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Associations between trace level thallium and multiple health effects in rural areas: Chinese Exposure and Response Mapping Program (CERMP)

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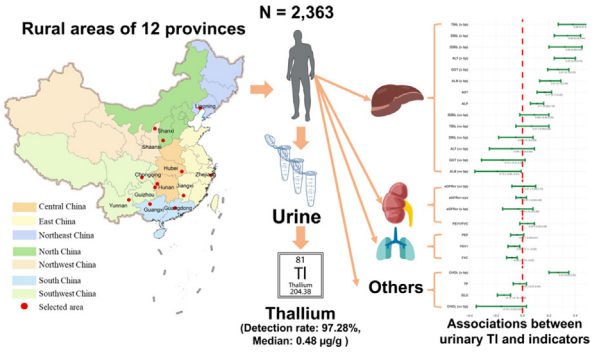
HIGHLIGHTS

- A study of 2363 participants from rural areas in 12 provinces of China
- The detection frequency of Tl in the urine of the participants was 97.28 %.
- Non-linear associations between urinary Tl and liver health indicators were found.
- Urinary Tl > 0.40 μg/g was positively associated with increases in serum bilirubin.
- Urinary Tl was negatively associated with increases in lung health indicators.

GRAPHICAL ABSTRACT



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ABSTRACT

Thallium (Tl) is a cumulative high toxicant in the environment, but few studies have investigated the comprehensive health effects underlying chronic Tl exposure at trace levels. This study aims to evaluate the liver, kidney, lung and other potential health effects associated with chronic Tl exposure at trace levels in rural areas of China. Urinary Tl concentrations of 2883 adults from rural areas of 12 provinces in China were measured and 2363 participants were involved in the final analysis. Indicators of liver and kidney functions in the serum, as well as the lung function indicators, were determined in the participants. General linear regression and restricted cubic spline regression were combined to study the associations between urinary Tl and health indicators or outcomes. In this study, the detected rate of Tl in the urine of the participants was 97.28 %. When the urinary Tl concentration was ranged at the fourth quintile, the risk of having liver function disorder was 70 % higher [Odds ratio (OR) = 1.70 (95 % confidence intervals (CI): 1.30, 2.22)] in all the participants, whereas the farmers were more likely to have the disorder [OR = 2.08 (95 % CI: 1.49, 2.92)] than the non-farmers [OR = 1.20 (95 % CI: 0.77, 1.88)]. Nonlinear associations between most of the liver health indicators and urinary Tl were identified, of which serum bilirubin was strongly associated with the elevation of urinary Tl when its concentration was >0.40 μg/g creatinine. Besides, urinary Tl was negatively associated with lung health indicators. Our study proposes the safety re-assessment of the current exposure level of Tl in the environment, especially in rural areas of China.

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1. Introduction

Thallium (Tl) is an odorless and water-soluble chemical for which both accidental intoxication and criminal poisoning have been reported (Osorio-Rico et al., 2017). Tl could be absorbed via inhalation or skin and the occupational exposure limit for Tl is 0.1 mg/m^3 (Liu et al., 2018). Although Tl was banned in the US in 1975, anthropogenic activities contributed to approximately 5000 tons of Tl emissions in the environment annually (Karbowska, 2016). Humans are still at high risk of being exposed to Tl through occupational exposures, accidental ingestions, the consumption of contaminated fish or drugs, or exposures to hazardous waste sites (Osorio-Rico et al., 2017). In China, Tl is a pollutant associated with epithermal metallogenesis of sulfide minerals, which could be dispersed in water, soil, and crops (Xiao et al., 2012). The acute and fatal effects of Tl intoxication have been well-documented (Al Hammouri et al., 2011; Leung and Ooi, 2000; Lin et al., 2019). Besides, the adverse effects of chronic exposure to Tl on aquatic biota have been reported recently (Hou et al., 2017; Nagel et al., 2021). However, the chronic effects underlying Tl exposure at non-lethal and trace levels on humans are still unclear.

A previous German study with 1265 participants living close to a Tl-contaminated cement plant showed strong associations between polyneuritic symptoms and the increases in the urinary Tl (Brockhaus et al., 1981). In China, a study reported that urinary Tl concentrations in the residents of a rural area were correlated to those in the nearby soil and crops of the local rural area (Xiao et al., 2007). Urinary Tl levels of the residents living close to the Tl-contaminated sites were high and some of which were over 500 μg/L. On the other hand, recent epidemiological studies demonstrated that low-level Tl exposure (medium urinary ranging from 0.062 μg/L to 0.58 μg/L) was associated with premature birth, low birth weight, gestational diabetes, cardiovascular disease and lung function decline (Dai et al., 2019; Jiang et al., 2018; Wang et al., 2022; Zhu et al., 2019). However, the association between comprehensive health effects, especially liver/kidney function disorder and chronic Tl exposure at trace levels are seldom reported. Besides, most of the epidemiological studies in China covered a restricted area, which may introduce strong biases because of the variation in Tl background levels and demographic properties (Liu et al., 2019). Therefore, it is a need to thoroughly investigate the potential health risks linked with Tl exposure at trace levels on a national scale. Urinary Tl is an reliable marker for indicating Tl exposure and is more accessible than serum Tl (Campanella et al., 2016; Xiao et al., 2007). Herein, we perform a cross-sectional study involving 2363 participants from rural areas of 12 provinces in China to study associations between the potential health effects and chronic exposure to Tl at trace levels. To achieve this, we measured the urinary Tl levels, liver and kidney health indicators in serum, as well as the lung function indicators of the participants.

2. Methodologies

2.1. Study design and participants

This study is derived from the Chinese Exposure and Response Mapping Program (CERMP). The details of CERMP are described in Text S1 in the supplementary file. In this study, 12 provinces covering all 7 (central, east, northeast, north, northwest, south, southwest) regions of China were selected. In each of the provinces, one rural area (the rural areas were "towns" or "townships" administrative divisions defined by the Chinese government, data is available in "China Statistical Yearbook 2021" complied by National Bureau of Statistics of China, http://www.stats.gov.cn/tjsj/ndsj/2021/indexeh.htm) was selected by the simple random sampling method. To obtain equal sampling size, approximately 200 to 300 adults (age > 18) were recruited from each of the rural areas. In total, 2883 participants were recruited from 12 provinces between 2020 and 2021. The age and gender of the participants were collected by their ID cards. Questionnaires were delivered to the participants to collect their basic information including years of residence, the status of tobacco smoking and alcohol drinking, educational levels, occupation, exercise condition, annual income and disease history. The details of the questionnaires were described in Text S2 in the supplementary file. Blood and urine of the participants were collected by trained phlebotomists who also conducted the measurement of the weight (kg) and height (cm) of the participants. After the removal of missing data in urinary Tl and the outliers in urinary Tl [1.5 times of the interquartile range (IQR)], 2363 participants were retained. The investigation was conducted following a Chinese technical regulation of field investigation for environment and health-cross-sectional study (standard number: HJ 839-2017, released by the Chinese Ministry of Ecology and environment). This study has received approval for research ethics from the Research Ethics Committee of Sun Yat-sen University and the proof of approval is available upon request.

2.2. Determination of Tl and other potentially toxic elements in urine

Urinary samples were collected from participants in the morning after an overnight fast (>12 h) and were stored at 4 °C prior to analysis. Urinary samples were centrifuged at 13,000 rpm for 5 min and the supernatants were filtered by 0.45 μm filters. Precisely 0.8 mL of the filtered sample was transferred into a 10 mL polypropylene tube and was added with 1.0 mL of internal standards and 8.2 mL of 2 % nitric acid (v: v). The mixed solution was analyzed by Inductively coupled plasma mass spectrometry (ICP-MS). The limit of detection (LOD), method recoveries, inter−/intra− day precisions, linearity of the standard curves of Tl and other potentially toxic elements, and the probable contaminant interference from reagents were examined (Text S3 and Table S1 in supplementary file).

