RESEARCH

Significant association between methyl mercury level and latent tuberculosis infection risk: a cross-sectional study

Hai-bo Hua[1] and Hui-jie Wang[1*]

Abstract

Objectives This cross-sectional study aimed to explore the association between methyl mercury (MeHg) level and latent tuberculosis infection (LTBI) risk based on the data from National Health and Nutrition Examination Survey (NHANES 2011–2012).

Methods A total of 5243 participants with 20 variables were enrolled. The importance of these variables on TB infection was first ranked by XGBoost and Random Forest methods. Then the association between MeHg level and infection risk was evaluated by restricted cubic spline, threshold effect, and generalized linear regression analyses. We also explored the factors correlated with the difference in MeHg level and finally conducted a mediation analysis to assess the mediating effect of MeHg in LTBI.

Results 521 participants were experiencing the LTBI, and 12 variables showed the differences between infection and non-infection groups (all $P < 0.05$). Of them, MeHg presented the highest importance on the LTBI. Restricted cubic spline (RCS) next revealed a significant non-linear correlation of MeHg with LTBI (all $P < 0.05$). Adjusted regression models further indicated their independent association (all $P < 0.05$), and infection risk increased with the increase of MeHg (P for trend < 0.05). We also found a significant turning point, and their association was significantly observed when MeHg > 5.75 μg/L ($P < 0.05$). In addition, asthma history was related to the difference in MeHg levels between LTBI and non-LTBI groups. Mediation analysis found that MeHg level partially mediated the association of asthma and LTBI risk (all $P < 0.05$).

Conclusions Our study identified MeHg as an independent risk factor for LTBI risk. Their causal relationship needs more investigation to verify.

Keywords Methyl mercury, Tuberculosis, Association, NHANES

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Introduction

Tuberculosis (TB) is a chronic and progressive disease caused by mycobacterium infection and has become a major public health problem. According to the Global Tuberculosis Report 2023 (https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023), 10.6 million people worldwide were infected with TB in 2020, and 46% of cases occurred in Southeast Asia. Additionally, 1.3 million people died from TB all over the world, with the highest mortality rate in Southeast Asia. In 2020, the number of new cases of TB in China was 748,000, and the incidence of TB was 52/100,000, ranking third among 30 countries with a high burden of TB, accounting for 7.1% of the global incidence. Research has shown that TB incidence was linked to various factors, including HIV infection, diabetes, male gender, hospitalization history, poor diet quality, and illiteracy [1, 2]. Identifying and impeding the risk factors may be an effective measure to control TB.

The harmful effects of heavy metal exposure on health have been paid more and more attention [3, 4]. Mercury is a highly toxic persistent pollutant, which has been listed as a global pollutant by the United Nations Environment Program. Methyl mercury (MeHg), as the organic form of mercury, is one of the most toxic mercury compounds, and the primary sources of human MeHg exposure are MeHg-riched fish, rice, and other aquatic products [5, 6]. MeHg has been reported to have strong neurotoxicity [7] and can affect fetal nerve development through the placental barrier [8]. Regarding TB infection, only one study reported a positive association between total mercury and latent tuberculosis infection [9]. Currently, few studies reported the association between mercury and TB infection risk. It should be taken seriously regarding the contamination of common food products and drinking water with heavy metals including MeHg.

In this study, we aimed to explore the association of MeHg level with the latent TB infection (LTBI) risk. We initially explored the importance of MeHg on LTBI and then evaluated their association by restricted cubic spline (RCS) analysis, threshold effect analysis, and adjusted generalized linear regression models. Finally, we explored potential factors that affect the MeHg level and disclosed the possible mediating effect of MeHg in LTBI.

Method

Data source and participants

The National Health and Nutrition Examination Survey (NHANES) database (https://www.cdc.gov/nchs/nhanes/) was used to obtain the related data. The data on TB was just recorded in 2011−2012 years. Hence, this cross-sectional study only collected the publicly available data from NHANES 2011−2012.

