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Association between serum thallium in early pregnancy and risk of gestational diabetes mellitus: The Ma'anshan birth cohort study

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ABSTRACT

Background: High blood glucose has been noted in case reports of acute thallium poisoning, however, effects of low-level exposure of thallium on risk of gestational diabetes mellitus (GDM) has not been explored yet.
Objectives: We aimed to explore the association of serum thallium concentration (STC) in early pregnancy and risk of GDM.
Methods: Data of 3013 women from the Ma'anshan birth cohort study (MABC), China was used. STC was measured by inductively coupled plasma mass spectrometry (ICP-MS). Multivariate logistic regression was performed to the association of STC and risk of GDM. Stratified analysis was carried out according to maternal age and pre-pregnancy BMI.
Results: We documented 383 incident GDM (12.7%). The STC ranged from 0.011 to 0.232 μg/L with a median of 0.062 μg/L. Women with advanced age and higher pre-pregnancy BMI tended to have higher level of STC. Individuals in GDM-group have higher level of STC than that in non-GDM group ($P = 0.007$). Maternal STC in early pregnancy was associated with risk of GDM, but the association attenuated to non-significance after adjusted for pre-pregnancy BMI. In the advanced age (> 30 years) group, STC was significantly associated with risk of GDM in a dose-response manner (P for trend < 0.05). Compared with the Quintile 1, the odds ratios (ORs) (95% confidence interval, CI) of Quintile 2, Quintile 3, Quintile 4, and Quintile 5 were 1.48 (0.62–3.53), 2.70 (1.21–6.03), 2.85 (1.29–6.31), 2.30 (1.05–5.05) in the most adjusted model (including pre-pregnancy BMI).
Conclusions: Our study was the first study to demonstrate an association of maternal STC in early pregnancy and risk of GDM, and the association was partly mediated by pre-pregnancy BMI. This association exhibited as an age-dependent manner. Our study highlights even very low-level of thallium exposure could already pose a threat to human's health.

1. Introduction

Gestational diabetes mellitus (GDM) is one of the most common complications during pregnancy. Its short-term [1] and long-term [2,3] harmful effects have brought huge concerns. So identify risk factors of GDM for primary prevention is of great importance.

Pregnant women are vulnerable to environmental toxicants and even low-exposure of metal and/or metalloid could cause harm to both mothers and their fetus [4]. Recently, the hazardous effects of gestational exposure of thallium (Tl), a non-essential but extremely toxic metalloid have caught the eyes of scientific community. Thallium toxicity to mammals is considered comparable to that of mercury, cadmium or lead [5,6], and is a US-Environmental Protection Agency (EPA) priority pollutant [7]. While much of the existing knowledge of the toxicity of thallium derived from case report of acute thallium poisoning [8,9]. The possibility and/or effects of chronic low-level exposure of thallium have received little attention despite a clear need to explore.

Several published papers [10,11] have advanced our knowledge of harmful effect of low-level thallium exposure on adverse birth outcomes. However, study regarding to pregnancy complications such as GDM has been spare. A broad set of studies [12–15] have suggested that

Abbreviations: BMI, body mass index; CI, confidence interval; GDM, gestational diabetes mellitus; ICP–MS, inductively coupled plasma mass spectrometry; MABC, Ma'anshan-Anhui Birth Cohort Study; OR, odds ratio; OGTT, oral glucose tolerance test; STC, serum thallium concentration

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thallium toxicity could induce reaction oxygen species (ROS) formation, and the increased oxidative stress could cause tissue damage and organ dysfunction. Oxidative stress has been widely proposed to be one of the underlying pathogenic mechanisms for insulin resistance and dysfunction of beta cells [16]and play an important role in the progression of GDM [17,18]. Results from animals indicated pancreas could be a target organ for thallium toxicity, because pancreas is among organs with the highest levels of thallium [19] and have been observed congestion after thallium poisoning [20]. Besides, high blood glucose has been noted in case reports of acute thallium poisoning [21]. Based on the evidences above, we hypotheses there might be an association between thallium exposure and risk of GDM. To our knowledge, no study to date examined the association between thallium exposure and the risk of GDM yet.

We used data from the Ma'anshan birth cohort study (MABC), China involving 3013 women first to reveal status of serum thallium concentration (STC) among pregnant women and second to assess the association of STC in early pregnancy and risk of GDM.