2.3. Measurements of health indicators

Seven liver function indicators: albumin (ALB), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), direct bilirubin (DBIL), γ-glutamyl transpeptidase (GGT), and total bilirubin (TBIL); two kidney function indicators: serum creatinine (CR), creatinine-cystatin (CYS); and three other indicators: total cholesterol (CHOL), glucose (GLU) and total protein (TP) were determined in serum samples of the participants via Automatic biochemical analyzer (AU5800, Beckman Coulter, Tokyo, Japan) and biochemical kits (Beijing Jiuqiang Reagent Company, Beijing, China). Indirect bilirubin (IDBIL) was calculated by the subtraction between TBIL and DBIL. Before the sample measurement, two trials of quality control (QC) samples of the above health indicators were measured by the biochemical analyzer every day from 1st November to 9th December 2020, to ensure the accuracy and stability of the instrument (Fig. S1, supplementary file). The descriptive statistics of the QC samples of health indicators measured by the biochemical analyzer are shown in Table S2 in the supplementary file. All the measurements were conducted in Sun Yat-sen University, Guangzhou, China. Three lung function indicators: forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1) and peak expiratory flow (PEF) were determined by spirometry testing. The detailed descriptions of the measurements of the health indicators and the QC/QA procedures are described in Text S4 in the supplementary file. Estimated glomerular filtration rate (eGFR) creatinine ($eGFR_{cr}$) and creatinine-cystatin C ($eGFR_{cr\text{-}cys}$) were calculated based on CR and CYS (Miller et al., 2022) (see the equations in Table S3). In total, 17 indicators were applied to evaluate the health conditions of the participants.

2.4. Outcome measurement

The determination of liver/kidney function disorder followed the published literature (Liu et al., 2022; Miller et al., 2022). Briefly, liver function disorder was determined by any observed abnormality from ALB, ALT, AST, ALP, GGT and DBIL. On the other hand, kidney function disorder was determined by $eGFR_{cr}$. The clinical references of ALB, ALT, AST, ALP, GGT, DBIL and $eGFR_{cr}$ are shown in Table S4 of the supplementary file.

2.5. Covariates

The covariates chosen in this study referred to previous studies on Tl exposures (Dai et al., 2019; Liu et al., 2018; Wang et al., 2022; Zhu et al., 2019), including age (years), body mass index (BMI; kg/m^2), gender (male/female), tobacco smoking (≥1 cigarette per day over six months: no/yes), alcohol drinking (≥1 time per week over six months: no/yes), exercise (≥1 h per week: no/yes), educational level (high school or higher/ middle school/ primary school/uneducated or primary school not graduated), occupation (non-farmer/farmer), exercise (≥1 h per week: yes/ no), and annual income (>30 thousand Chinese yuan or ≤30 thousand Chinese yuan). The detailed definitions of the covariates are shown in Text S2 in the supplementary file.

2.6. Sensitivity and subgroup analysis

Participants excluding smokers (N = 1831), excluding drinkers (N = 1913), excluding liver or kidney function disease in the self-disease report (N = 2336), and participants excluding urinary Tl > 3 times IQR (N = 2482) were applied to perform the sensitivity analysis. Besides, sensitivity analysis was performed by adjusting urinary creatinine as an additional covariate in all the regression models (N = 2363). The subgroup analysis was performed separately on males, females, farmers and non-farmers.

2.7. Mixed exposure model

In this study, some other potentially toxic elements including antimony (Sb), arsenic (As), barium (Ba), cadmium (Cd), cerium (Ce), chromium (Cr), iron (Fe), lead (Pb), nickel (Ni), silicon (Si), strontium (Sr), titanium (Ti), tin (Sn), uranium (U) and yttrium (Y), in urine were measured and were combined with urinary Tl to perform the mixed exposure model. In the study of the association between urinary Tl and liver/kidney function disorders, the above elements were added as additional covariates to adjust the model. Besides, the quantile g-computation algorithm was applied to study the mixed effects of elements on liver/kidney function disorders. The details methods in the mixed exposure model are shown in Text S5 in the supplementary file.

2.8. Statistical analysis

All the data processing procedures, statistical computations and figure construction were done in R (v. 4.1.1). Missing data in covariates were filled by *Mice* R package (3.14.0) with random forest approach (van Buuren and Groothuis-Oudshoorn, 2011). Urinary Tl concentration (μg/L) in each sample was adjusted by the corresponding urinary creatinine (CREA) and was natural log transformed (logTl_{CREA}). All health indicators were standardized and normalized by the *scale* command of *base* R package. Restricted cubic spline (RCS) regression (5 knots) (Marrie et al., 2009) was applied to test the nonlinearity association between logTl_{CREA} and normalized health indicators via the *rms* R package (6.3–0). When any nonlinearity was observed (p < 0.05), segmented regression was performed to explore the potential breakpoint by implementing the *segmented* R package (v. 1.5–0) (Muggeo, 2017). Multiple linear regression was performed by the *glm* command of *stats* R package to explore the association between logTl_{CREA} and health indicators. In the mixed exposure model, quantile g-computation was performed by *qgcomp* R package. Logistic regression was performed by the *glm* command of *stats* R package to study the odds ratio (OR) of liver and kidney function disorders across the quartiles of logTl_{CREA}, and to predict the disorder of ALB, ALT, AST, ALP, GGT and DBIL based on their clinical references. The ratio of the data size between the training set and the testing set was set as 7:3. The construction of receiver operating characteristic curve (ROC) and the calculation area under curve (AUC) were conducted by the *pROC* R package (v. 1.18.0). The Wilcoxon Rank Sum test or Chi-square test was performed to test the significant differences. The p values of multiple comparisons were adjusted by false discovery rate (FDR) by *stats* R package.

3. Results

3.1. Characteristics of the study participants

After the removal of missing data and outliers in urinary Tl, 2363 participants were involved in the following analysis (numbers of missing data in urinary Tl and health indicators are shown in Table S5). Among the participants, 99.3 % and 99.0 % of them had been living in the studied regions for >3 and 5 years, respectively. The participants were divided into lower (N = 1182) and higher exposure (N = 1181) groups by the concentration of Tl_{CREA} (medium = 0.48 μg/g creatinine, Table 1). Average Tl_{CREA} was four times significantly higher (FDR < 0.001) in the higher exposure group (1.13 ± 0.60 μg/g creatinine) than in the lower group (0.28 ± 0.12 μg/g creatinine). Five out of eight liver indicators (ALB, ALT, AST, IDBIL and TBIL), $eGFR_{cr}$, $eGFR_{cr\text{-}cys}$, as well as CHOL were significantly higher (FDR < 0.001) in the higher exposure group compared with the lower group. On the contrary, FVC and GLU were significant (FDR < 0.001) lower in the higher exposure group.

When the participants were grouped by liver function disorder (normal: N = 1489, disorder: N = 734), the average Tl_{CREA} was found significantly higher (FDR < 0.001) in the disordered group (0.80 ± 0.65 μg/g creatinine) compared with that in the normal group (0.66 ± 0.56 μg/g creatinine). Not surprisingly, almost all the liver health indicators were significantly higher in the disordered group in contrast to the normal group (FDR < 0.001). Interestingly, participants of the disordered group showed significantly higher (FDR < 0.05) CHOL, GLU and TP compared with the normal. On the other hand, Tl_{CREA} was significantly lower (FDR < 0.01) in the participants grouped as kidney function disorder (0.76 ± 0.62 μg/g creatinine) compared with the normal (0.63 ± 0.56 μg/g creatinine).