The LTBI was regarded as the dependent variable in this study. The LTBI was identified according to the QuantiFERON-TB Gold In-Tube test (QFT-GIT) [10]. Positive QFT-GIT was considered LTBI, and negative QFT-GIT was regarded as non-LTBI. The following criteria were used to define positive QFT-GIT, (1) Nil value must be ≤8.0 IU gamma interferon (IF)/ml, and (2) TB antigen value minus Nil value must be ≥0.35 IU gamma interferon (IF)/ ml, and (3) TB antigen value minus Nil value must be ≥25% of the Nil value.

The inclusion criteria were as follows: age>18 years old; had complete data of QFT-GIT and methyl mercury level. The exclusion criteria were as follows: had history experiencing TB disease; individuals with indeterminate QFT-GIT results; had history of active tuberculosis. A total of 9756 samples were obtained from the NHANES 2011−2012 cycle, and 7111 samples had the QFT-GIT data. After removing participants with age<18 years old, 5257 samples were retained. We also removed the samples missing the data on methyl mercury level. Finally, 5243 samples were enrolled in our analysis.

Variables collection

The baseline characteristics of participants included gender (male, female), age (≤55, >55), education level (less than high school, high school, greater than high school), marital status (never married, married/living with a partner, widowed/divorced/separated), the ratio of family income to poverty (PIR), asthma (yes, no), hypertension (yes, no), diabetes (yes, no), smoking status (yes, no), and obesity (yes, no). We also collected the laboratory indexes including red cell distribution width (RDW, %), hemoglobin (g/dL), monocyte (1000 cells/μL), lymphocyte (1000 cells/μL), white blood cell (1000 cells/μL), urea nitrogen (mmol/L), creatinine (μmol/L), uric acid (mmol/L), apolipoprotein B (APOB, g/L), and methyl mercury (MeHg, μg/L).

Statistical analysis

The quantitative variables were presented with the median and quartile due to their non-normal distribution. The difference in quantitative variables between LTBI and non-infection groups was compared with the Mann-Whitney U test. The categorical variables were expressed as frequency and percent, and the distribution difference of categorical variables between the 2 groups was analyzed by χ^2 test. The importance of significant variables showing differences between the 2 groups on the TB infection was initially assessed by XGBoost and Random Forest methods. The restricted cubic spline (RCS) analysis was then conducted to evaluate the correlation between MeHg and LTBI among whole populations and subgroups stratifying with age and gender. Threshold effect analysis was used to reveal

Table 1 The baseline characteristics grouped by LTBI status

	Subgroups	Non-LTBI (N = 4722)	LTBI (N = 521)	P
Gender	male	2293 (48.560)	300 (57.582)	<0.001
	female	2429 (51.440)	221 (42.418)	
Age	≤ 55	3158 (66.878)	231 (44.338)	<0.001
	> 55	1564 (33.122)	290 (55.662)	
Education	< high school	952 (21.369)	191 (37.087)	<0.001
	high school	937 (21.033)	105 (20.388)	
	> high school	2566 (57.598)	219 (42.524)	
marital status	m1	649 (25.332)	34 (12.500)	<0.001
	m2	1430 (55.816)	180 (66.176)	
	m3	483 (18.852)	58 (21.324)	
PIR	< 2.2	2356 (54.186)	279 (60.652)	0.008
	≥ 2.2	1992 (45.814)	181 (39.348)	
Asthma	yes	729 (15.448)	56 (10.769)	0.005
	no	3990 (84.552)	464 (89.231)	
Hypertension	yes	1577 (33.439)	213 (40.962)	<0.001
	no	3139 (66.561)	307 (59.038)	
Diabetes	yes	534 (11.556)	96 (18.861)	<0.001
	no	4087 (88.444)	413 (81.139)	
smoking status	never	2564 (57.605)	272 (52.816)	0.034
	former	999 (22.444)	141 (27.379)	
	current	888 (19.951)	102 (19.806)	
Obesity	yes	2967 (63.806)	346 (66.925)	0.161
	no	1683 (36.194)	171 (33.075)	

Note: All the data were presented with number and percent. The distribution difference of baseline features between the 2 groups were analyzed by χ^2 test. Abbreviation for marital status: m1, never married; m2, widowed/divorced/separated; m3, married/living with a partner

