation in the body. Long-term residuals lead to adverse health effects in the area, which enter the body through water and food cultivated in the area and accumulate in the body. The at-risk population must thus be made aware of the perceived susceptibility, severity, and benefits of avoiding cadmium availability in the body, as well as the necessity of reducing risky behavior. Chaiwong et al. (2010) developed a program to improve health perceptions in the sample group and reduce risk factors for cadmium bioavailability, such as preventing the occurrence of iron deficiency in women. The experimental group scored higher on the Cd exposure prevention test than the control group ($p < 0.01$). After receiving the appropriate education, the experimental group had a significantly higher mean score for preventing cadmium exposure ($p < 0.01$) [23]. Therefore, protecting and supporting the health of people in high-risk locations reduces the risk behavior for cadmium accumulation in the body with essential, sufficient intakes, such as ingesting enough zinc, iron, and calcium; avoiding barefoot walking, which causes hookworms and radish threads to enter the system and become parasites, sucking blood from the small intestine, resulting in iron loss; and avoiding smoking, because tobacco is a plant known to accumulate high amounts of cadmium [24].

2. The highest concentration of MT-1 was identified in the Prathadpadeang region, and the highest concentration of KIM-1 was observed in the Mae Ku region.

The Mae Sot district zinc mine is located in the Phathatphadaeng subdistrict (as in Figure 9); hence, the area has a greater possibility than others of acquiring cadmium through the food chain. The Mae Tao irrigation system connects the region to the Mae Tao and Mae Ku subdistricts. When leached water obtained from an untreated zinc mine is released into Mae Tao irrigation canals and used for agricultural activities, it significantly contributes to cadmium's entry into the food chain [10]. Mae Tao is an important rice-growing region in the Tak Province due to its good soil and ample water resources. Both the Mae Tao and Mae Ku streams, which flow through zinc mines upstream, supply substantial water resources for the irrigation of rice crops downstream. As a result, it was determined that the Zn and Cd levels in the rice planted in this area were significantly elevated. Between the years 2002 and 2004, the IWMI and MOA [2005] conducted surveys and analyses of Cd concentrations in rice grains and soil in polluted areas. They determined that both rice grains and soil contained levels of Cd that exceeded the Codex and European Union maxima [25].

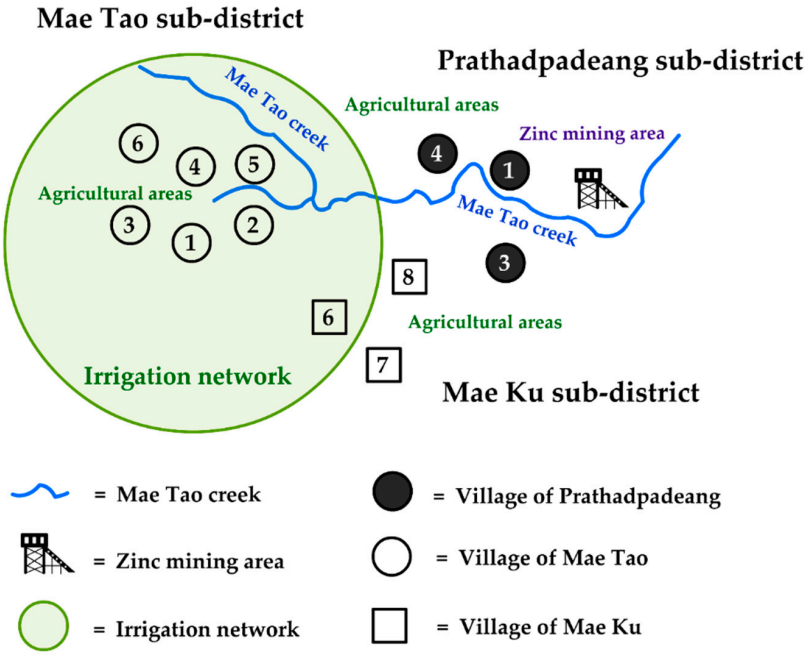

Figure 9. An overview of the study's topic of inquiry.

