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Approval Sheet

Ambient particulate matter (PM2.5 and PM10) exposure during the first trimester and increased risk of maternal thyroid dysfunction

By

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Degree to be awarded: MPH

Epidemiology

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Abstract Cover Page

Ambient particulate matter (PM2.5 and PM10) exposure during the first trimester and increased risk of maternal thyroid dysfunction

By

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B.Sc.
George Washington University
2018

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An abstract of
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Abstract

Ambient particulate matter (PM2.5 and PM10) exposure during the first trimester and increased risk of maternal thyroid dysfunction
By Xichi Zhang

Background: It is known that maternal thyroid dysfunction during early pregnancy can cause adverse pregnancy complications and birth outcomes. This study was designed to examine the association between ambient particulate matter with diameters ≤2.5 micrometers ($PM_{2.5}$) and particulate matter with diameters ≤10 micrometers (PM_{10}) exposure and maternal thyroid function during early pregnancy.

Methods: This study is based on data from a birth cohort study of 921 pregnant women in China. We estimated associations between ambient $PM_{2.5}$ and PM_{10} exposure during the first trimester of pregnancy (estimated with land-use regression models) and maternal thyroid hormone concentrations (free thyroxine (FT4), free tri-iodothyronine (FT3), and thyroid-stimulating hormone (TSH)) collected between weeks 10 and 17 of gestation using linear regression models adjusting for potential confounders. Ambient $PM_{2.5}$ and PM_{10} concentrations were modeled per interquartile range (IQR) increment and as tertiles based on the distribution of the exposure levels.

Results: An IQR increment (68μg/m^3) in $PM_{2.5}$ exposure was associated with a significant decrease in maternal FT4 levels (β = -0.60, 95% CI: –1.17, –0.12); and a significant decrease in FT4/FT3 ratio (β = -0.13, 95% CI: –0.25, –0.02). Further analyses showed that, relative to the lowest tertile, women in both the middle and highest tertiles of $PM_{2.5}$ had significantly lower concentrations of maternal FT4 and FT4/FT3 ratio. No significant associations were found between $PM_{2.5}$ and FT3 or TSH levels. PM_{10} exposure was not significantly associated with maternal thyroid function.

Conclusions: Our study suggests that higher ambient $PM_{2.5}$, not PM_{10}, exposures during the first trimester of pregnancy are associated with a significant decrease in maternal serum FT4 concentrations and FT4/FT3 ratio. Studies in populations with different exposure levels are needed to replicate our study results.

Cover Page

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Introduction

Studies have shown that maternal thyroid hormones, thyroxine (T4) and triiodothyronine (T3), are pivotal for embryogenesis and normal fetal growth, development, and maturation[1-4]. Maternal uncontrolled hypothyroidism (an underactive thyroid that does not produce enough thyroid hormones), even subclinical types, can have a severe impact on fetal growth,[5-8] birth outcomes,[9-15] children's psychomotor and cognitive development,[16-23] and other adverse pregnancy complications (e.g., pregnancy loss and neonatal death).[24-26] Untreated maternal hyperthyroidism (an overactive thyroid that produces too much thyroid hormones), while less common than maternal hypothyroidism, can also cause severe pregnancy and neonatal outcomes.[27-34]

Thyroid gland cells produce T4 and T3 by combining iodine and tyrosine.[35, 36] The amount of thyroid hormones produced by the thyroid gland is regulated by thyroid stimulating hormone (TSH), a hormone produced by the pituitary gland that is regulated by the hypothalamic–pituitary–thyroid (HPT) axis.[35, 36] After being released into the bloodstream, the majority of T4 and T3 are bound to specific transport proteins, with only a small percentage of unbounded "free" T4 (FT4) or T3 (FT3) that are able to directly control and regulate body metabolism. During pregnancy, maternal thyroid hormones reach the fetus through the placenta, the amniotic fluid and the umbilical cord starting in the first weeks of pregnancy to maintain normal fetal growth.[1-4, 36-38]

Fetal dependence on maternal thyroid hormones is particularly critical during early pregnancy. Starting in the second trimester, the fetal thyroid gland begins to produce thyroid hormones, but does not produce significant amounts of thyroid hormones until about 18–20 weeks of gestation when the fetus's HPT axis is fully developed.[3, 4] Compared to the first trimester, the fetal reliance of maternal thyroid hormones decreases during the second trimester, yet remains at lower levels until birth when the fetal thyroid reaches full maturity.[3, 4, 35-38] It is essential to maintain normal maternal thyroid hormone levels during early pregnancy for the growth, metabolism, and development of the fetus.[5-8] Thus, identification of factors that can modify maternal thyroid hormone levels during early gestation period is of central importance for preventing thyroid hormone-related adverse pregnancy and birth outcomes.

During the past few years there has been a growing concern regarding the potential adverse effects of maternal exposure to particulate matter air pollution during pregnancy on maternal[39-42] and fetal[39, 40, 43, 44] thyroid function. Results from the four studies[39-42] of the relationship between particulate matter (PM) exposures during pregnancy and maternal thyroid functions showed that higher exposure to maternal $PM_{2.5}$ during the first trimester[40] or second trimester[41] was associated with a significant decrease in maternal blood FT4 levels measured during the second trimester, while the $PM_{2.5}$ exposure during third-trimester[39] was not significantly associated with maternal blood FT4 levels collected 1 day after delivery. Higher exposure to maternal PM during the first trimester[42] was also associated with a significant decrease in FT4 levels

measured across gestation although exposure to PM_{10} was not found to be associated with a significant decrease.