Table 2 The differences in blood indicators between non-LTBI and LTBI groups

	Non-LTBI	LTBI	P
RDW, %	12.7 [12.3, 13.5]	12.8 [12.3, 13.5]	0.890
Hemoglobin, d/dL	13.9 [12.9, 15.0]	13.9 [12.9, 14.8]	0.405
Monocyte, 1000 cells/μL	0.5 [0.4,0.6]	0.5 [0.4, 0.6]	0.180
Lymphocyte, 1000 cells/μL	2.0 [1.6, 2.4]	2.0 [1.6, 2.4]	0.749
White blood cell 1000 cells/μL	6.6 [5.5, 8.1]	6.4 [5.4, 7.8]	0.017
Urea nitrogen, mmol/L	4.28 [3.21, 5.36]	4.64 [3.57, 5.71]	<0.001
Creatinine, μmol/L	75.14 [63.65,88.40]	73.37 [61.00 ,90.17]	0.324
Uric acid, mmol/L	315.2 [261.7, 374.7]	321.2 [267.7, 380.7]	0.110
APOB, g/L	0.87 [0.71, 1.04]	0.89 [0.71, 1.05]	0.316
MeHg, μg/L	0.64 [0.27, 1.61]	0.95 [0.37, 2.86]	<0.001

Note: All the data were presented with median and quartile. The difference of indicators between the 2 groups were analyzed by Mannwhitney-U test

the important turning point that affected their association. Three adjusted generalized linear regression models were used to assess the independent association between them. We also compared the difference in MeHg level between the 2 groups among different subgroups stratifying with baseline characteristics. The characteristics affecting the MeHg level were then rolled into the subsequent mediation effect analysis, and we disclosed the mediating effect of MeHg on the association between baseline characteristics and LTBI. $P < 0.05$ was considered statistical significance.

Results

The baseline characteristics of participants

A total of 5243 participants were enrolled in this study, and 521 participants experienced the LTBI. The baseline characteristics of all participants were presented in Table 1. The obesity showed no difference between LTBI and non-LTBI groups, but the remaining 9 baseline variables all showed significant differences between 2 groups (all $P < 0.05$).

In addition, we compared the differences of 10 blood indicators between the 2 groups (Table 2), finding that the levels of white blood cell ($P = 0.017$), urea nitrogen

(P<0.001), and MeHg (P<0.001) showed a significant difference between LTBI and non-LTBI groups. LTBI group had higher white blood cell and MeHg levels compared with the non-LTBI group.

Further, we ranked the importance of significant variables showing differences between LTBI and non-LTBI groups (including 9 baseline variables and 3 blood indicators). Both the XGBoost and Random forest methods (Fig. 1) suggested the highest importance of methyl mercury on LTBI.

The association between mercury methyl level and LTBI risk

Next, we initially explored the correlation between mercury methyl level and LTBI risk by RCS analysis. The results showed that mercury methyl level had a significant non-linear correlation with LTBI risk among all whole populations (Fig. 2A, P for overall<0.001, P for nonlinear<0.001). After stratifying populations with age and gender, their nonlinear correlation was partially changed (Fig. 2B and C). It was nonlinear correlation in subgroups with age≤55 and gender of male (all P for overall<0.001, all P for nonlinear<0.01). However, among subgroups with age>55 and gender of female, their correlation was linear (all P for overall<0.001, all P for nonlinear>0.05).

Further, we explored the association between MeHg level and LTBI risk by threshold effect analysis (Table 3). The results supported that MeHg level was significantly associated with LTBI risk in a non-linear relationship (Crude model: P for LRT test<0.001). There existed an important turning point (MeHg=5.75 µg/L) that affected their association. Their association was significantly observed on the left of the turning point (OR=1.223, P<0.001), but insignificant on the right of the turning point. After adjusting for several significant variables

(Adjusted model), the turning point was similar with that in Crude model.

Due to the non-linear correlation, we then performed a generalized linear regression analysis to reveal the detailed association between MeHg level and LTBI risk (Table 4). Their positive association was significantly found in crude model and adjusted models (all P<0.001) when setting the MeHg level as the continuous variable. We also set the MeHg level as a categorical variable and performed a trend regression analysis, finding that the association between MeHg level and LTBI risk was increased with the increase of MeHg level (all P for trend<0.001 among 3 models). Our results highlighted the significant independent association between them.