2. Material and methods

2.1. Cohort study

The Ma'anshan-Anhui Birth Cohort Study (MABC) is a population-based prospective study aims to investigate the effects of prenatal exposures on adverse pregnant outcomes, child health and development. A total of 3474 pregnant women have been recruited when they came to maternal and child health care centers for their first prenatal visit in Ma'anshan city of Anhui province in China between May 2013 and September 2014. For the current study, eligible participants were the women had both clinical record of 75 g oral glucose tolerance test (OGTT) for diagnosis for GDM and data of STC. Women who didn't take the OGTT, had pre-pregnancy diabetes or had no serum samples in the first trimester were excluded. The flow chart of the excluding process was presented in Fig. 1, and 3013 women were finally included in our study. The present study obtained ethics approval from the ethics committee of Anhui Medical University. Oral and written consents were obtained from all pregnant women.

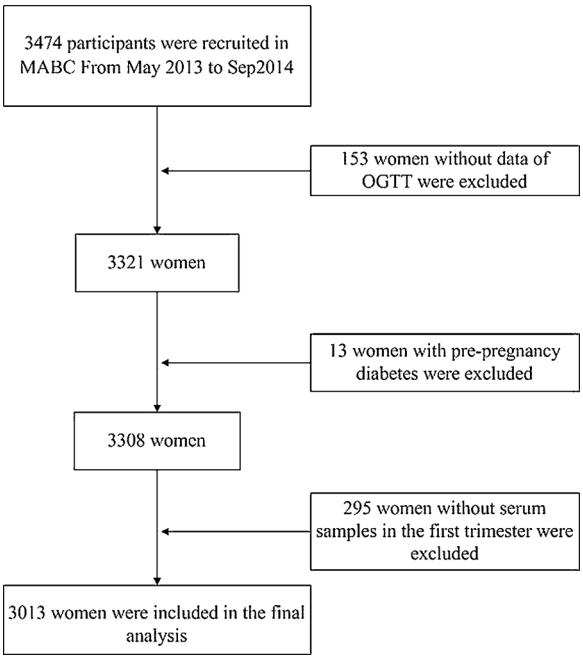

Fig. 1. Flow chart of participant inclusion and exclusion of our study.

2.2. Diagnosis of GDM

Approximately at 28 weeks of gestation, these women were screened by a "one-step" standardized 75 g OGTT. Venous blood samples were collected at 0, 1, and 2 h after the glucose load. According to current guidelines from American Diabetes Association (ADA) [22], the diagnosis of GDM was made when any of the following criteria were met on the 75 g OGTT: fasting plasma glucose ≥5.1 mmol/L, at 1 h ≥ 10 mmol/L, and at 2 h ≥ 8.5 mmol/L.

2.3. Data collection

Extensive data were collected using a structured self-report questionnaire supervised by trained interviewers. Detailed data collected included age, race, education, social-economic status, family diabetes history, smoking, alcohol consumption and anthropometric measures.

2.4. Serum thallium measurement

Blood samples were collected in early pregnancy (before 14 weeks) when women visited for routine health-check. Fasting blood were withdrawn in the morning before 10am. Blood sample was rested for 30 min and serum was extracted and stored in metal-free polypropylene (PP) tubes in -80° for future use. STC was measured by inductively coupled plasma mass spectrometry (ICP-MS) using Perkin Elmer NexION 350X ICP-MS instrument (Shelton, CT, USA) along with other 18 serum elements. The recovery rates of these 19 elements ranged from 79.54 to 107.90%. Individuals were randomly assayed and measured in a blinded manner. For quality control, standard substances from Beijing Bohui Innovation Optoelectronic Technology Co.Ltd. (GBW (E) 080,920) and seronorm corporation (Billingstad, Norway) were both determined using our method, which was proven to be reliable. The intra-assay and inter-assay coefficients of variation of serum thallium were both < 5%. The recovery rate of thallium was 99.59%. All participants had STC above the detection limit. More detail information on our method can be reached out from our previously published paper [23].