Similarly, with soil samples, Cd concentrations ranging from 0.1 to 284 mg/kg exceeded the EU's permitted threshold of 3.0 mg/kg [25]. The majority of Mae Tao residents are farmers, and rice is the primary agricultural product locally grown and consumed. Residents of the Mae Ku subdistrict may have adverse health effects as a result of Cd exposure through rice consumption. In 1991, the IWMI observed that the concentration of water in jasmine rice was 300 times higher than the national average. Cadmium was identified in the urine of Pratadpadaeng, Mae Tao, and Mae Ku inhabitants living near zinc-mining sites [3]. Cadmium was identified in the urine of Pratadpadaeng, Mae Tao, and Mae Ku inhabitants living near zinc-mining sites [25].

Due to the diversity of transport systems involved in Cd uptake and translocation, it is consistent with the notion that Cd, as a non-essential element, hijacks the transport pathways of micronutrients, such as Fe, Mn, and Zn, in order to enter the plant through its roots and be distributed to all of its organs. Additionally, the mechanisms utilized by Cd vary amongst plant species. Hence, the food chain from the consumption of vegetables or meats is the most significant determinant in human cadmium exposure. The quantity of cadmium accumulation in several plant species was identified via an environmental study. As a result, food crops grown in this region, notably rice, contain increased levels of cadmium. In 2005, the IWMI identified for the first time Cd pollution in paddy soils and rice grains in the area [25]. The following are some strategies utilized for addressing the problem of cadmium exposure from polluted regions and reducing the long-term health concerns associated with cadmium in the food chain: soil pH modification utilizing calcium carbonate ($CaCO_3$) in an optimum ratio to elevate pH > 8.5 [26], and information technology, such as the Internet of Things (IoT), to regulate the irrigation system in the rice fields to control the water level to flood the rice fields in order to induce a redox reaction, particularly during the seedling stage [27]. This reaction aids in the reduction in cadmium dissolved from CdS, maintaining the soil redox level between −150 and −200 mV; the modification of soil adsorption capacity by adding clay minerals, such as bentonite, kaolinite, and zeolite; coal-washing fines and water-treatment biosolids in order to reduce the amount of cadmium that plants can absorb via their roots, collecting information about acceptable plant species, including planning for area rehabilitation, increasing soil quality to fit plant species, as well as introducing or spreading planting knowledge that decreases heavy metal absorption by persons engaged in the activity; and agriculture of non-food crops. If the region is incapable of producing food crops, it may be transformed into commercially significant rapid-growing perennials, such as eucalyptus plantations for piling and furniture, etc.

Hence, KIM-1 is one of the proteins employed as a biomarker to evaluate kidney function during the early phases of renal damage produced by cadmium contamination in the environment [28]. KIM-1 resides in the apical membrane area of the kidney under normal circumstances and increases in response to ectodomain and ex vivo activation. In pharmaceutical research, the genomic technique has been utilized to examine the increase in genes linked with nephrotoxic cisplatin-induced kidney injury, and it has been shown that KIM-1 increases the expression of more than 30,000 genes [29]. According to the research conducted on KIM-1 levels in urine, they increase with age due to the extended exposure of older adults to cadmium in the body, which causes an accumulation of cadmium in the proximal tubular region of the kidney and renal failure in polluted areas [14]. Ruangyuttikarn et al. (2013) reported on individuals residing in the Mae Sot, Tak Province, cadmium-contaminated region. These results suggest that U-KIM-1 values are related to BCd and age [21]. According to these results, U-KIM-1 is a sensitive indicator for measuring kidney failure at the beginning of the renal tubules and can be used to predict Cd content in individuals who reside in Cd-contaminated areas or who have been exposed to elevated Cd levels for an extended period of time. Since the level of KIM-1 observed in the urine sample indicated that kidney function was in jeopardy, a campaign should be conducted to persuade the sample group to adopt a low-sodium diet (Thai people consume 3636 mg of sodium/day on average) [30]. A high salt intake is one of the