Several factors could have contributed to the discrepancies in the results across these four studies, including 1) how air pollution exposure was defined (e.g. first trimester, second trimester or third trimester); 2) when blood was collected for measurement of thyroid hormones (e.g. second trimester, after delivery or across gestation; 3) what specific thyroid hormones were measured (e.g. only FT4 or four thyroid hormone indicators); and 4) the populations under study and the levels of air pollution exposure. In this birth cohort study in Wuhan, China, we further evaluated the associations between $PM_{2.5}$ and PM_{10} exposures during the first trimester of pregnancy and maternal thyroid hormone concentrations measured between weeks 10 and 17 of gestation.

Methods

Study population

This study utilizes data from a birth cohort study in Wuhan City, China. Pregnant women who came to the Wuhan Women and Children Healthcare Centre for their first prenatal care examination between January 2013 and October 2014 were invited to participate in the cohort study.[45-47] Pregnant women with a singleton gestation were considered to be eligible if they were residents of Wuhan city and resided in the city at least one year before pregnancy. Further inclusion criteria were willingness to have prenatal care and give

birth at the study hospital, and agreement to in-person interviews. We restricted our analysis to pregnant women who had blood thyroid hormone concentrations tested between 10-17 weeks of gestation. After excluding 4 women without air pollution data, 921 pregnant women were included for final analysis. All participants signed informed consents at the time of the cohort enrollment. The research protocol was approved by the ethics committees of the Wuhan Women and Children Healthcare Centre and the Tongji Medical College, Huazhong University of Science and Technology.

Assessment of ambient $PM_{2.5}$ and PM_{10}

A spatial-temporal land use regression (LUR) model was used to evaluate the residential daily $PM_{2.5}$ and PM_{10} exposure in the pregnant women in their first trimester. The assessment of individual daily PM exposure levels of the pregnant women has been described previously.[45-47] The Wuhan Birth Cohort Study has collected data on daily average concentration of $PM_{2.5}$ and PM_{10} from the local Chinese Environmental Protection Agency (EPA) stations in Wuhan City for the period from January 1, 2013 to December 31, 2016. There are 10 air monitoring stations of the Wuhan Air Automatic Monitoring System that are evenly distributed in the Wuhan metropolitan area obtaining representative background pollution levels of Wuhan City. The residential home addresses of pregnant women were geocoded using ArcGIS 9.3. Digital road network data in Wuhan were obtained from the National Geomatics Center of China, including road types of national level, county level and street level which were reported to be associated with traffic-related air pollution. Enterprises associated with air pollution

were obtained from the online surveillance system supported by the Wuhan Environmental Protection Agency. The cohort study team geocoded the addresses of these enterprises and calculated the industry-related predictor variables and obtained weather data from 7 national routine monitoring weather stations within or nearby Wuhan City from the Chinese Meteorological Bureau. Each weather station recorded daily average temperature, cumulative rainfall, average relative humidity, duration of sunshine, and average wind speed. A spatial-temporal land use regression (LUR) model with short-term (week) and long-term (season) variations was used to evaluate the residential daily $PM_{2.5}$ and PM_{10} exposure in pregnant women. Daily estimated $PM_{2.5}$ and PM_{10} concentrations from the 1st week to the gestational 12th week were averaged to assess $PM_{2.5}$ and PM_{10} exposures in the first trimester.

Thyroid hormone measurements

About 3 mL of fasting blood was collected at the time of prenatal care between 10th and 17th weeks of gestation at the study hospital in a pro-coagulation tube and then centrifuged for 5 minutes at 3500 revolutions per minute (rpm). Concentrations of thyroid hormone FT4, FT3, and TSH were measured using ADVIA Centaur XP automatic chemiluminescence immunoassay analyzer by professional clinical laboratorians following the standard operating procedures of the instruments in the hospital laboratory of Wuhan Medical and Healthcare Center for Women and Children that routinely conducts clinical measurements. The laboratory reference ranges were 3.5-6.5 pmol/L, 11.5-22.7 pmol/L, 0.55-4.78 μIU/ml for FT3, FT4 and TSH,

respectively.[48] In addition to FT3, FT4 and TSH, we also included FT4/FT3 ratio in the analyses, since it is an indicator of how effectively the body is able to convert T4 into T3.[39, 49]

Potential confounders

The in-person interviews at the hospital also included information on demographic and lifestyle factors, including maternal age at pregnancy (years), gestational age at blood draw (days), prepregnancy BMI (kg/m^2), education (<9, 10-12, and ≥13 years), family yearly income (<50,000, ≥ 50,000 Yuan), smoking and passive smoking, alcohol drinking, weight before the pregnancy and adult height, as well as reproductive and past medical history. Information on the date of last menstrual period, diagnosis of gestational hypertension and gestational diabetes were obtained from medical records.

Statistical analyses

Univariate analyses were performed to obtain summary statistics for thyroid hormone concentrations of FT4, FT3, and TSH. FT4 and FT3 values were used to calculate the FT4/FT3 ratio. For $PM_{2.5}$ and PM_{10} levels in the first trimester, standard summary statistics were calculated and presented including medians and interquartile ranges (IQR). Spearman's correlation coefficients were calculated for maternal blood levels of FT3, FT4, and TSH, and for ambient $PM_{2.5}$ or PM_{10} exposure during the first trimester.