3.2. Associations between urinary Tl and liver/kidney function disorders

Quantile ORs of liver function disorder and kidney function disorder in this study were determined to study the potential health risk of Tl exposure (Fig. 1a-b). Significant associations were only observed at the fourth quantile of the logTl_{CREA} (Fig. 1a). Covariate-adjusted/non-adjusted ORs of liver function disorder shared similar values at the four quantiles of logTl_{CREA} [adjusted OR: 1.70 (95 % CI: 1.30, 2.22); non-adjusted OR: 1.68 (95 % CI 1.30, 2.17)]. However, at the same quantile of logTl_{CREA}, the odds of males having liver function disorder [OR: 1.94 (95 % CI: 1.25, 3.00)] was higher than that of females [OR: 1.79 (95 % CI: 1.26, 2.55)], whereas the odds of farmers having liver function disorder [OR: 2.08 (95 % CI: 1.49, 2.92)] was higher than that of non-farmers [OR: 1.94 (95 % CI: 1.25, 3.00)].

On the other hand, the OR of kidney function disorder varied by the quantiles of logTl_{CREA} and subgroups of gender and occupation (Fig. 1b). A unit change of logTl_{CREA} was negatively associated with kidney function disorder at the fourth quantile of logTl_{CREA} [adjusted OR: 0.63 (95 % CI: 0.48, 0.82)]. However, no significant associations were found in males and in non-farmers at any quantile of logTl_{CREA}.

3.3. Linear/nonlinear association between urinary Tl and health indicators

The linearities between logTl_{CREA} and most of the health indicators were weak (R^2 < 0.1), while some apparent nonlinear relationships between logTl_{CREA} and indicators such as ALB, ALT, DBIL, eGFRcr and CHOL were observed in the local regression (Fig. S2, supplementary file). In the RCS regression (covariates adjusted, 5 knots), nonlinear relationship was observed (FDR < 0.05) between logTl_{CREA} and ALB (breakpoint: logTl_{CREA} = −1.36; Tl_{CREA} = 0.26 μg/g creatinine), ALT (breakpoint: logTl_{CREA} = −1.23; Tl_{CREA} = 0.29 μg/g creatinine), DBIL (breakpoint: logTl_{CREA} = −0.92; Tl_{CREA} = 0.40 μg/g creatinine), GGT (breakpoint: logTl_{CREA} = −1.12; Tl_{CREA} = 0.33 μg/g creatinine), IDBIL (breakpoint: logTl_{CREA} = −0.71; Tl_{CREA} = 0.49 μg/g creatinine), TBIL (breakpoint: logTl_{CREA} = −0.84; Tl_{CREA} = 0.43 μg/g creatinine), eGFRcr (breakpoint:

Table 1
Characteristics of the study participants.