The role of methyl mercury level as a mediator in LTBI

Due to the importance of methyl mercury level in the LTBI, we subsequently explored the potential baseline factors that affected its level between LTBI and non-LTBI groups. The results (Fig. 3) showed that methyl mercury levels had significant differences between the 2 groups regardless of education level, smoking status, age, gender, hypertension, and diabetes (all P<0.05). However, marital status and asthma history had influences on the level of methyl mercury among LTBI and non-LTBI groups. The difference in methyl mercury between LTBI and non-LTBI groups was only found in populations without asthma (P<0.001) and marital status with widowed/divorce/separate (P=0.004).

The above results indicated that asthma and marital status can affect the methyl mercury level in LTBI. Our analysis also found the independent association of asthma history and marital status with the LTBI risk in our previous regression analysis (all P<0.05, data not shown). Populations with asthma had lower LTBI risk. Therefore, we speculated that methyl mercury may exert
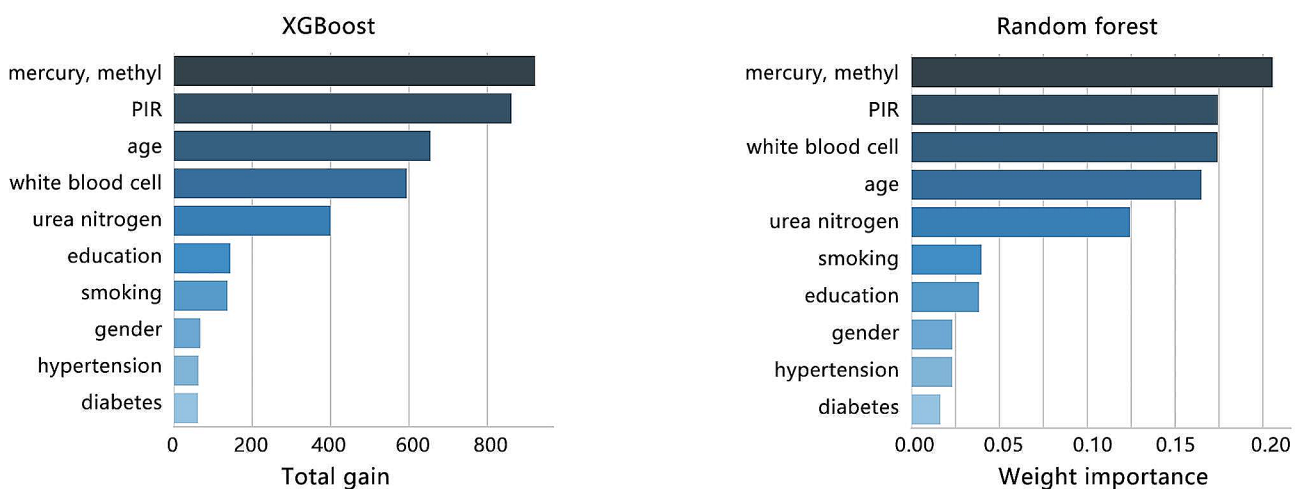