Multiple linear regression models were used to assess the associations between $PM_{2.5}$ or PM_{10} exposures during the first trimester of gestation and maternal thyroid hormone concentrations measured between the 10th and 17th week of gestation. Exposure to $PM_{2.5}$ and PM_{10} was modeled continuously in interquartile range (IQR) increments so that the strength of the association for the different air pollutants could be compared. Adjusted spline analyses were used to assess the significance of curvature association between $PM_{2.5}$ or PM_{10} exposures during the first trimester and maternal thyroid hormone levels. Women were also classified into tertiles of ambient $PM_{2.5}$ and PM_{10} exposure and in the regression models the lowest tertile group served as the reference. All models were adjusted for maternal age at pregnancy (years); gestational age of thyroid function measures (days); prepregnancy BMI (kg/m^2); passive smoking (no or yes); parity (1 or 2); average family yearly income (<50,000, ≥ 50,000 Yuan or missing); maternal education levels (<9, 10-12, and ≥13 years); and season of blood collection (Spring (Apr-Jun), Summer (Jul-Sept), Autumn (Oct–Dec), and Winter (Jan–Mar). Selection of confounding variables was *a priori* and selected based on the reported confounding effects of the factors in studying PM exposure and thyroid function in pregnant women or in general population.[39-44, 50-55] Maternal age at pregnancy (years) was adjusted since advanced maternal age is not only associated with exposure to air pollution, but also associated with reduced maternal serum FT3 and FT4 levels[50]. Obesity, BMI and gestational age[51, 55] are known to influence thyroid functions. Season of blood collection [Spring (Apr-Jun); Summer (Jul-Sept); Autumn (Oct–Dec); Winter (Jan–Mar)] was also included in the final model since thyroid hormones show a seasonal pattern[52, 53] and air pollution levels are

well known to change with seasonal variation. Variables in the final models also included passive smoking status (yes or no during the pregnancy), parity (1 or ≥ 2), average family yearly income (<50,000, ≥ 50,000 Yuan or missing), maternal education (<9, 10-12, and ≥13 years). We did not include $PM_{2.5}$ and PM_{10} in the same models because of the strong correlation between the two PM exposures (r = 0.88).

We conducted the following sensitivity analyses: Both active and passive smoking[54] or nicotine administration[56] have been shown to influence thyroid hormone levels and thus, we conducted an analysis between maternal serum thyroid hormones and PM exposures by excluding passive smokers. We further performed a sensitivity analysis, in which we stratified the pregnant women based on the weeks of gestation when thyroid hormone levels were measured (10-12 weeks vs 13-17 weeks of gestation). As studies have shown that gestational hypertension and diabetes may be associated with pregnancy thyroid hormones, [57, 58] we also conducted an analysis, in which we excluded 23 subjects diagnosed with gestational hypertension and 56 subjects diagnosed with gestational diabetes late in the pregnancy.

All the statistical analyses were performed using the SAS version 9.4 (SAS Institute Inc. Cary, NC, USA). Two-sided p-values are reported and findings with p-values less than 0.05 are referred to as being statistically significant.

Results

As shown in Table 1, the women (n=921) in our study were, on average, 28 years of age at pregnancy, had a pre-pregnancy BMI of 20.6 kg/m^2, and about 90% of them this was their first pregnancy. None of the women reported alcohol drinking or tobacco smoking while 24% of them reported exposure to secondhand smoking during this pregnancy. About 77% of them had ≥13 years of formal school education and 68% of them had a yearly average family income of ≥50,000 Yuan.

The median exposure concentration of ambient $PM_{2.5}$ exposure during the first trimester was 90 $\mu g/m^3$ (IQR = 68 $\mu g/m^3$). For the ambient PM_{10} exposure levels, the median was 125$\mu g/m^3$ and the IQR value was 70 $\mu g/m^3$ (Table 2). A strong positive correlation (r = 0.88) was observed between ambient $PM_{2.5}$ and PM_{10} exposure levels (Table 3).

The median (IQR) thyroid hormone concentrations in maternal blood were 14.9 (2.35) pmol/L for FT4, 4.41 (0.62) pmol/L for FT3, and 1.25 (1.10) mU/L for TSH (Table 2). FT4, FT3 and FT4/FT3 ratios were negatively correlated with maternal blood TSH levels, while FT4 was positively correlated with FT3 and FT4/FT3 ratio (Table 3).

After adjustment for maternal age, pre-pregnancy BMI, parity, passive smoking, maternal education, season of blood collection, the spline analyses showed a nonlinear relation between $PM_{2.5}$ exposure during the first trimester and FT4 level, with an overall significance of the curve (p=0.0016), and a linear relation between $PM_{2.5}$ exposure and FT4/FT3 level (p=0.0080). An IQR increment (68 $\mu g/m^3$) in $PM_{2.5}$ exposure during the

first trimester was associated with a significant decrease of maternal FT4 levels (β = -0.60, 95% CI: –1.17, –0.12); and a significant decrease in the FT4/FT3 ratio (β = -0.13, 95% CI: –0.25, –0.02) (Table 4 and Figure 1A). $PM_{2.5}$ exposure was not associated with maternal TSH (β = 0.21, 95% CI: -0.08, 0.50) or FT3 levels (β = 0.00, 95% CI: -0.13, 0.13), also no nonlinear or linear relation was found (Figure 1A). These results were confirmed in analyses where $PM_{2.5}$ exposure was modelled in tertiles. Relative to women in the lowest tertile, women in both the middle and highest tertiles of $PM_{2.5}$ exposures had significantly lower maternal FT4 levels and FT4/FT3 ratio, but there were no differences in levels of maternal FT3 or TSH (Table 4). No associations were found between PM_{10} exposure during the first trimester and maternal thyroid concentrations (Table 4 and Figure 1B). However, the spline analyses of the first trimester's PM_{10} exposure and TSH level showed a nonlinear relation with an overall significance of the curve (p=0.0202, Figure 1B). The most influential confounders for the observed associations were seasons and gestational age at blood draw as shown in Table S1 and S2.