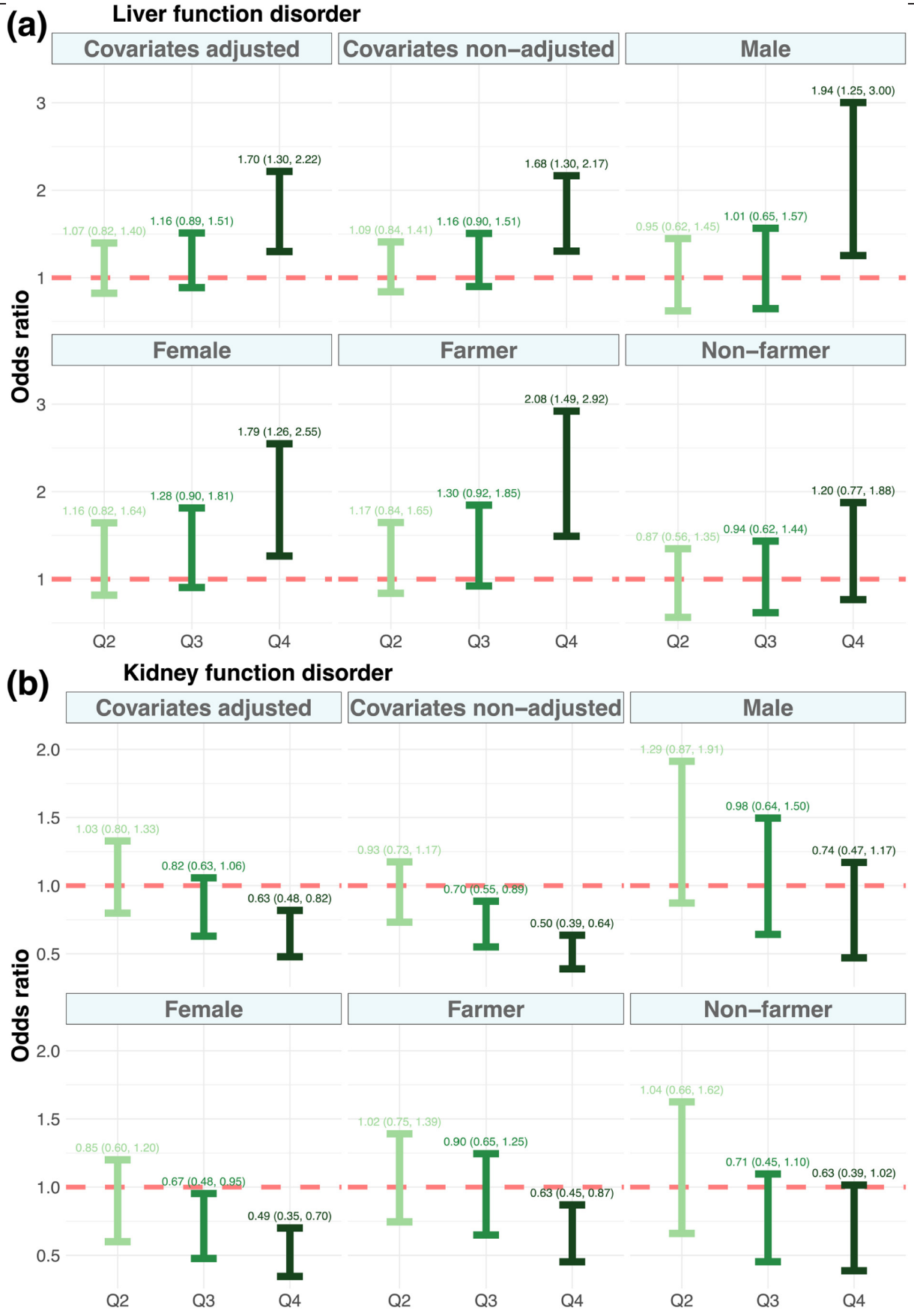
Item/indicators	Urinary Tl (Median = 0.48 μg/g creatinine)			Liver function disorder			Kidney function disorder		
	Low exposure (*N* = 1182) Mean (sd) or N (%)	High exposure (*N* = 1181) Mean (sd) or N (%)	FDR	Normal (*N* = 1489) Mean (sd) or N (%)	Disorder (*N* = 734) Mean (sd) or N (%)	FDR	Normal (*N* = 1251) Mean (sd) or N (%)	Disorder (*N* = 975) Mean (sd) or N (%)	FDR
Tl_{CREA} (μg/g creatinine)	0.28 (0.12)	1.13 (0.60)	**	0.66 (0.56)	0.80 (0.65)	**	0.76 (0.62)	0.63 (0.56)	**
Gender									
Female	658 (27.85)	815 (34.49)	**	988 (40.46)	548 (22.44)	**	822 (33.65)	715 (29.27)	
Male	524 (22.18)	366 (15.49)		667 (27.31)	239 (9.79)		516 (21.12)	390 (15.96)	
AGE (years)	61.86 (12.32)	57.82 (12.89)	**	59.81 (13.00)	60.35 (12.18)		56 (12.80)	64.92 (10.76)	**
BMI	24.28 (3.73)	24.34 (3.85)		24.35 (3.73)	24.49 (3.80)		24.49 (3.71)	24.29 (3.81)	
Education									
Uneducated/primary school not graduated	454 (19.21)	462 (19.55)		653 (26.74)	316 (12.94)		443 (18.13)	527 (21.57)	
Primary school	238 (10.07)	288 (12.19)	*	376 (15.4)	170 (6.96)		288 (11.79)	258 (10.56)	**
Middle school	359 (15.19)	303 (12.82)		463 (18.96)	209 (8.56)		435 (17.81)	237 (9.7)	
High school or higher	131 (5.54)	128 (5.42)		163 (6.67)	92 (3.77)		172 (7.04)	83 (3.4)	
Occupation									
Farmer	757 (32.04)	712 (30.13)		1040 (42.59)	482 (19.74)		789 (32.3)	734 (30.05)	**
Non-farmer	425 (17.99)	469 (19.85)		615 (25.18)	305 (12.49)		549 (22.47)	371 (15.19)	
Smoking (≥1 cigarette per day over six month)									
Yes	308 (13.03)	224 (9.48)	**	394 (16.13)	151 (6.18)	*	307 (12.57)	238 (9.74)	
No	874 (36.99)	957 (40.5)		1261 (51.64)	636 (26.04)		1031 (42.2)	867 (35.49)	
Drinking (≥1 time per week over six month)									
Yes	237 (10.03)	213 (9.01)		323 (13.23)	152 (6.22)		299 (12.24)	176 (7.2)	**
No	945 (39.99)	968 (40.96)		1332 (54.55)	635 (26)		1039 (42.53)	929 (38.03)	
Exercise (≥1 h per week)									
No	810 (34.28)	772 (32.67)		1086 (44.47)	510 (20.88)		908 (37.17)	688 (28.16)	*
Yes	372 (15.74)	409 (17.31)		569 (23.3)	277 (11.34)		430 (17.6)	417 (17.07)	
Annual income									
≤30 thousand	691 (29.24)	673 (28.48)		994 (39.29)	439 (17.35)	**	766 (30.24)	668 (26.37)	*
>30 thousand	491 (20.78)	508 (21.50)		686 (27.11)	411 (16.25)		635 (25.07)	464 (18.32)	
Liver									
ALB (g/L)	42.58 (6.73)	44.08 (7.47)	**	43.05 (6.36)	44.13 (8.61)		43.53 (7.12)	43.26 (7.29)	
ALP (U/L)	85.94 (28.06)	89.18 (29.82)		83.82 (24.38)	98.5 (34.87)	**	85.71 (29.25)	92.1 (28.27)	**
ALT (U/L)	12.70 (7.59)	15.04 (7.97)	**	12.84 (6.73)	16.62 (9.54)	**	14.14 (7.88)	13.75 (7.84)	
AST (U/L)	23.10 (7.00)	24.57 (7.52)	**	22.54 (5.96)	27.34 (9.17)	**	23.59 (7.39)	24.5 (7.44)	*
DBIL (μM/L)	4.58 (1.76)	4.72 (1.97)		4.41 (1.65)	5.3 (2.20)	**	4.69 (1.9)	4.7 (1.88)	
GGT (U/L)	23.85 (13.08)	24.78 (12.77)		23.19 (10.98)	28.05 (16.05)	**	23.74 (12.83)	25.69 (12.82)	**
IDBIL (μM/L)	6.78 (3.01)	7.70 (3.46)	**	6.94 (3.05)	8.06 (3.77)	**	7.46 (3.38)	7.11 (3.28)	*
TBIL (μM/L)	11.42 (4.62)	12.39 (5.09)	**	11.37 (4.45)	13.35 (5.73)	**	12.15 (5.01)	11.81 (4.93)	
Kidney									
$eGFR_{cr\text{-}cys}$	82.50 (19.99)	86.78 (21.13)	**	85.78 (20.49)	80.79 (21.17)	**	95.69 (16.31)	69.58 (16.38)	**
$eGFR_{cr}$	87.46 (17.1)	93.28 (18.07)	**	90.76 (17.62)	88.92 (18.56)		103.12 (9.56)	73.63 (11.36)	**
Lung									
FEV1 (L)	2.23 (0.72)	2.20 (0.69)		2.24 (0.7)	2.15 (0.69)	*	2.3 (0.70)	2.09 (0.68)	**
FVC (L)	2.80 (0.89)	2.70 (0.84)	*	2.77 (0.85)	2.68 (0.86)	*	2.83 (0.86)	2.62 (0.84)	**
FEV1/FVC	84.92 (9.51)	86.26 (9.44)	*	85.66 (9.52)	85.48 (9.32)		85.8 (9.29)	85.33 (9.67)	
PEF (L/s)	4.65 (1.89)	4.54 (1.79)		4.69 (1.83)	4.42 (1.78)	**	4.8 (1.85)	4.33 (1.75)	**
Others									
CHOL (mM/L)	4.51 (1.28)	4.85 (1.37)	**	4.65 (1.25)	4.82 (1.51)	*	4.69 (1.36)	4.73 (1.33)	
GLU (mM/L)	4.96 (1.19)	4.67 (1.29)	**	4.77 (1.19)	4.94 (1.36)	*	4.73 (1.18)	4.95 (1.31)	**
TP (g/L)	76.31 (8.81)	75.98 (9.68)		75.78 (8.9)	77.46 (10.33)	**	75.45 (9.34)	77.38 (9.4)	**

* FDR < 0.05.
** FDR < 0.001.

$logTl_{CREA} = -0.66$; $Tl_{CREA} = 0.52$ pg/L) and CHOL (breakpoint: $logTl_{CREA} = -1.34$; $Tl_{CREA} = 0.26$ μg/g creatinine) (Fig. 2).

The β values of the normalized health indicators were calculated by multiple linear regression with covariate adjusted (Fig. 3). At the same time, the covariates non-adjusted β values were computed (Table S6). Per unit change of $logTl_{CREA}$ was positively associated with normalized TBIL, DBIL, IDBIL, ALT, GGT and ALB when the Tl_{CREA} concentrations were greater than corresponding breakpoints, where the covariate-adjusted β

Fig. 1. Quantile odds ratios (OR) of (a) liver function disorder and (b) kidney function disorder. Logistic regression was applied. The first quantile was set as the reference dashed line in red (OR = 1). Bars in light green to deep green are error bars representing ORs of the disorders at different quantiles (Q2 - Q4) of $logTl_{CREA}$. The adjusted covariates were gender, age, BMI, education level, occupation, smoking, drinking, exercise, and annual income. In the subgroups analysis of male/female and farmer/non-farmer, gender and occupation were separately removed from the covariates.