Fig. 1 The importance ranking of significant variables involved in LTBI.
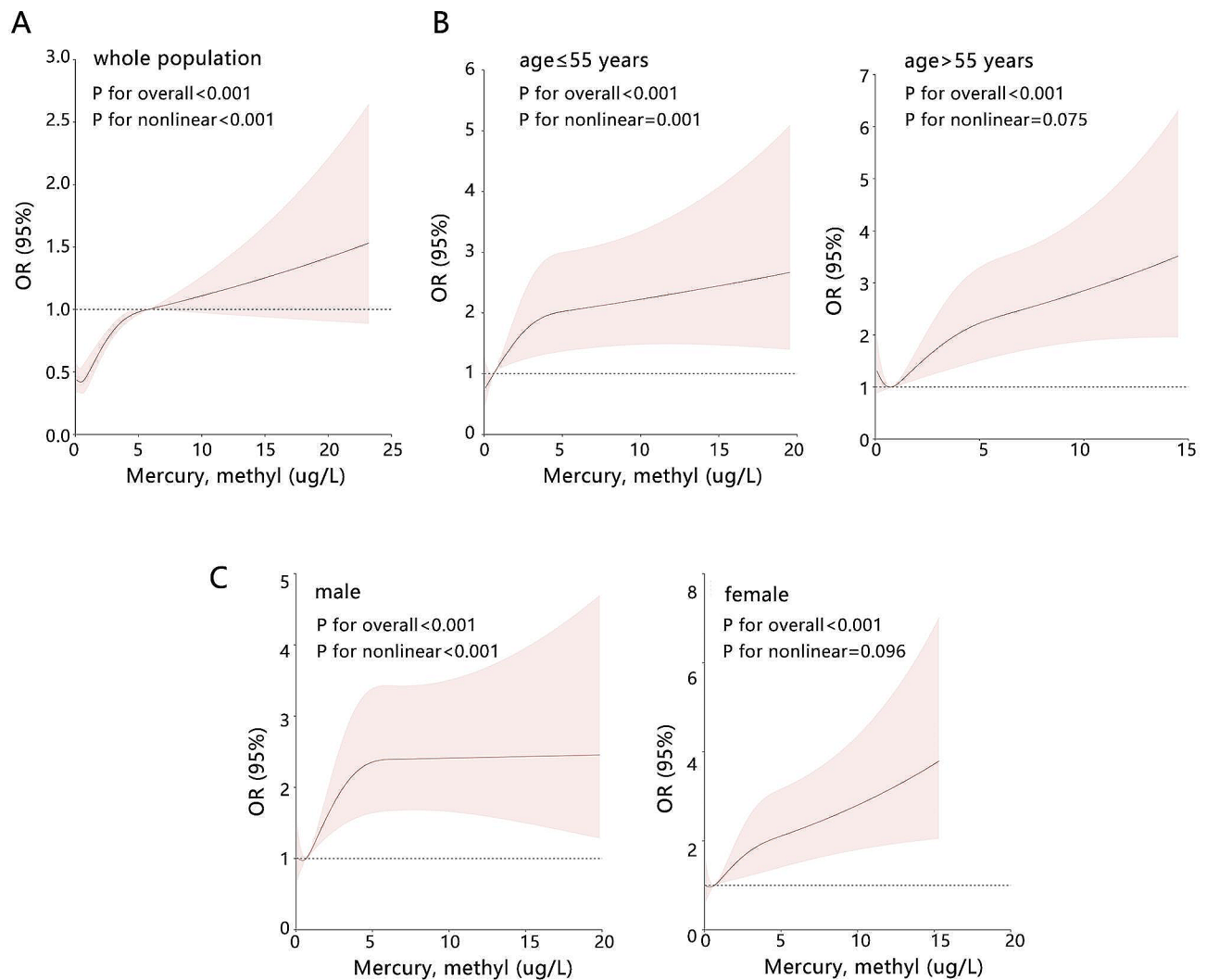
Fig. 2 The correlation between methyl mercury level and TB infection risk by restricted cubic spline (RCS) analysis. (**A**) Whole populations. Subgroups stratified by (**B**) age and (**C**) gender. The shades referred to the 95% confidence interval

Table 3 The threshold effect analysis on MeHg

	Crude model (OR, 95%CI)	Adjusted model (OR, 95%CI)
Model I		
One line effect	1.074 (1.048, 1.110) < 0.001	1.052 (1.003, 1.299) < 0.001
Model II		
Turning point (K)	5.75 µg/L	5.79 µg/L
< K effect 1	1.223 (1.160, 1.290) < 0.001	1.187 (1.124, 1.355) 0.023
> K effect 2	1.002 (0.963, 1.042) 0.940	1.009 (0.823, 1.547), 0.489
Effect 2 − 1	0.819 (0.758, 0.884) < 0.001	0.822 (0.670, 0.921) < 0.001
LRT test	< 0.001	< 0.001

Note: LRT, log likelihood ratio. OR, odds ratio; CI, confidence interval

Adjusted model was adjusted with age, gender, education, marital status, PIR, asthma, hypertension, diabetes, and smoking status

an important mediating effect on the association between asthma condition or marital status and LTBI risk. Hence, we finally conducted a mediation analysis to reveal its potential mediating effect (Table 5). The mediation analysis showed that methyl mercury partially mediated the association of asthma condition or marital status with LTBI risk (all *P* < 0.05 for the indirect effect).