2.5. Statistical analysis

Age in years was divided into four categories: < 25, ≥25 to < 30, ≥30 to < 35, ≥35, and pre-pregnancy BMI (kg/m^2) was categorized as four groups: < 18.5, 18.5~24, 24~28, ≥28 [24]. We used chi-square test or student's *t*-test to examine whether there were differences of characteristics between individuals included and excluded. The distribution of STC was tested using the Kolmogorov–Smirnov normality test. We used the Mann-Whitney-U-test to compare the differences in thallium levels between two groups and used Kruskal-Wallis test within multiple groups. Based on the quintiles distribution of the thallium concentrations in the non-GDM group, the maternal STCs were categorized into five levels. Then, logistic regression models were used to assess the relationship between the STC and risk of GDM. Dummy variables were constructed for the missing values in the regression model. We performed a univariate analysis and multivariate analysis to estimate crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for different levels of thallium exposure, respectively. Potential covariates were included in the models based on biologic plausibility and literature review. In the final models, we adjusted for maternal age, pre-pregnancy BMI, family history of diabetes, parity, smoking, drinking, gestational week at blood draw, income, education, serum concentration of arsenic, copper and cadmium. Including the concentrations of arsenic, copper and cadmium in the adjusted model was because our data showed the three metals were significantly or marginally significantly associated with risk of GDM (data now shown). Stratified analysis was also carried out according to maternal age and pre-pregnancy BMI to see if these two factors modified the effect of thallium on

Table 1
Descriptive characteristics of included verse excluded individuals.

Variables	Included (n = 3013)				Excluded (n = 461)		$P^{\dagger}$
	Mean ± SD	N (%)	Thallium concentration Median (Quintile 1- Quintile 4) (μg/L)	P^{*}	Mean ± SD	N (%)	
Age	26.5 ± 3.7			**0.027**	26.4 ± 3.7		0.71
< 25		1079 (32.8)	0.061 (0.048–0.080)			138 (29.9)	
25~30		1648 (50.1)	0.062 (0.049–0.081)			244 (52.9)	
30~35		436 (13.3)	0.064 (0.051–0.083)			60 (13.0)	
≥35		126 (3.8)	0.065 (0.051–0.086)			19 (4.1)	
Pre-pregnancy BMI	20.9 ± 2.8			**0.002**	21.0 ± 3.0		0.59
< 18.5		558 (18.5)	0.061(0.048–0.079)			79 (17.1)	
18.5~24		2090 (69.4)	0.062 (0.049–0.081)			317 (68.8)	
24~28		294 (9.8)	0.065 (0.050–0.088)			49 (10.6)	
≥28		71 (2.4)	0.063(0.051–0.086)			16 (3.5)	
Gestational weeks							
First visit	10.0 ± 2.1				9.7 ± 2.0		**0.005**
Second visit	25.6 ± 1.0				25.7 ± 1.2		0.60
Parity				0.772			0.70
Nulliparous		2659(88.3)	0.062 (0.049–0.081)			404 (87.6)	
Multiparous		354 (11.7)	0.062 (0.048–0.084)			57 (12.4)	
Education				0.443			0.21
Primary school or below		39 (1.3)	0.063 (0.049–0.089)			2 (0.4)	
Middle school		578 (19.2)	0.062 (0.048–0.084)			100 (21.7)	
High school		682 (22.6)	0.062 (0.048–0.081)			104 (22.6)	
Junior college		932 (30.9)	0.063 (0.049–0.082)			127 (27.5)	
Undergraduate or above		782 (26.0)	0.060 (0.049–0.079)			128 (27.8)	
Monthly income (Chinese Yuan)				0.657			0.92
< 1000		52 (1.7)	0.063 (0.047–0.087)			6 (1.3)	
1000~2500		747 (24.8)	0.063 (0.049–0.081)			113 (24.5)	
2500~4000		1292 (42.9)	0.062 (0.048–0.083)			201 (43.6)	
> 4000		922 (30.6)	0.061 (0.049–0.080)			141 (30.6)	
Smoking in early pregnancy				0.433			**0.01**
No		2893 (96.0)	0.062 (0.049–0.082)			431 (93.5)	
Yes		120 (4.0)	0.062 (0.047–0.078)			30 (6.5)	
Drinking				0.545			
Never		2778 (92.2)	0.062 (0.049–0.081)			420 (91.1)	0.72
Occasionally		230 (7.6)	0.064 (0.050–0.082)			40 (8.7)	
Regularly		5 (0.2)	0.057 (0.046–0.072)			1 (0.2)	
Family history of diabetes				0.795			
Yes		249 (8.3)	0.062 (0.050–0.082)			28 (6.1)	< **0.001**
No		2360 (78.3)	0.062 (0.048–0.082)			254 (55.1)	
Uncertain		404 (13.4)	0.061 (0.049–0.081)			179 (38.8)	