(a)
Liver function disorder
Covariates adjusted
Covariates non−adjusted
Male
Female
Farmer
Non−farmer
Odds ratio
1.07 (0.82, 1.40)
1.16 (0.89, 1.51)
1.70 (1.30, 2.22)
1.09 (0.84, 1.41)
1.16 (0.90, 1.51)
1.68 (1.30, 2.17)
0.95 (0.62, 1.45)
1.01 (0.65, 1.57)
1.94 (1.25, 3.00)
1.16 (0.82, 1.64)
1.28 (0.90, 1.81)
1.79 (1.26, 2.55)
1.17 (0.84, 1.65)
1.30 (0.92, 1.85)
2.08 (1.49, 2.92)
0.87 (0.56, 1.35)
0.94 (0.62, 1.44)
1.20 (0.77, 1.88)
Q2
Q3
Q4
(b)
Kidney function disorder
Covariates adjusted
Covariates non−adjusted
Male
Female
Farmer
Non−farmer
Odds ratio
1.03 (0.80, 1.33)
0.82 (0.63, 1.06)
0.63 (0.48, 0.82)
0.93 (0.73, 1.17)
0.70 (0.55, 0.89)
0.50 (0.39, 0.64)
1.29 (0.87, 1.91)
0.98 (0.64, 1.50)
0.74 (0.47, 1.17)
0.85 (0.60, 1.20)
0.67 (0.48, 0.95)
0.49 (0.35, 0.70)
1.02 (0.75, 1.39)
0.90 (0.65, 1.25)
0.63 (0.45, 0.87)
1.04 (0.66, 1.62)
0.71 (0.45, 1.10)
0.63 (0.39, 1.02)
Q2
Q3
Q4

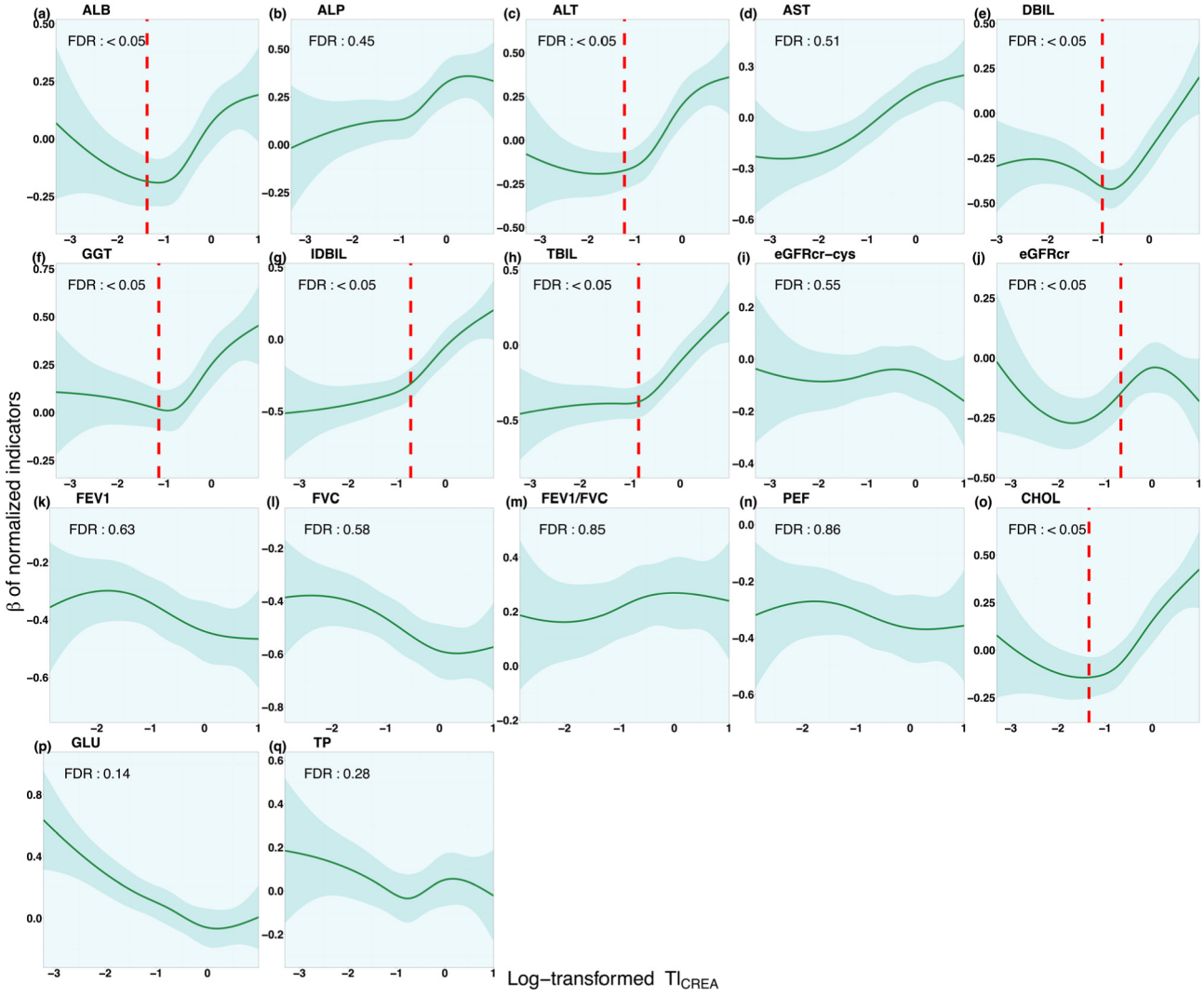


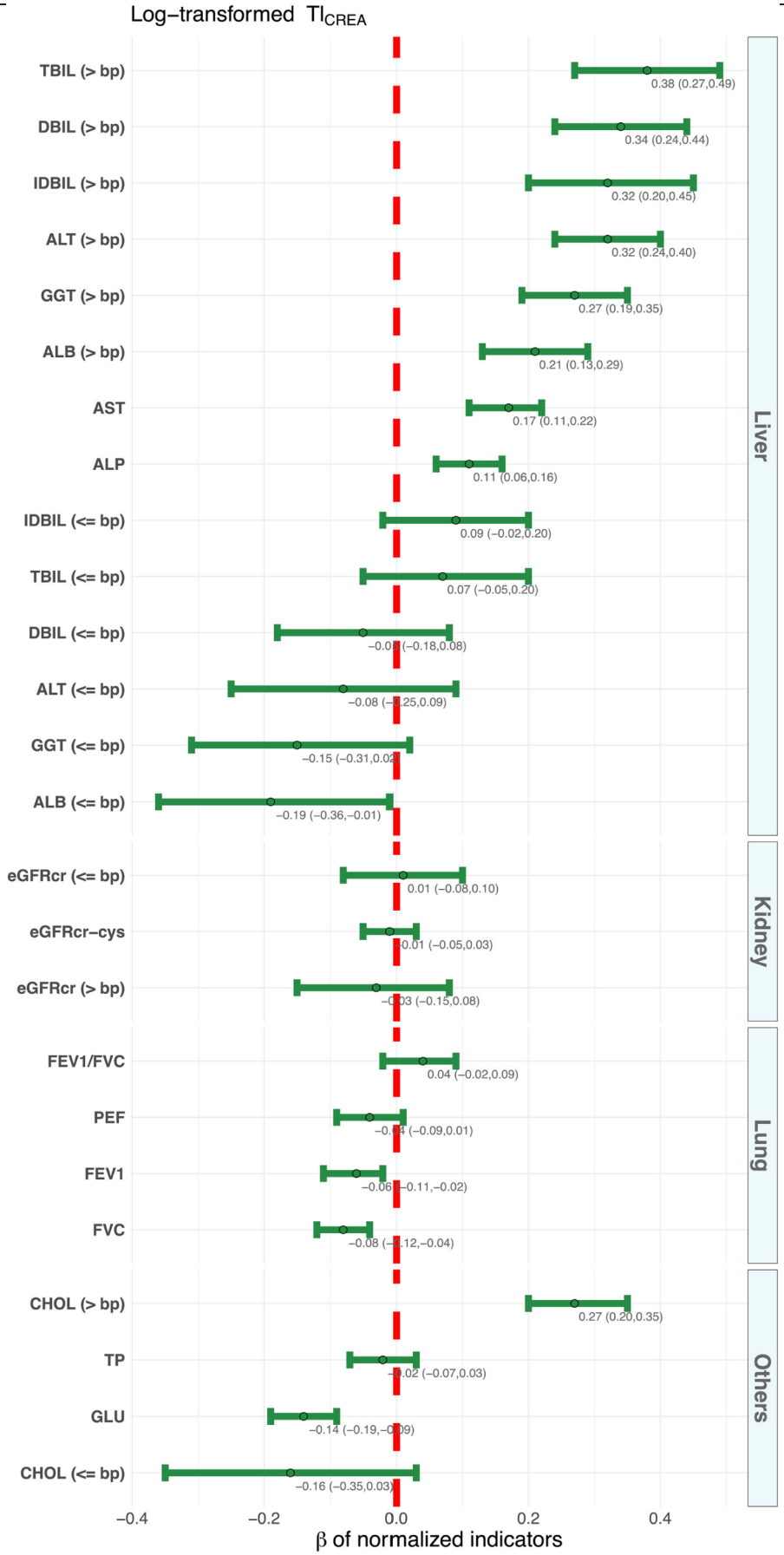
Fig. 2. Non-linear association between $logTl_{CREA}$ and health indicators. (a) - (q) Predicted associations between health indicators and $logTl_{CREA}$. Restricted cubic spline (RCS) regression (5 knots) plots was applied. Green solid lines stand for the predicted fit line of the RCS regression. Red dashed lines represent the breakpoints calculated from the segmented regression. The adjusted covariates were gender, age, BMI, education level, occupation, smoking, drinking, exercise, and annual income. ALB: albumin; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; DBIL: direct bilirubin; GGT: γ-glutamyl transpeptidase; IDBIL: indirect bilirubin; TBIL: total bilirubin (TBIL); $eGFR_{cr}$: estimated glomerular filtration rate creatinine; $eGFR_{cr\text{-}cys}$: estimated glomerular filtration rate creatinine-cystatin C; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; PEF: peak expiratory flow; CHOL: serum cholesterol, GLU: serum glucose; TP: total protein.