Discussion

Fish and seafood bring a lot of health benefits as they are a good source for the intake of energy, proteins, minerals, and vitamins. Fish consumption is the most common way for humans to be exposed to mercury, and cooking fish does not diminish its content [11]. The previous study showed that older population (>40 years old) significantly consumed more fish compared to adolescents, and the author also found that the hazard quotient value for overall consumption of fish and seafood by 2 populations

Table 4 The association between MeHg level and LTBI risk by trend regression analysis

	Model 1 (OR, 95%CI)	Model 2 (OR, 95%CI)	Model 3 (OR, 95%CI)
Continuous	0.010 (0.007, 0.013) ***	0.006 (0.003, 0.01) **	0.008 (0.005, 0.012) ***
Quartile			
Q1	reference	reference	reference
Q2	0.007 (−0.016, 0.030)	−0.025 (0.056, 0.006)	0.005 (0.019, 0.030)
Q3	0.009 (−0.014, 0.032)	0.001 (0.030, 0.032)	0.005 (0.019, 0.030)
Q4	0.073 (0.050, 0.095) ***	0.056 (0.025, 0.088) ***	0.067 (0.043, 0.091) ***
P for trend	< 0.001	< 0.001	< 0.001

Note: **$P < 0.01$ and ***$P < 0.01$; OR, odds ratio; CI, confidence interval

Model 1: no adjustment

Model 2: adjusting for the PIR, gender, marital status, and education level

Model 3: adjusting for the white blood cell, urea nitrogen, hypertension, diabetes, asthma, and smoking status

exceeded one, which suggested a nonacceptable level of

noncarcinogenic adverse health effects [12]. Uncertainties exist regarding the level of exposure to mercury from fish consumption and the potential health effects resulting from this chronic exposure, which have received considerable critical attention.

Among the ingested mercury contents from fish, methyl mercury (MeHg), as an organic form, is predominant. The ingestion of fish contaminated with MeHg can lead to adverse health outcomes [7, 13]. In terms of LTBI infection, only one study showed a significant association between total mercury and LTBI among adults rather than in adolescents [9]. However, few studies reported the influence of MeHg on the LTBI risk currently.