In sensitivity analyses, we first stratified the pregnant women into two groups based on whose thyroid hormone levels measured at 10-12 weeks or at 13-17 weeks of gestation, and we reached the same conclusion as the entire study population. That is, higher exposure to ambient $PM_{2.5}$ during the first trimester of gestation was associated with a significant decrease in maternal serum levels of FT4 but was not significantly associated with FT3 or TSH levels. PM_{10} exposure also had no significant impact on maternal thyroid hormone levels for either group of the women. Figure 2 presents the associations for each

IQR increment in $PM_{2.5}$ (Figure 2A) and in PM_{10} (Figure 2B) exposure during the first trimester and the four maternal thyroid hormones after adjustment for major confounders. Exclusion of passive smokers (Table S3) and women diagnosed with gestational hypertension (Table S4) or gestational diabetes (Table S5), and all people with these preconditions (Table S6) did not change the observed associations between maternal $PM_{2.5}$ or PM_{10} exposure during the first trimester and maternal thyroid hormone concentrations.

Discussion

In this birth cohort study, we found that higher exposure to ambient $PM_{2.5}$ during the first trimester of pregnancy was associated with a significant decrease in maternal serum FT4 concentrations and FT4/FT3 ratio. We did not, however, find a significant association with maternal serum FT3 or TSH concentrations. We also did not find associations between PM_{10} and maternal thyroid hormone concentrations in this study. These results provide further evidence that ambient $PM_{2.5}$ exposure during early pregnancy may be associated with maternal thyroid function.

Our results are in general consistent with the findings of the four recent studies that have reported a positive association between maternal exposure to PM during pregnancy and

maternal thyroid hormone function. Specifically, the first study from Belgium by Janssen et al.[39] involving 431 mother–child pairs reported an inverse but non-significant association between $PM_{2.5}$ exposure during the third trimester of gestation and maternal blood FT4 levels collected 1 day after delivery. A subsequent study from Nanjing, China by Wang et al.[40] including 433 pregnant women found a significant inverse association between maternal $PM_{2.5}$ exposure during the first trimester and maternal FT4 levels measured during the second trimester. A large study involving 8,077 pregnant women from Shanghai, China by Zhao et al.[41] also reported a significant inverse association between $PM_{2.5}$ exposure during the first and second trimester of pregnancy and maternal serum FT4 levels measured in the second trimester of pregnancy. A large cohort study involving 9,931 pregnant women from four European cohorts and one US cohort by Ghassabian et al.[42] reported that $PM_{2.5}$ exposure during first trimester was associated with a significant decrease in FT4 levels measured across gestation.

Our results are also supported by several recent studies[39, 40, 44, 59] that have reported a positive association between maternal exposure to PMs during pregnancy and fetal thyroid dysfunctions although the results are inconsistent. For example, two studies[39, 43] found that $PM_{2.5}$ exposure during the third trimester of gestation was associated with a significant decrease of FT4/FT3 ratio and cord blood serum TSH levels while another study[40] reported no significant association between maternal $PM_{2.5}$ exposure during the first trimester and neonatal TSH levels measured <72 hours after birth. In a national database-based study in China, Shang et al.[44] reported that maternal exposure to $PM_{2.5}$

during pregnancy was associated with a significantly increased risk of congenital hypothyroidism (CH, characterized by a reduced serum FT4 and increased serum TSH) in the offspring.

We found significant associations of $PM_{2.5}$ exposure with maternal serum FT4 concentrations and FT4/FT3 ratio, but not between PM_{10} and maternal hormone levels. The study by Ghassabian et al.[42] and our own current study are the only two studies that have examined both $PM_{2.5}$ and PM_{10} and maternal thyroid function and both showed that ambient $PM_{2.5}$ exposure, not PM_{10}, was associated with an increased risk of maternal thyroid dysfunction during pregnancy. The actual PM fraction that might be responsible for the observed effects on thyroid hormone concentration, however, is not clear considering the high correlation between PM_{10} and $PM_{2.5}$. Nevertheless, early studies of air pollution and human health suggest that smaller particles may poses greater risk relative to larger particles because, while both $PM_{2.5}$ and PM_{10} can be inhaled, larger particles of PM_{10} are more likely either filtered out through the nose or deposit on the surfaces of the larger airways of the upper region of the lung while $PM_{2.5}$ can easily cross the alveoli and enter the bloodstream.[60]

Studies have shown that cigarette smoking and nicotine alter thyroid function through affecting deiodinase activity or thyroid secretion, inducing iodine deficiency, or through changes in thyroid hormone transporters or receptors.[56] In the sensitivity analyses, exclusion of passive smokers (Table S3) and women diagnosed with gestational

hypertension (Table S4) or gestational diabetes (Table S5) did not seem to change the observed associations between maternal $PM_{2.5}$ or PM10 exposure during the first trimester and maternal thyroid hormone concentrations. These results suggest that residual confounding from these factors is an unlikely explanation for the observed association. Our study, however, cannot exclude the potential interaction of these factors with the exposure of interest due to the small numbers of the study subjects with exposure to these factors.

The mechanisms by which $PM_{2.5}$ exposure affects the maternal thyroid function, however, remain unclear. A recent study by Dong et al.[61] in year 2021 suggests that activation of the hypothalamic-pituitary-thyroid (HPT) axis and altered hepatic transthyretin levels may play a crucial role in $PM_{2.5}$-induced thyroid dysfunction. The study showed that $PM_{2.5}$ treatment in female Sprague Dawley rats caused a significant decrease in serum levels of T3, T4, and TSH, and treatment of $PM_{2.5}$ perturbs thyroid hormone (TH) homeostasis by affecting TH biosynthesis, biotransformation, and transport, affecting TH receptor levels, and inducing oxidative stress and inflammatory responses. A role of HPT axis in the relationship between $PM_{2.5}$ exposure and maternal thyroid function is biologically plausible since the production, conversion and transportation of thyroid hormones are controlled by the HPT axis, a negative feedback loop with a complex hormone signaling system. PMs and their detached components are reactive oxygen species (ROS) or known to increase production of ROS that leads to oxidative stress.[62-66] Riggs et al.[67] recently suggested that increased levels of oxidative

stress and inflammation following exposure to $PM_{2.5}$ could cause activation of the HPT axis. Oxidative stress and systemic inflammatory reaction induced by $PM_{2.5}$ can cause chronic liver injury and dysfunction.[68] Liver is known to be the main organ that converts T4 to T3, the functional type of thyroid hormones.[69] Several early experimental studies have also suggested that environmental endocrine disrupting chemicals (e.g., bisphenol A and n-butylbenzyl phthalate) could bind to transthyretin (a major thyroid hormone-binding protein in plasma) or thyroid hormone receptor,[70-72] and hyperthyroidism may increase the levels of oxidative damage induced by environmental metabolites.[73]