values were 0.38 (95 % CI: 0.27, 0.49), 0.34 (95 % CI: 0.24, 0.44), 0.32 (95 % CI: 0.20, 0.45), 0.32 (95 % CI: 0.24, 0.40), 0.27 (95 % CI: 0.19, 0.35)] and 0.21 (95 % CI: 0.13, 0.29). Besides, normalized AST [β: 0.17 (95 % CI: 0.11, 0.22)] and ALP [β:0.11 (95 % CI: 0.06, 0.16)] were positively associated with $logTl_{CREA}$. However, when the Tl_{CREA} concentrations were smaller than the breakpoint, the associations between $logTl_{CREA}$ and most of these lung health indicators were insignificant. Besides, the association between $logTl_{CREA}$ and most of the health indicators of kidney and lung were insignificant, except for the normalized FEV_1 [β: -0.06 (CI: −0.11, −0.02)] and normalized FVC [β: -0.08 (CI: −0.12, −0.04)]. In addition, $logTl_{CREA}$ was positively associated with CHOL (Tl_{CREA} > breakpoint) [β: 0.27 (CI: 0.20, 0.35)], while negatively associated with GLU [β: -0.14 (CI: −0.19, −0.09)].

3.4. Sensitivity analysis

Logistic, RCS and multiple linear regression were performed on data excluding smokers (N = 1831), data excluding drinkers (N = 1913), data excluding participants with self-reported liver/kidney diseases (N = 2336), and data excluding participants with urinary Tl > 3 times IQR (N = 2482), the results are shown in Fig. S3-S14. The results of the above sensitivity analysis were similar to the results of the main analysis. For instance, all the results showed that $logTl_{CREA}$ was significantly and positively associated with the odds of having liver function disorder while negatively associated with the odds of having kidney function disorder at the fourth quantile of $logTl_{CREA}$ (Fig. S3, S6, S9 and S12). In addition, sensitivity analysis was performed on models adjusting urinary creatinine as an additional

Fig. 3. The β values of the normalized health indicators. When the health indicators were nonlinearly associated with $logTl_{CREA}$ in the RCS regression, multiple linear regression was performed on the data before (≤) and after (>) concentration breakpoints of Tl_{CREA} separately. The vertical dashed line in red is the reference line (β = 0). The adjusted covariates were gender, age, BMI, education level, occupation, smoking, drinking, exercise, and annual income. ALB: albumin; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; DBIL: direct bilirubin; GGT: γ-glutamyl transpeptidase; IDBIL: indirect bilirubin; TBIL: total bilirubin; $eGFR_{cr}$: estimated glomerular filtration rate creatinine; $eGFR_{cr\text{-}cys}$: estimated glomerular filtration rate creatinine-cystatin C; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; PEF: peak expiratory flow; CHOL: serum cholesterol, GLU: serum glucose; TP: total protein.


Log−transformed TI$_{CREA}$
TBIL (> bp)
0.38 (0.27,0.49)
DBIL (> bp)
0.34 (0.24,0.44)
IDBIL (> bp)
0.32 (0.20,0.45)
ALT (> bp)
0.32 (0.24,0.40)
GGT (> bp)
0.27 (0.19,0.35)
ALB (> bp)
0.21 (0.13,0.29)
AST
0.17 (0.11,0.22)
ALP
0.11 (0.06,0.16)
IDBIL (<= bp)
0.09 (−0.02,0.20)
TBIL (<= bp)
0.07 (−0.05,0.20)
DBIL (<= bp)
−0.05 (−0.18,0.08)
ALT (<= bp)
−0.08 (−0.25,0.09)
GGT (<= bp)
−0.15 (−0.31,0.02)
ALB (<= bp)
−0.19 (−0.36,−0.01)
eGFRcr (<= bp)
0.01 (−0.08,0.10)
eGFRcr−cys
0.01 (−0.05,0.03)
eGFRcr (> bp)
−0.03 (−0.15,0.08)
FEV1/FVC
0.04 (−0.02,0.09)
PEF
−0.04 (−0.09,0.01)
FEV1
−0.06 (−0.11,−0.02)
FVC
−0.08 (−0.12,−0.04)
CHOL (> bp)
0.27 (0.20,0.35)
TP
−0.02 (−0.07,0.03)
GLU
−0.14 (−0.19,−0.09)
CHOL (<= bp)
−0.16 (−0.35,0.03)
Liver
Kidney
Lung
Others
−0.4
−0.2
0.0
0.2
0.4
β of normalized indicators

covariate ($N = 2363$) (Fig. S15-S17). In this sensitivity analysis, the results of the positive association between $logTl_{CREA}$ and the odds of having liver function disorder were close to the main analysis (Fig. S15a). However, the association between $logTl_{CREA}$ and the odds of having kidney function disorder returned to non-significant compared to the main analysis (Fig. S15b).

3.5. Mixed exposure of Tl and other potentially toxic elements

In this study, urinary As, Ba, Cd, Ce, Cr, Fe, Pb, Ni, Sb, Si, Sn, Sr, Ti, U and Y were measured to study their mixed effect with urinary Tl. After adjusting these elements as additional covariates, the odds of having liver or kidney function disorder were 1.65 (95 % CI: 1.21, 2.26) and 0.52 (95 % CI: 0.38, 0.72) associated urinary Tl (Fig. 4a-b), which were close to the results without adjusting (Fig. 1a-b). Besides, the performance of the ORs was similar in the subgroups. The results of quantile g-computation showed that urinary Tl was the strongest positive contributor to the odds of having liver function disorder in the mixed exposure model (Fig. 4c). On the other hand, urinary Fe was the most, while urinary Tl was the second most negative contributor to the odds of having kidney function disorder (Fig. 4d).

3.6. Predictions of liver health indicators through urinary Tl

In this study, serum ALB, ALT, AST, ALP, GGT and DBIL levels were the indicators to study the liver function disorder. In order to test the ability of urinary Tl to predict the liver function disorder, these indicators were transferred as individual outcomes referring to their corresponding clinical references (Table S2). The ROC curve was generated and the AUC was calculated to study the performance of the predictions (Fig. S18). The calculated AUC ranged from 0.54 to 0.71 in predicting these indicators. The values of AUC were found over 0.7 when predicting ALP and DBIL disorders.