In this study, we explored the potential association of MeHg level with LTBI, finding a positive association between them. Among several variables, the importance of MeHg ranked the first involved in LTBI. Our study initially revealed MeHg as a risk factor for LTBI, suggesting that controlling for environmental MeHg may be an effective measure to control LTBI.
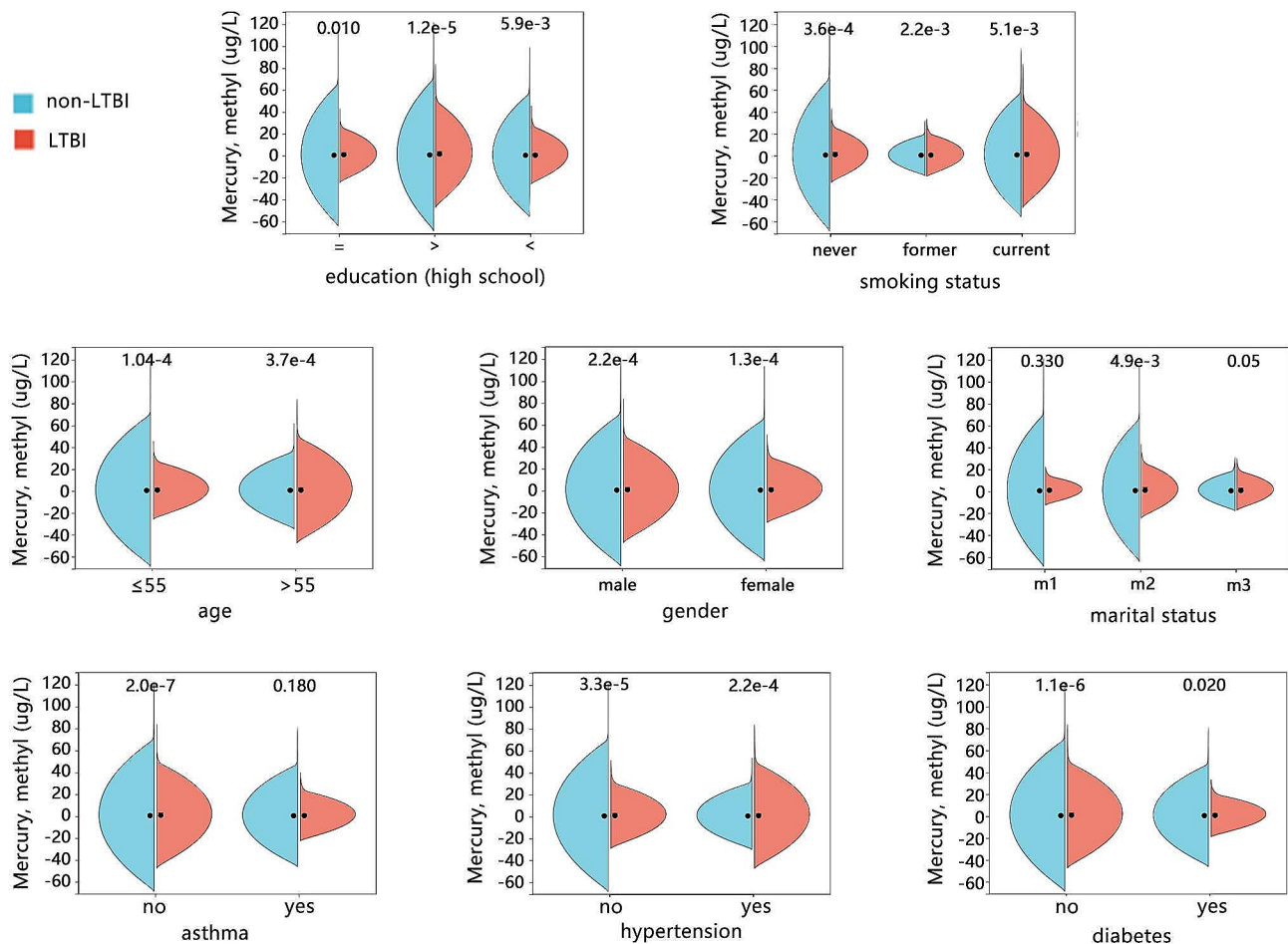

Fig. 3 The difference in mercury methyl level between non-LTBI and LTBI groups among subgroups by stratifying patients with baseline characteristics including education, smoking status, age, gender, marital status, asthma, hypertension, and diabetes. Marital status: m1, never married; m2, widowed + divorce + separate; m3, married + living with partner

Table 5 The mediation analysis by setting methyl mercury as a mediator

	Coef (95%CI)	P	Sig
Path 1: asthma as independent variable			
asthma (X) ~ mercury methyl (M)	0.294 (0.081, 0.506)	0.007	Yes
mercury methyl (M) ~ tuberculosis (Y)	0.010 (0.007, 0.013)	< 0.001	Yes
total	0.033 (0.010, 0.056)	0.005	Yes
direct	0.030 (0.007, 0.053)	0.009	Yes
indirect	0.003 (0.001, 0.005)	< 0.001	Yes
Path 2: marital status as independent variable			
marital status (X) ~ mercury methyl (M)	0.179 (0.043, 0.315)	0.010	Yes
mercury methyl (M) ~ tuberculosis (Y)	0.007 (0.003, 0.010)	< 0.001	Yes
total	0.029 (0.016, 0.042)	< 0.001	Yes
direct	0.028 (0.015, 0.040)	< 0.001	Yes
indirect	0.001 (0.0001, 0.003)	0.008	Yes

Note: X refers to independent variable; M refers to mediator; Y refers to dependent variable. The wavy line has no special meaning, and it just showed a connection between 2 variables that we analyzed. Coef, coefficient; CI, confidence interval; Sig, statistical significance