Abbreviations: BMI, body mass index; SD, standard deviation.
P* for Mann-Whitney-U-test or Kruskal-Wallis test to detect if there are differences of thallium level between different groups.
$P^{\dagger}$ for chi-square test or student's *t*-test to detect if there are differences between included and excluded individuals.
The significance of bold is $P < 0.05$.

risk of GDM. Furthermore the *P* value for interactions was calculated by a pair-wise analysis under multiplicative interaction model which was evaluated by a likelihood ratio test in the logistic regression. All analyses were conducted using SPSS v20.0 and statistical significance was set at $P < 0.05$.

3. Results

Fig. 1 showed the process of excluding subjects, 3013 pregnant women with both known status (GDM/non-GDM) and data of STC in early pregnancy were finally included. Table 1 showed the description of the characteristics of the included and excluded individuals, differences were detected regarding gestational age at first visit, and smoking in early pregnancy and family diabetes history information. Among 3013 women, we documented 383 incident GDM (12.7%). The STC presents as non-normal distribution. One hundred percentage women's STC was above detection limits. The concentration ranged from 0.011 to 0.232 μg/L with a median of 0.062 μg/L. The levels of STC according to different characteristics were also presented in Table 1. Women with advanced age and higher pre-pregnancy BMI tended to have higher STC.

Table 2 showed the results of the logistic regression of STC against GDM. In the crude model, we found compared with the Quintile 1, the risks of GDM of Quintile 5 significantly increased 59% (*P* for trend < 0.05). However, the association slightly missed the margin of significance when adjusted for maternal age, family history of diabetes, parity, smoking, drinking, gestational week at blood draw, income, education and serum concentration of arsenic, copper and cadmium (OR (95%CI) = 1.41 (0.99–2.01) for Quintile 5 vs. Quintile 1). When added pre-pregnancy BMI in the model, the association further attenuated to non-significance.

Table 3 presented the results of stratified analysis. In the advanced age (> 30 years) group, level of STC was significantly associated with risk of GDM in a dose-response manner (P for trend < 0.05), compared with the Quintile 1, the risks of GDM of Quintile 5 significantly increased 130%. However, P value of interaction between age and thallium concentration did not reach significance (P = 0.22). When stratified according to pre-pregnancy BMI, in neither group was the STC associated with risk of GDM. There was no interaction between pre-pregnancy BMI and STC either.

4. Discussion

To the best of our knowledge, this is the first study suggested that maternal STC in early pregnancy was associated with risk of GDM, and the association was partly mediated by pre-pregnancy BMI.

Table 2
Association between in early pregnancy and subsequent risk of GDM.

Serum thallium (μg/L)	Non-GDM N (%)	GDM N (%)	Crude model OR (95%CI)	Model 1 OR (95%CI)	Model 2 OR (95%CI)
Quintile 1 (≤ 0.048)	537 (20.4)	60 (15.7)	1.00	1.00	1.00
Quintile 2 (> 0.048-0.056)	501 (19.0)	63 (56.4)	1.13 (0.77–1.64)	1.11 (0.76–1.63)	1.11 (0.76–1.64)
Quintile 3 (> 0.056-0.066)	523 (19.9)	85(22.2)	1.46 (1.02–1.64)	1.39 (0.97–1.99)	1.32 (0.92–1.90)
Quintile 4 (> 0.066-0.080)	533 (20.3)	80 (20.9)	1.34 (0.94–1.92)	1.30 (0.90–1.86)	1.30 (0.90–1.87)
Quintile 5 (≥0.080)	536 (20.4)	95 (24.8)	**1.59 (1.12–2.24)**	1.41 (0.99–2.01)	1.33 (0.93–1.91)
P for trend			**< 0.05**	0.26	0.45

Model 1 adjusted for age, family history of diabetes, parity, smoking, drinking, gestational week at blood draw, income, education and serum concentration of arsenic, copper and cadmium. Model 2 adjusted for Model 1 plus pre-pregnancy BMI.
Abbreviations: BMI, body mass index; OR, odds ratio; CI, confidence interval.
The significance of bold is $P < 0.05$.