4. Discussion

Our study is the first to investigate the associations between comprehensive health effects and urinary Tl on a national scale in China. The detection of Tl in urine by ICP-MS is known to be stable and accurate (Goullé et al., 2005). A recent epidemiological study reported a strong association between levels of Tl in contaminated drinking water and urine samples of the participants (Aprea et al., 2020). Besides, several studies indicated that urinary Tl is an accurate marker of Tl exposure (Campanella et al., 2016; Xiao et al., 2007). In this study, the detected frequency of Tl in urine was 97.28 %, which implied that the participants in rural areas of China are extensively exposed to Tl. In contrast to serum indicators, the urinary indicator is ideal to predict health effects because of its easy accessibility. In our study, the high detection frequency of urinary Tl and the strong association with liver health indicators implied that urinary Tl is a potential indicator for liver health. Consequently, the ability of urinary Tl to predict the disorders of ALP and DBIL was acceptable (AUC ≥ 0.7), however, was lower than some mixed indicators of liver disease (AUC > 0.8) (Li et al., 2022; Wang et al., 2019). The relatively low AUC obtained in this study may mainly be attributed to the non-linear relationship between most of the liver health indicators and urinary Tl. Besides, Urinary Tl may not be the only factor affecting the liver health indicators. Further studies are

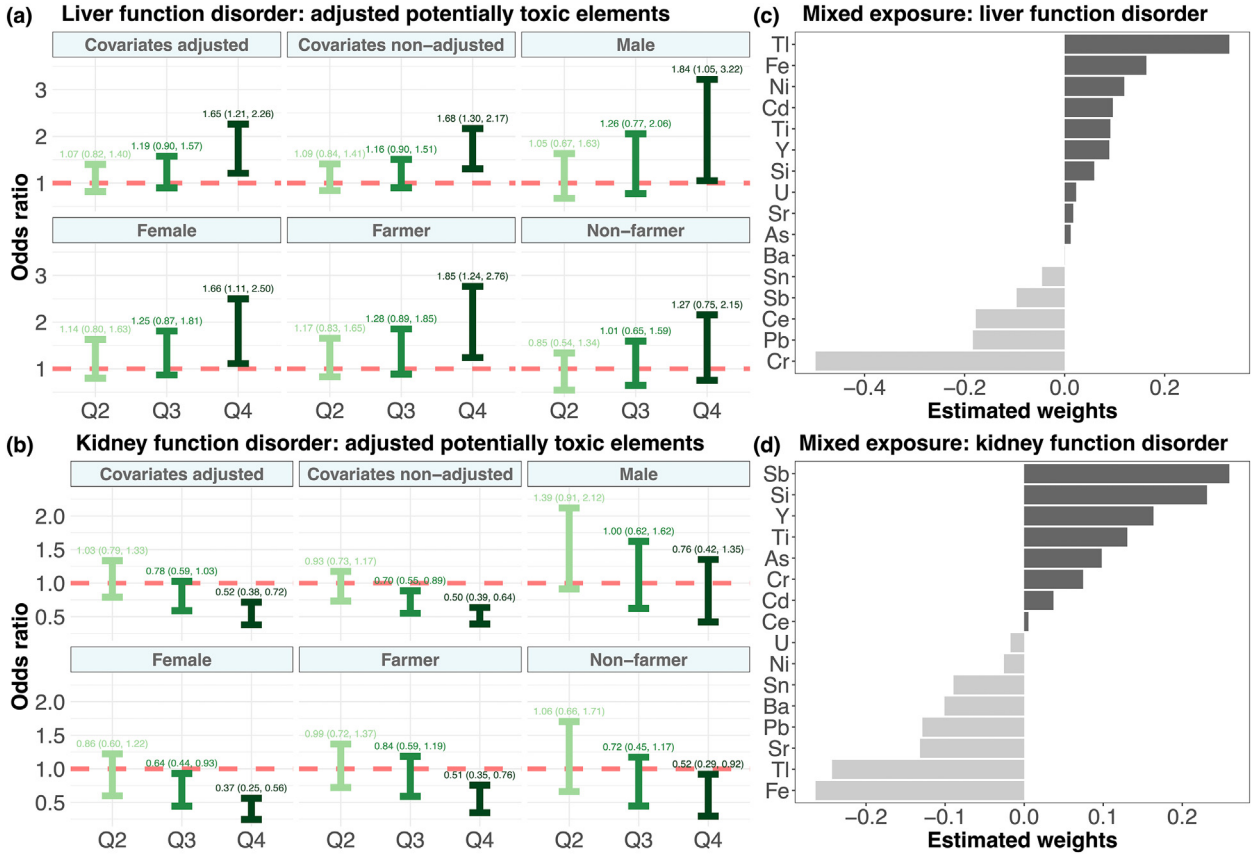


Fig. 4. Mixed exposure models. Quantile odds ratios (OR) of (a) liver function disorder and (b) kidney function disorder calculated by logistic regression adjusting potentially toxic elements. The first quantile was set as the reference dashed line in red (OR = 1). Bars in light green to deep green are error bars representing ORs of the disorders at different quantiles (Q2 - Q4) of $logTl_{CREA}$. Quantile g-computation studying the mixed effects of Tl and other potentially toxic elements on (c) liver function disorder and (d) kidney function disorder. Bars in black and gray stand for the positive and negative estimated weights of the elements affecting the disorders. For both of the models, the adjusted covariates contained gender, age, BMI, education level, occupation, smoking, drinking, exercise, annual income. In the calculation of quantile odds ratios, natural log transformed urinary As, Ba, Cd, Ce, Cr, Fe, Pb, Ni, Sb, Si, Sn, Sr, Ti, U and Y were additionally adjusted in the logistic regression.

required on mixed predictors to improve the corresponding performance of prediction by a more comprehensive prediction model.

4.1. Association between urinary Tl and liver function disorder

Heavy metals such as cadmium and chromium are widely reported contributors to liver function disorder in epidemiological studies (Hyder et al., 2013; Zhao et al., 2022). In the case of Tl exposure, studies related to liver function disorder are limited, though its lethality is well known. Moreover, the association between chronic exposure to Tl at trace levels and liver function disorder has never been reported. In this study, the risk of farmers having liver function disorder was two times higher when the urinary Tl concentration was at the fourth quantile. Previous studies have reported that Tl could accumulate in soil and crops (Xiao et al., 2007, 2012). Therefore, farmers in rural areas are more likely to expose to Tl through the inhalation and consumption of Tl-contaminated crops. However, Tl concentration in soils varied from different regions of China (Xiao et al., 2004; Zhou et al., 2005). Tl concentrations in the environment and foods in our study regions should be measured in future studies to track the exact exposure source of Tl. The risk of the participants having liver function disorder after adjusting all the covariates was still 70 % higher when the urinary Tl concentration was ranged at the last quantile. The sudden increase in the risk implied that Tl exposure might be nonlinearly associated with liver function disorder. The nonlinear relationship between liver function disorder and Tl exposure has never been reported. Though the relationships between Tl exposure and health effects such as lung function decline, kidney function disorder, and preterm birth in recent epidemiological studies were mostly linear (Dai et al., 2019; Jiang et al., 2018; Kremer et al., 2022). The most recent study with over 6800 adult participants revealed that the association between thallium and cardiovascular disease was nonlinear (Wang et al., 2022), which supports our study that Tl exposure is possible to cause health outcomes in a nonlinear manner. In this study, after adjusting other toxic elements such as Cd and Cr, which were known elements that would adversely affect liver functions, the association between the fourth quantile of urinary Tl and the odds of having liver function disorder remained positive and significant. Besides, urinary Tl was found as the most positive contributor in the mixed exposure model in this study. These results suggested that chronic exposure to Tl at trace levels may dominate the risk factors of liver function disorder. However, further toxicological studies on mixed exposure of these elements are required to validate the results in this study.