The strengths of our study include having both ambient $PM_{2.5}$ and PM_{10} exposures and all major thyroid hormones of interest (FT4, FT3, FT4/FT3 ratio, and TSH) measured in a prospective Chinese birth cohort with much higher levels of PM exposures than the WHO air quality standards.[74] Our focus on first trimester PM exposure and thyroid hormones measured right before the 18th week of gestation addresses a critical window of gestation during which the fetus almost totally depends on the mother for the production of thyroid hormones. None of the women in this study smoked tobacco or drank alcohol during the pregnancy. Our sensitivity analyses in which we excluded women with exposure to secondhand smoking did not change the overall conclusions. Finally, our focus on a population of pregnant women from one metropolitan area helped us avoid heterogeneity due to variations in PM exposure levels and components.

The limitations of our study include that only maternal residence was used to calculate the daily average exposure to $PM_{2.5}$ and PM_{10} as our in-person interviews did not collect

information on location of the woman's workplace. Lack of workplace information probably introduces an unsystematic measurement error, which usually leads to bias toward the null. We do not have information on how much time the women actually spent in/outside her home (e.g., a time activity diary) that could have improved our exposure assessment. Our study also does not have the information on if the woman had previous thyroid disorders prior to pregnancy or use of thyroid medication or other endocrine disrupting chemicals that have thyroid-disrupting effects (such as polybrominated diphenyl ether, polychlorinated biphenyls, and certain metals).[75-78] Finally, our study population had relatively high levels of PM exposure, which might affect the generalizability of our study finding to areas with very different exposure levels.

In conclusion, our study found that ambient $PM_{2.5}$ exposure during the first trimester of pregnancy was associated with lower maternal serum FT4 concentrations and FT4/FT3 ratio. Considering the vital importance of maternal thyroid hormone concentrations during early pregnancy to ensure a normal embryo and fetal development, our results have important implications particularly among pregnant women in low-to-middle income countries who carry a higher burden of $PM_{2.5}$ exposure. Future work focused on $PM_{2.5}$ reduction strategies during early pregnancy and its effects on maternal thyroid concentrations is encouraged. If successful, these strategies could be used to help prevent thyroid dysfunction-related adverse pregnancy outcomes and the subsequent detrimental effects on children's development.

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The author(s) assume(s) full responsibility for analyses and interpretation of these data.

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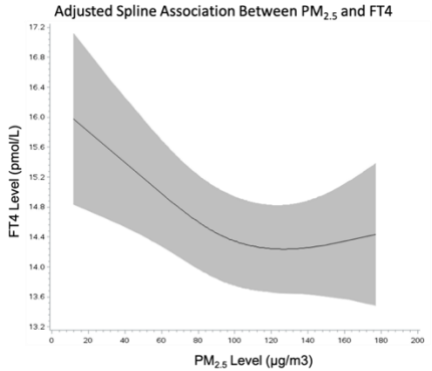
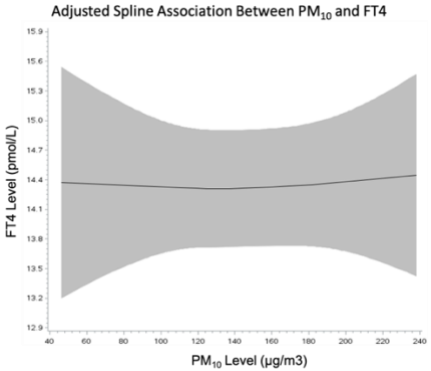
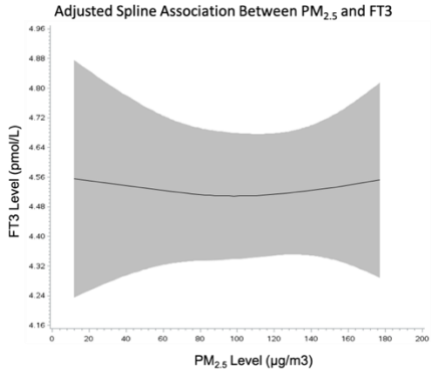
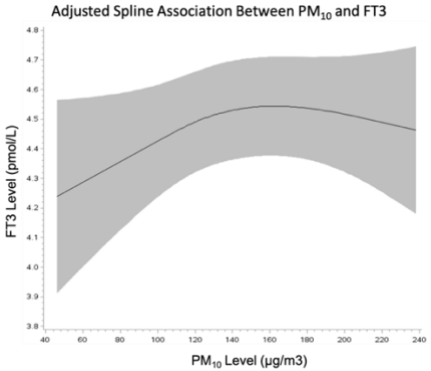
A. $PM_{2.5}$	B. PM_{10}
a. FT4  Overall significance of the curve: p=0.0016	a. FT4  Overall significance of the curve: p=0.8976
b. FT3  Overall significance of the curve: p=0.7215	b. FT3  Overall significance of the curve: p=0.0573