Interestingly, we found thallium exposure exerts effect on risk of GDM in an age-dependent manner, only among women with advanced age was the STC significantly associated with risk of GDM (in the most adjusted model including pre-pregnancy BMI).

Human health effects from thallium at low environmental exposures are unknown. Thallium minerals and mineralization are rare in nature, thus thallium is often not included in the list of metals to be analyzed despite its high toxicity. Because of recent rapid economic development in China, thallium emissions from mineral extraction and processing have been remarkably increasing. Comparing current data between China and other countries, we could see the level of Tl exposure among non-occupation population in China [10,25] were higher than that in the United States [26], Spain [27] and Germany [28]. In our study, 100% women detected thallium in their serum samples indicating that thallium exposure are wide and its hazardous effects need more attention. In the study [29] comprised 172 pregnant women, 45.3% individuals have blood thallium concentration above limits of detection. In the IMEPOGE study [30] conducted in general population, thallium was detected in over 90% individuals' blood samples. Majority of previous studies used urine [10,31–33] as medium, and a few used the whole blood [29,30]. Our study is the first study presented the status of STC among pregnant women. Only one study [34] we tracked intended to present the normal level of serum thallium in a healthy non-exposed general population and they suggested the reference value range was 0.02-0.34 μg/L. The individuals in our study were perfectly within that range, however, the harmful effect has already been observed. This indicated that even very low exposure of thallium could pose a threat to human's health.

Exploring factors which determine an individual's exposure to thallium is of critical importance. Of those factors, the most extensively studied are socioeconomic status and BMI. Using data from NHANES 2001–2010 [35], urinary thallium was found to be positively associated with socioeconomic status, and shellfish consumption partly mediated this association. However, this association was not reflected in our

Table 3
Stratified analysis of serum thallium concentration in early pregnancy and subsequent risk of GDM according to age and pre-pregnancy BMI.

Variables	Serum thallium (μg/L)	Non-GDM N (%)	GDM N (%)	Crude model OR (95%CI)	Model 1 OR (95%CI)	*P* for interaction
Age (< 30y)						0.22
	Quintile 1 (≤0.048)	463 (20.8)	49 (18.6)	1.00	1.00	
	Quintile 2 (0.048–0.056)	422 (18.9)	47 (17.9)	1.05 (0.69–1.60)	1.05 (0.69–1.63)	
	Quintile 3 (0.056–0.066)	444 (19.9)	58 (22.1)	1.23 (0.83–1.85)	1.10 (0.72–1.66)	
	Quintile 4 (0.066–0.080)	456 (20.5)	49 (18.6)	1.02 (0.67–1.54)	1.00 (0.65–1.53)	
	Quintile 5 (≥0.080)	442 (19.8)	60 (22.8)	1.28 (0.86–1.91)	1.14 (0.76–1.72)	
	P for trend			0.62	0.96	
Age (> 30y)						
	Quintile 1 (≤0.048)	74 (18.4)	11 (9.2)	1.00	1.00	
	Quintile 2 (0.048–0.056)	79 (19.6)	16 (13.3)	1.36 (0.59–3.13)	1.48 (0.62–3.53)	
	Quintile 3 (0.056–0.066)	79 (19.6)	27 (22.5)	2.30 (1.07–4.96)	2.70 (1.21–6.03)	
	Quintile 4 (0.066–0.080)	77 (19.1)	31 (25.8)	2.71 (1.27–5.78)	2.85 (1.29–6.31)	
	Quintile 5 (≥0.080)	94 (23.3)	35 (29.2)	2.51 (1.19–5.27)	2.30 (1.05–5.05)	
	P for trend			< 0.05	< 0.05	
BMI (< 24)						0.98
	Quintile 1 (≤0.048)	488 (20.7)	50 (17.1)	1.00	1.00	
	Quintile 2 (0.048–0.056)	458 (19.4)	47 (16.0)	1.00 (0.66–1.52)	0.98 (0.64–1.50)	
	Quintile 3 (0.056–0.066)	463 (19.7)	66 (22.5)	1.39 (0.94–2.05)	1.29 (0.86–1.92)	
	Quintile 4 (0.066–0.080)	483 (20.5)	62 (21.2)	1.25 (0.85–1.86)	1.22 (0.81–1.83)	
	Quintile 5 (≥0.080)	463 (19.7)	68 (23.2)	1.43 (0.97–2.11)	1.30 (0.87–1.93)	
	P for trend			0.20	0.48	
BMI (> 24)						
	Quintile 1 (≤0.048)	49 (17.8)	10 (11.1)	1.00	1.00	
	Quintile 2 (0.048–0.056)	43 (15.6)	16 (17.8)	1.82 (0.75–4.44)	1.81 (0.72–4.55)	
	Quintile 3 (0.056–0.066)	60 (21.8)	19 (21.1)	1.55 (0.66–3.64)	1.39 (0.58–3.35)	
	Quintile 4 (0.066–0.080)	50 (18.2)	18 (20.0)	1.76 (0.74–4.20)	1.64 (0.67–4.02)	
	Quintile 5 (≥0.080)	73 (26.5)	27 (30.0)	1.81 (0.81–4.08)	1.53 (0.66–3.57)	
	P for trend			0.65	0.77	