Our study is the first to investigate the nonlinear relationships between liver health indicators and urinary Tl levels. In the acute or fatal case of Tl intoxication, alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transpeptidase and total bilirubin increased significantly in the liver (Al Hammouri et al., 2011; Lin et al., 2019; Riyaz et al., 2013). Similar results were found in our study that elevations of these indicators were significantly associated with the changes of urinary Tl, which indicated that chronic exposure to Tl at even trace levels may have similar effects to acute Tl intoxication. Additionally, our study also found that ALB, ALP, DBIL and indirect bilirubin were significantly associated with the changes of urinary Tl in either a linear or nonlinear manner, which indicated that chronic exposure to Tl at trace levels would adversely affect multiple liver functions.

Previous studies found that low-level Tl exposure was associated with premature birth, low birth weight, gestational diabetes, cardiovascular disease and lung function decline with a medium urinary Tl concentration up to 0.58 μg/L (0.41 μg/g creatinine) (Dai et al., 2019; Jiang et al., 2018; Wang et al., 2022; Zhu et al., 2019). In our study, significant and positive associations were found between the changes of urinary Tl and all the liver health indicators, of which 6 out of 8 of the associations were nonlinear and were only positively associated when urinary Tl was greater than a range from 0.26 to 0.49 μg/g creatinine was observed. The critical breakpoints of urinary Tl concentration in our study are lower than some of the medium Tl associated with other diseases (Dai et al., 2019; Jiang et al., 2018; Wang et al., 2022). Therefore, our study suggested the reassessment of the safety of Tl exposure at current trace levels in rural areas of China and alarms the possible liver health risk when urinary Tl is >0.26 μg/g creatinine.

In an early study, the toxicity of Tl on the liver has been studied through mice models (Leung and Ooi, 2000). Previous studies have shown that Tl exposure could induce reactive oxygen species formation and mitochondria ATP depletion in rat hepatocyte (Eskandari et al., 2015; Leung and Ooi, 2000), which could explain the positive association between Tl exposure and liver function disorder in this study. Notably, total bilirubin, direct bilirubin and indirect bilirubin were the three liver health indicators found to be most positively associated with the changes of urinary Tl in this study in a nonlinear manner, of which the breaking point concentrations of urinary Tl for these associations were close, ranging from 0.40 to 0.49 μg/g creatinine. Nonlinear relationships between serum bilirubin and manganese-exposed workers have been recently revealed (Ge et al., 2020). Therefore, serum bilirubin might be a nonlinear response to some metal exposure such as manganese and thallium. However, further studies are required to illustrate and prove the intrinsic mechanism. In the cases of acute Tl intoxication, total bilirubin increased significantly in the liver of the patient (Al Hammouri et al., 2011; Lin et al., 2019; Riyaz et al., 2013). Therefore, our study proposes that chronic exposure to Tl even at trace levels would alter the serum bilirubin level and is likely to induce severe liver function disorder.

4.2. Kidney, lung and other potential health risks associated with Tl exposure

A previous study on rats has demonstrated the nephrotoxicity of Tl (Leung and Ooi, 2000). However, this is contradicted by a recent cohort study ($N = 672$) where plasma Tl levels were positively associated with eGFR (Kremer et al., 2022), which implied that Tl exposure may be negatively correlated with the risk of having kidney function disorder. The urinary Tl level in our study was negatively associated with kidney function disorder when the urinary Tl level was at the fourth quantile. However, this study observed no significant association between eGFRcr or eGFRcr-cys and $\log Tl_{CREA}$. Besides, the associations between urinary Tl and kidney function disorder returned to non-significant when adjusting urinary creatinine in the model. Considering the inconsistent results, our study has no sufficient confidence to prove the association between chronic Tl exposure and the risk of kidney function disorder. On the other hand, two of the lung health indicators (FEV1 and FVC) were negatively associated with the changes of urinary Tl in this study, which implied that chronic Tl exposure at trace levels may reduce the lung function. Our results are in line with a recent prospective cohort study that the changes of urinary Tl is associated with the decline of FEV1 and FVC (Dai et al., 2019). Though the mechanism is still unclear, some researchers speculated that chronic exposure to Tl caused oxidative stress and inflammation which induced subsequent lung function impairment (Dai et al., 2019; Rahman and Adcock, 2006). One of the significant nonlinear associations was found between the serum total cholesterol and urinary Tl, where the break point concentration of urinary Tl was as low as 0.26 μg/g creatinine. The elevation of serum total cholesterol is linked to cardiovascular disease in many of studies (Carson et al., 2020; Contreras et al., 2010; Szatrowski et al., 1984; Thomas et al., 2002). Therefore, the positive association between urinary Tl and serum total cholesterol found in this study implied the potential cardiovascular disease through chronic Tl exposure. Several studies demonstrated the reactive oxygen species formation, membrane lipid peroxidation, and reductions of glutathione content and GPx enzyme activity through Tl exposures (Hanzel et al., 2005; Puga Molina et al., 2018), which indicated that Tl exposure could likely induce complicated biological consequences in human bodies. In this study, in addition to the explicit association between urinary Tl and liver function disorder, chronic exposure to trace levels of Tl was connected with potential lung function reduction. In addition, trace levels of urinary Tl should be studied as it may be associated with the abnormal elevation of serum total cholesterol.

4.3. Limitations

Several limitations need to be addressed in this study. This is a cross-sectional study that is insufficient to resolve the causal relationship between Tl and health indicators. Besides, because of the nature of the cross-sectional, the urinary Tl level detected in this study may not be an accurate representation of the level after chronic Tl exposure. Prospective studies are required in the future to prove the associations in this study. The age distribution of the participants (56 years) was slightly skewed. More participants with younger ages should be recruited in further studies to validate the robustness of the findings. In this study, 12 provinces were selected to represent all 7 regions of China. In each of the provinces, we randomly selected one rural area for the sampling. However, several hundred rural areas were available in each of these provinces for selection. In the future study, more rural areas should be assigned to each of these provinces and a larger population size should be recruited. This study did not test the kidney or urinary diseases such as polycystic kidney disease and ureteral malformation, which could affect the kidney function indicators of the participants. Future studies should consider related kidney or urinary diseases of the participants to confirm the association between urinary Tl and kidney function disorder. Tl in the environment (e.g.: soil, water, crops) of the studied regions should be profiled in future studies to track the exposure source of Tl. Tl in the serum of the participants should be measured in future studies to support the internal exposure of Tl.

5. Conclusions

This study is the first to investigate the relationships between urinary Tl and multiple health indicators. We identified that chronic exposure to Tl at even trace levels was positively associated with several liver function indicators in a nonlinear fashion. Our results showed that chronic exposure to Tl at trace levels was likely to elevate serum bilirubin and induce liver function disorder. Our study could contribute to establishing the reference level of chronic Tl exposure and enlightens the public that even trace levels of Tl in the environment could induce adverse health effects through chronic exposure.

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CRediT authorship contribution statement

Yun-Jiang Yu: Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition. **Zhen-Chi Li:** Methodology, Software, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Visualization, Funding acquisition. **Yang Zhou:** Conceptualization, Methodology, Funding acquisition. **Chen-Yin Dong:** Conceptualization, Methodology. **Hong-Xuan Kuang:** Conceptualization, Methodology. **Tong Zheng:** Formal analysis, Visualization. **Ming-Deng Xiang:** Investigation. **Xi-Chao Chen:** Investigation. **Hong-Yan Li:** Investigation. **Xiao-Wen Zeng:** Investigation. **Shu-Li Xu:** Investigation. **Li-Wen Hu:** Investigation. **Guang-Hui Dong:** Conceptualization, Methodology, Writing – review & editing, Funding acquisition.

Data availability

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2022.160466.

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