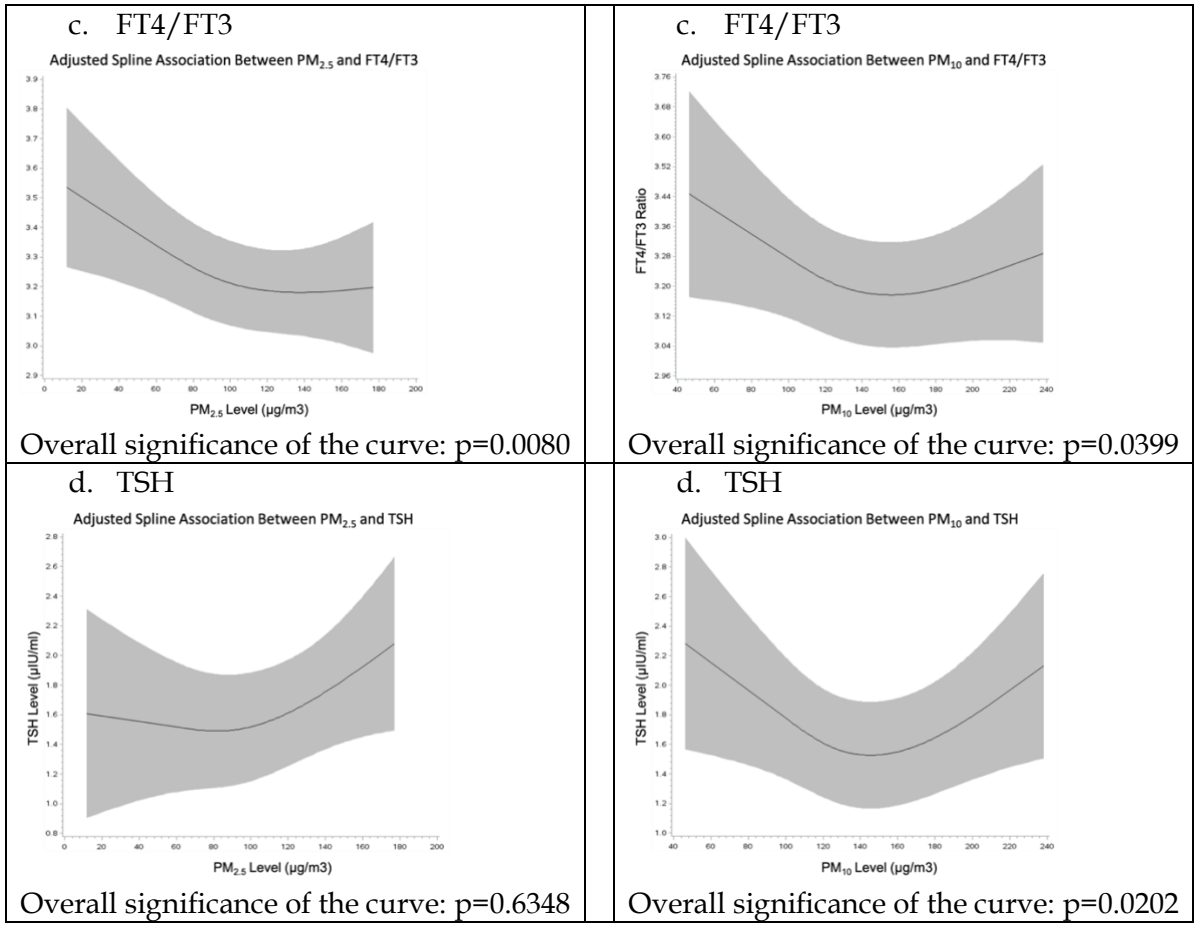


Figure 1. Adjusted association between $PM_{2.5}$, PM_{10} and maternal thyroid hormones. The lines show the estimates and the shadowed areas represent the 95% confidence intervals. Models adjusted for maternal age at pregnancy (mean = 28.18 years); gestational age at blood draw (mean = 98.37 days); prepregnancy BMI (mean = 20.61); passive smoking (no or yes); parity (1 or 2); average family yearly income (<50,000, ≥ 50,000 Yuan or missing); maternal education levels (<9, 10-12, and ≥13 years); and season of blood collection (Spring (Apr-Jun), Summer (Jul-Sept), Autumn (Oct–Dec), and Winter (Jan–Mar)).