leading causes of noncommunicable diseases, such as hypertension and cardiovascular disease. It may also increase the future risk of having chronic renal disease. Depending on the level of cigarette smoking, a smoker's exposure to cadmium may vary. A cigarette contains 1–2 g of cadmium; a person who smokes 20 cigarettes per day absorbs about 1 g of cadmium. Approximately 10% of cadmium is inhaled, with a lung absorption rate of 40–50% [11]. Urine cadmium concentration and renal function are influenced by nutritional status, particularly serum copper and zinc levels (CZR). This study demonstrated that Cu and Zn balance impact renal failure, particularly in populations with low Cd levels. CZR is superior to concentrations of trace metals for assessing these imbalances. Prolonged exposure to low Cd concentrations reduces Cu and Zn absorption and is negatively correlated with blood Zn concentrations. Cu/Zn imbalances lead to kidney problems [31]. Thus, these at-risk populations should consume copper- and zinc-rich foods, such as oysters, almonds, chocolate, walnuts, mushrooms, and beef liver. Finally, the public's knowledge of how to prevent cadmium bioavailability, as well as the need for minimizing risk behaviors, must be increased. In order to tackle the problem of cadmium contamination in regions performing activities, such as soil preparation for mining or open-land dumping sites, it must be understood that these activities release cadmium into the environment. The consumption of vegetables and fruits poses a health risk to local populations due to the presence of contaminants that have entered the ecosystem through the food chain (soil/water, vegetation, and humans). The long-term effects on public health include renal failure or dysfunction, osteomalacia, osteoporosis, and socioeconomic factors.

3. Prevalence of MT-1 in the serum and KIM-1 in the urine of adolescent females aged 15 to 18 and 19 to 21 years.

Cd accumulation in the human body encourages the creation of extra MT-1, a low-molecular-weight protein (LMWP), with sulfur as a component of the chemical structure capable of binding to heavy metals as a defense or preventative measure against heavy metals. MT-1 is a single-molecule amino acid involved in food metabolism that protects the human body against harmful heavy metals [32]. The interaction between MT-1 and Cd in the form of MT–Cd and Cd binding in the colon can alter adsorption rates, leading to tissue deposition and gallbladder excretion. Numerous organs in the human body are involved, including the kidney, bones, lungs, liver, and immune systems [33]. The current study observed the presence of MT-1 in serum samples, indicating that individuals living in this area were similarly poisoned by Cd and other heavy metals present in the local environment. Heavy metal binding to MT–Cd reduces the occurrence of heavy metal toxicity. This study discovered a statistically significant inverse connection between age and serum MT-1 levels. Natural MT mitigates the toxicity of Cd by attaching to it and producing MT–Cd, which is then transported to the kidneys [34]. Higher UCd concentrations are associated with increased serum MT levels. In addition, chronic Cd exposure in mice is associated with the development of cancer in a variety of states, which is correlated with MT gene expression failure [11]. It can be inferred that MT-1 has a protective effect against Cd toxicity in humans. Daily cadmium exposure can be directed to the liver and transported to the bloodstream via interacting with RBC and albumin in the liver, where cadmium creates metal complexes by binding to metallothionein. Cd produces metal complexes with metallothionein [35]. The kidney is then transferred to Cd–MT metal complexes [14]. Cadmium's half-life in the human body ranges from 10 to 30 years; therefore, its accumulation in the kidneys and liver increases with age [11].

The absorption of essential trace elements in the human gastrointestinal tract, including calcium, iron, copper, zinc, and protein, can improve the exposure status. In addition to the different metals that induce MT-1 to participate in the function of building bonds with that element to prevent poisoning, it is also possible to form a bond with that element. Another study indicated that individuals with lower calcium levels are more susceptible to cadmium, which enhances cadmium exposure in the human body by triggering the synthesis of MT-1 [36].

As illustrated by Figure 7, females frequently exhibited higher Cd levels than males ($p < 0.05$). Cadmium has caused damage to women living in contaminated areas because they are a high-risk category for cadmium availability due to menstrual iron loss. Cadmium-related body burden in females, particularly those suffering from iron deficiency, is generally more common than in males. This is because the duodenal iron transporter is overexpressed in females due to iron deficiency, resulting in the increased absorption of dietary cadmium by the intestinal system, particularly the uterus. Areas with considerable zinc contamination levels may have a negative impact on trace levels of essential metals, such as copper, which is a component of RBC and is associated with iron absorption activity, which cannot be absorbed when zinc levels in the environment are high. This indicates that the body is more vulnerable to heavy metals, such as Cd and Pb [17]. A moderately negative connection between age and MT-1 and KIM-1 contents was observed to be statistically significant, as presented in Table 4. Nonetheless, there was a substantial negative relationship between UCd and high levels ($p< 0.05$). The comparisons between age groups were statistically significant ($p < 0.05$), as were the comparisons between sexes (Figure 8). The early indicator of renal tubular function was modest. Similar research conducted by revealed a moderate connection between KIM-1 and UCd (r = 0.33); however, no association with UCd levels was determined [37]. Cd's effect on the kidney is the loss of renal function that occurs during its elimination from the body. While cadmium may impair kidney function, KIM-1 has been investigated in zinc-contaminated populations who reside in regions with high levels of zinc pollution, and it may have a negative impact on trace amounts of essential elements, such as copper [18]. Due to the fact that elevated levels of ambient zinc limit copper absorption, which is a component of RBC and is associated with decreased iron intake, the body is more sensitive to the entry of heavy metals, such as Cd and Pb. KIM-1 levels in the urine increase with age due to senior persons' prolonged exposure to cadmium in the body, which leads to cadmium accumulation in the proximal tubular region of the kidney and renal failure in the population of polluted areas.