Model 1 adjusted for age, pre-pregnancy BMI, family history of diabetes, parity, smoking, drinking, gestational week at blood draw, income, education and serum concentration of arsenic, copper and cadmium.
Abbreviations: BMI, body mass index; OR, odds ratio; CI, confidence interval.
The significance of bold is $P < 0.05$.

study when using education and family average income level as proxy. While a birth cohort study [11] in Wuhan, China found that maternal urinary thallium concentrations varied by educational attainment. Data from NHANES 1999–2002 showed thallium concentration was positively associated with BMI and waist circumference [33]. And some other studies [36,37] also suggested that body thallium load was positively associated with body weight or BMI. Nevertheless, data form NHANES 2003–2010 [38] indicated thallium concentration was inversely associated with pre-pregnancy BMI. But in that paper, the words description kind of contradicts to the data presented in the table. Other studies did not observe significant association between BMI and thallium concentration [29,11]. However, our study suggested maternal age and pre-pregnancy BMI related to serum thallium level the most. These discrepancies might derive from the different medium we used or dietary factors related to thallium exposure.

The underlying mechanism of thallium toxicity remains unclear. The most well-known propose is the interference with the vital potassium-dependent processes [39], substitution of potassium in the (Na +/K+)-ATPase [40]. In our current study, we speculated it might through oxidative stress to involve in the pathogenesis of GDM. Interestingly, we found thallium exposure exerts effect on risk of GDM in an age-dependent manner, only among women with advanced age (> 30 y) thallium exposure was significantly associated with risk of GDM, even independent of pre-pregnancy BMI. One possible pathway crossed our mind was through coping with oxidative stress. As we age, oxidative damage increases, antioxidant capacity decreases and the efficiency of reparative systems become impaired [41]. And this decreasing antioxidant capacity with advanced age might interact with thallium exposure. Yet, this also could be individuals with advanced age have higher level of thallium or other characteristics related to advanced age interact with thallium exposure and needs more efforts to further elucidate.

The strengths and the novelty should be noted. First, our study is the first longitudinal study to reveal an association of higher level of serum thallium in early pregnancy and an increased risk of GDM. Second, the large sample size render us considerable statistical powder to identify effect size of low-level exposure of thallium. Third, age-dependent effect of thallium exposure on risk of GDM revealed in our study might have public significance, cause with China's universal second-child policy implemented, the number of advanced age pregnant women will largely increase.

Several limitations of our study need to be acknowledged. First, we used serum as the detection material, and its stability might be a concern. Thallium disappears from the blood with a half-life of several days, and distributes into other tissues. However, in our case we focused on the harmful effects of long term and low exposure, STC could be an appropriate proxy. Because researchers have already indicated that urinary and blood levels of thallium offer better matrices than hair when identifying people exposed chronically [42]. Second, dietary information was lack in our study which might be an unadjusted confounding.

In conclusion, our current study demonstrated an association of maternal STC in early pregnancy and risk of GDM, and the association was partly mediated by pre-pregnancy BMI. More importantly, this association exhibited as an age-dependent manner. Our study highlights even very low-level of thallium exposure could already pose a threat to human's health. Our exploration shed a light on the environmental risk factors related to GDM and shall have critical public significance.

Declarations of interest

None.

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