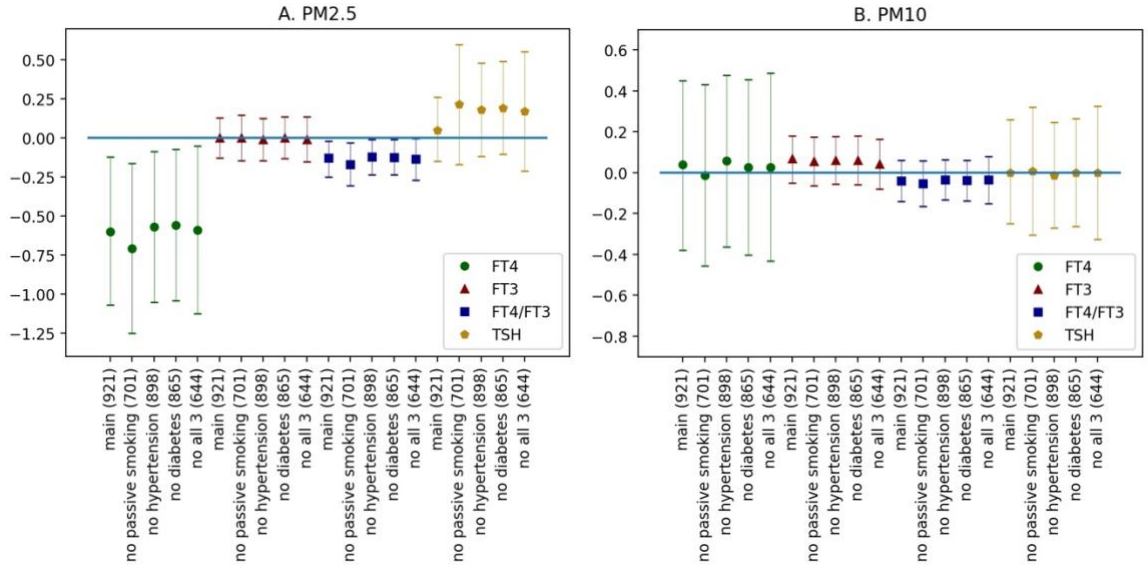


Figure 2. Sensitivity analyses of the association between PMs and maternal thyroid hormones by status of passive smoking, gestational hypertension, and gestational diabetes. Models adjusted for maternal age at pregnancy (years); gestational age of thyroid function measures (days); prepregnancy BMI (kg/m^2); passive smoking (no or yes); parity (1 or 2); average family yearly income (<50,000, ≥ 50,000 Yuan or missing); maternal education levels (<9, 10-12, and ≥13 years); and season of blood collection (Spring (Apr-Jun), Summer (Jul-Sept), Autumn (Oct–Dec), and Winter (Jan–Mar)).

Table 1. Demographic characteristics of the 921 pregnant women in Wuhan, China.

	All	$PM_{2.5}$			PM_{10}		
		Low	Medium	High	Low	Medium	High
Characteristics, N (%)							
Number of subjects	921	307	308	306	307	307	307
Age at pregnancy (years)	28.18 ± 3.13	28.12 ± 3.07	28.26 ± 3.08	28.17 ± 3.26	28.21 ± 2.98	28.11 ± 3.22	28.24 ± 3.20
Pre-pregnancy BMI (kg/m^2)	20.61 ± 2.58	20.63± 2.47	20.63± 2.67	20.57± 2.60	20.69 ± 2.61	20.47 ± 2.49	20.67 ± 2.64
Age at menarche (years)	13.14 ± 1.20	13.14 ± 1.18	13.15 ± 1.21	13.12 ± 1.22	13.12 ± 1.18	13.19 ± 1.18	13.12 ± 1.24
Parity							
1	831 (90.23)	286(93.16)	281(91.23)	264(86.27)	284(92.51)	281(91.53)	266(86.64)
2	90 (9.77)	21(6.84)	27(8.77)	42(13.73)	23(7.49)	26(8.47)	41(13.36)
Passive smoking during pregnancy							
No	701 (76.11)	230(74.92)	246(79.87)	225(73.53)	234(76.22)	242(78.83)	225(73.29)
Yes	220 (23.89)	77(25.08)	62(20.13)	81(26.47)	73(23.78)	65(21.17)	82(26.71)
Family income (Yuan/Year)							
< 50,000	282 (30.62)	82(26.71)	95(30.84)	105(34.31)	85(27.69)	106(34.53)	91(29.64)
≥ 50,000	627 (68.08)	221(71.99)	209(67.86)	197(64.38)	217(70.68)	198(64.50)	212(69.06)
Missing	12 (1.30)	4(1.30)	4(1.30)	4(1.31)	5(1.63)	3(0.98)	4(1.30)
Education levels (years)							
≤ 9	55 (5.97)	12(3.91)	19(6.17)	24(7.84)	15(4.89)	16(5.21)	24(7.82)
10−12	153 (16.61)	53(17.26)	45(14.61)	55(17.97)	61(19.87)	42(13.68)	50(16.29)
≥13	713 (77.2)	242(78.83)	244(79.22)	227(74.18)	231(75.24)	249(81.11)	233(75.90)
Gestational hypertension							
No	898 (97.50)	297(96.74)	302(98.05)	299(97.71)	298(97.07)	299(97.39)	301(98.05)
Yes	23 (2.50)	10(3.26)	6(1.95)	7(2.29)	9(2.93)	8(2.61)	6(1.95)
Gestational diabetes							
No	865 (93.92)	292(95.11)	289(93.83)	284(92.81)	295(96.09)	284(92.51)	286(93.16)
Yes	56 (6.08)	15(4.89)	19(6.17)	22(7.19)	12(3.91)	23(7.49)	21(6.84)
Season							
Spring (Apr-Jun)	192 (20.85)	0	108(35.06)	84(27.45)	11(3.58)	123(40.07)	58(18.89)
Summer (Jul-Sept)	309 (33.55)	200(65.15)	109(35.39)	0	253(82.41)	56(18.24)	0
Autumn (Oct–Dec)	225 (24.43)	107(34.85)	90(29.22)	28(9.15)	43(14.01)	124(40.39)	58(18.89)
Winter (Jan–Mar)	195 (21.17)	0	1(0.32)	194(63.40)	0	4(1.30)	191(62.21)
Gestational age (in days) at blood collection	98.38 ± 11.08	96.49 ± 10.26	98.17 ± 11.00	100.49 ± 11.59	96.79 ± 10.77	98.21 ± 10.82	100.15 ± 11.40

Table 2. Maternal thyroid hormones and ambient levels of particulate matter (PMs) air pollution during the first trimester.

A. Maternal thyroid hormones					
	Mean	Median	Q1	Q3	IQR
FT4 (pmol/L)	15.1	14.9	13.8	16.1	2.35
FT3 (pmol/L)	4.44	4.41	4.10	4.72	0.62
FT4/FT3	3.43	3.41	3.09	3.70	0.61
TSH (μIU/ml)	1.42	1.25	0.77	1.86	1.09
B. Ambient levels of PMs during the first trimester					
	Mean	Median	Q1	Q3	IQR
$PM_{2.5}$ ($\mu g/m^3$)	100	90	65	133	68
PM_{10} ($\mu g/m^3$)	143	125	107	177	70

Table 3. Spearman's Correlation Coefficients for particulate matters (PMs) during the first trimester and maternal thyroid hormones.