We developed an integrated co-operation strategy between local administrative organizations and public health agencies to monitor health consequences for at-risk individuals over the age of 15 years in the region, separated into three categories: environmental surveillance, encompassing surveillance, such as measuring cadmium levels in the blood (short-term exposure) and urine (long-term exposure), and protection against different types of cadmium in the environment; exposure surveillance, where those who have been exposed to cadmium, but present no symptoms or moderate symptoms, are subject to observation; and health effect surveillance focusing on renal function in participants evaluated with UCd levels higher than 0.2 μg/gCr, bone porosity in menstruating women, and nutrition, such as reducing the consumption of natural foods high in cadmium, including sunflower seeds (*Helianthus annuus*), maize (*Zea mays*), poplar, or willow, as well as the consumption of protein-rich foods, including red meat, high-zinc foods, such as seafood, and foods high in calcium, such as fish and various types of milk, to meet the body's nutritional requirements [38]. Thus, persons who adopt a vegetarian diet because they are part of the group that consumes mostly fibrous foods are at risk of iron deficiency; therefore, this was perceived as a separate category in the study. Another area where cadmium pollutants should be monitored is promoting the intake of high-protein supplements to reduce cadmium availability in the body. In relation to age-based surveillance owing to gender-specific disparities in adolescents in high-risk locations, care should be taken to prevent the absorption of cadmium into the body.

During the commencement of menstruation, female adolescents develop at a more rapid rate than male adolescents. Due to menstrual iron loss, female adolescents are more likely to be exposed to cadmium at this age than male adolescents [38]. However, in males aged 15 years and older, the rapid growth of their body structure and muscles increases the requirements of the circulatory system and oxygen levels, which, in turn, affects the body's demand for hemoglobin. Iron in the RBC increases proportionally, resulting in an increased risk of iron deficiency in adolescent boys' bodies [38]. However,

managing the release of cadmium into the environment is challenging in research, since it is generated by human activity, particularly in industrial and mining operations where cadmium is a byproduct of smelting, along with other heavy metals, depending on the kind of mineral, or is removed directly for use, depending on the characteristics of cadmium (specific gravity: 8.65, Mohs hardness: 2.0, refractive index: 1.13, melting point: 321.1 °C, boiling point: 766.8 °C [39]. Cadmium metal is utilized in electrical plate materials, as an alloying component in nickel–cadmium batteries, as a stabilizer in polyvinyl chloride, as a coloring agent for plastics and glass, and as an ingredient in dental amethyst [40]. Although cadmium has several advantages, its usage causes environmental damage. It is the primary source of cadmium pollution in the environment over an extended period of time (a half-life of 30 years) and enters the human body via the food chain [38].

4. Conclusions

The findings of the research can be divided into three distinct categories in accordance with the objectives of the study. Due to the level of cadmium that was discovered, the 19–21-year-old sample group that lived in an area where there was a risk of detecting cadmium in the urine at 0.02–0.49 μg/gCr may have a shorter cadmium half-life than the 15–18-year-old sample group. Serum protein MT-1, which acts as a protective index in the environment and reduces the number of cadmium compounds in the body, demonstrates this. The propensity of Cd–MT to accumulate in the kidneys demonstrated that risk groups in the Phatadpadaeng subdistrict were more likely to be exposed to cadmium via the food chain than those in other areas. People in the Mae Ku subdistrict were more likely to have early renal tubule dysfunction based on the biological index of primary renal tubule dysfunction than those in other areas. We also discovered that female adolescents between the ages of 19 and 21 are a high-risk group for health and kidney function monitoring because they are more likely than other adolescents to have cadmium accumulation in their bodies because menstruation depletes their iron stores.

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