The underlying biological mechanism between MeHg and LTBI remains unclear. The potential mechanism of LTBI may be related to the organ damage induced by mercury. MeHg preferentially accumulates in the kidney and can induce renal function impairment by increasing the MMP9 expression by promoting demethylation of its regulatory region [14]. DNA methylation and histone post-translation modifications are predominant types of mercury epigenetic alterations [15]. Further, the decline in kidney function is assumed to increase the LTBI risk. The previous study has indicated that in patients with impaired kidney function, the risk of TB increased from stage 3 of chronic kidney disease [16]. In addition, MeHg may also influence the immune cell function. In the presence of mercury exposure, the expressions of toll-like receptors 4a, CD86, and arginase were significantly upregulated in macrophages, and the numbers of macrophages were increased [17]. Further, CD86 and arginase contribute to the macrophage polarization to M2 macrophage [18, 19]. The M2-polarized macrophages fight germs less effectively, which increases the TB infection risk. In turn, the mycobacterium tuberculosis can induce M2 polarization of macrophages by activating the PI3K/Akt1/mTOR signaling pathway, and the bactericidal ability of these polarized M2 macrophages decreases remarkably, resulting in the increased survival of mycobacterium tuberculosis [19]. It follows that there exists a complex interaction between macrophages and mycobacterium tuberculosis, the potential effect of MeHg on the LTBI infection by inducing macrophage polarization needs further verification.

In this study, we also revealed the mediating effect of MeHg on the association of asthma history and marital status with the LTBI infection risk. This study first focused on the discussion of asthma history. We initially found that populations with asthma had lower LTBI risk. The prospective study has indicated that asthma or sino-nasal disease can reduce the incidence of active TB in the adult population [20]. Asthma is predominantly a Th2 inflammatory disease, and Th2 cells can release the cytokines, and recruit and activate the eosinophils. Eosinophils can be recruited to sites of granulomas and inhibit mycobacteria growth in a toll-like receptor-dependent manner via the action of α-defensin [21]. Eosinophils have been found to have antibacterial and anti-mycobacterial actions [22]. This knowledge may explain the lower risk of LTBI among individuals with a history of asthma. In addition, our study also suggested the effect of asthma history on the level of MeHg, and we found that populations with asthma had lower levels of MeHg. Asthma can induce the increase of eosinophils number, and a previous study has indicated that eosinophils can degrade MeHg into inorganic mercury [23]. Another study also reported the inverse relationship between mercury concentrations and the number of eosinophils [24]. This knowledge may explain the lower level of MeHg among individuals with an asthma history. The effect and potential mechanism of MeHg on the LTBI risk have been discussed above. According to this knowledge, we can see that asthma condition not only directly inhibits the mycobacteria growth by increasing the eosinophils number, but also indirectly inhibits LTBI formation by regulating the level of MeHg via the degradation effect of eosinophils.

In addition, we also found that the difference of methyl mercury level between LTBI and non-LTBI groups was mainly observed in marital status of widowed/divorce/separate. We suggested that this result may also indirectly reflect the influence of age on methyl mercury level. The populations (widowed/divorce/separate) showed higher age, with a median age of 61 (data not shown). Those populations (never married/married/living with partner) had relatively lower age, with median age of 27 and 46, respectively (data not shown). With the increase of age, the level of methyl mercury may be higher. We indeed found a significant correlation between age and level of

methyl mercury (data not shown). A previous study also showed that populations with higher age had higher mercury level [25]. This may partially explain the influence of marital status on the level of methyl mercury.

Our study initially revealed the significant association between MeHg and LTBI risk and highlighted the importance of fish consumption on LTBI. However, several limitations should be stated. Due to the lack of genome-wide association studies data on MeHg, therefore we failed to reveal the causal relationships between MeHg and LTBI by Mendelian randomization analysis. In addition, we found the mediating effect of MeHg on the association between asthma and LTBI. The literature review also supported the rationality of the mediating effect of MeHg. In this study, we failed to verify the potential regulatory effect using molecular experiments. More investigations including prospective studies and molecular experiments should be conducted to verify these findings.

Conclusions
This study found that methyl mercury level was significantly related to the LTBI risk in a positive relationship. There was an important turning point that affected their association. In addition, asthma history was related to the level of methyl mercury. Methyl mercury can partially mediate the association between asthma and LTBI risk. Our study suggested methyl mercury as a risk factor for LTBI risk.

Declarations

Ethics approval and consent to participate
The Ethics Committee of Zhejiang Hospital of Integrated Traditional Chinese and Western Medicine deemed that this research is based on open-source data, so the need for ethics approval was waived.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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