Variables	TSH	FT3	FT4	FT4/FT3	$PM_{2.5}$	PM_{10}
TSH	1					
FT3	-0.16	1				
FT4	-0.29	0.24	1			
FT4/FT3	-0.13	-0.52	0.66	1		
$PM_{2.5}$	0.11	0.01	-0.17	-0.18	1	
PM_{10}	0.06	0.03	-0.10	-0.14	0.88	1

Table 4. Associations between ambient $PM_{2.5}$ and PM_{10} exposure at the first trimester and maternal thyroid hormone levels measured for women between 10th and 17th week of gestation.

$PM_{2.5}$					**PM_{10}**				
	N*	**Adjusted†**				**N***	**Adjusted†**		
		β	95%CI	P			β	95%CI	P
FT4									
1st Tertile	307		Reference		1st Tertile	307		Reference	
2nd Tertile	308	-0.85	-1.18, -0.51	<0.01	2nd Tertile	307	-0.34	-0.74, 0.06	0.10
3rd Tertile	306	-0.51	-1.03, 0.00	0.05	3rd Tertile	307	0.08	-0.44, 0.60	0.77
Per IQR		-0.60	-1.07, -0.12	0.01	Per IQR		0.04	-0.38, 0.45	0.87
FT3									
1st Tertile	307		Reference		1st Tertile	306		Reference	
2nd Tertile	284	-0.08	-0.17, 0.02	0.11	2nd Tertile	284	-0.04	-0.15, 0.07	0.48
3rd Tertile	306	0.01	-0.13, 0.16	0.86	3rd Tertile	307	0.03	-0.12, 0.17	0.71
Per IQR		0.00	-0.13, 0.13	1.00	Per IQR		0.07	-0.05, 0.18	0.26
FT4/FT3									
1st Tertile	307		Reference		1st Tertile	306		Reference	
2nd Tertile	284	-0.13	-0.21, -0.05	0.00	2nd Tertile	284	-0.04	-0.14, 0.05	0.38
3rd Tertile	306	-0.12	-0.24, 0.01	0.06	3rd Tertile	307	0.01	-0.11, 0.13	0.90
Per IQR		-0.13	-0.25, -0.02	0.02	Per IQR		-0.04	-0.14, 0.06	0.40
TSH									
1st Tertile	307		Reference		1st Tertile	307		Reference	
2nd Tertile	307	0.05	-0.15, 0.26	0.61	2nd Tertile	306	-0.03	-0.28, 0.22	0.81
3rd Tertile	306	0.09	-0.23, 0.41	0.57	3rd Tertile	307	-0.02	-0.34, 0.30	0.91
Per IQR		0.21	-0.08, 0.50	0.16	IQR		0.00	-0.25, 0.26	0.98

†Adjusted for maternal age at pregnancy (years); gestational age of thyroid function measures (days); prepregnancy BMI (kg/m^2); passive smoking (no or yes); parity (1 or 2); average family yearly income (<50,000, ≥ 50,000 Yuan or missing); maternal education levels (<9, 10-12, and ≥13 years); and season of blood collection (Spring (Apr-Jun), Summer (Jul-Sept), Autumn (Oct–Dec), and Winter (Jan–Mar)).

Table S1. Confounder assessment of associations between ambient $PM_{2.5}$ exposure at the first trimester and maternal thyroid hormone levels measured for women between 10th and 17th week of gestation

$PM_{2.5}$										
	N*	**Unadjusted**			**Adjusted (1)**			**Adjusted (total)**		
		β	95%CI	P	β	95%CI	P	β	95%CI	P
FT4										
1st Tertile	307		Reference			Reference			Reference	
2nd Tertile	308	-1.04	-1.35, -0.73	<0.01	-0.87	-1.21, -0.54	<0.01	-0.85	-1.18, -0.51	<0.01
3rd Tertile	306	-0.89	-1.2, -0.59	<0.01	-0.50	-1.02, 0.02	0.06	-0.51	-1.03, 0.00	0.05
IQR		-0.53	-0.75, -0.31	<0.01	-0.58	-1.06, -0.10	0.02	-0.60	-1.07, -0.12	0.01
FT3										
1st Tertile	307		Reference			Reference			Reference	
2nd Tertile	284	-0.07	-0.16, 0.01	0.00	-0.07	-0.17, -0.02	0.12	-0.08	-0.17, 0.02	0.11
3rd Tertile	306	-0.01	-0.10, 0.07	0.78	0.00	-0.15, 0.15	0.98	0.01	-0.13, 0.16	0.86
IQR		.002	-0.06, 0.06	0.95	-0.01	-0.14, 0.13	0.91	0.00	-0.13, 0.13	1.00
FT4/FT3										
1st Tertile	307		Reference			Reference			Reference	
2nd Tertile	284	-0.17	-0.24, -0.10	<0.01	-0.13	-0.21, -0.05	0.00	-0.13	-0.21, -0.05	0.00
3rd Tertile	306	-0.19	-0.26, -0.12	<0.01	-0.11	-0.24, 0.02	0.09	-0.12	-0.24, 0.01	0.06
IQR		-0.12	-0.17, -0.07	<0.01	-0.12	-0.24, -0.01	0.03	-0.13	-0.25, -0.02	0.02
TSH										
1st Tertile	307		Reference			Reference			Reference	
2nd Tertile	307	0.10	-0.09, 0.28	0.30	0.06	-0.15, 0.26	0.60	0.05	-0.15, 0.26	0.61
3rd Tertile	306	0.22	0.03, 0.40	0.02	0.06	-0.26, 0.38	0.71	0.09	-0.23, 0.41	0.57
IQR		0.18	0.05, 0.31	<0.01	0.18	-0.11, 0.47	0.22	0.21	-0.08, 0.50	0.16

(1)Adjusted for gestational age of thyroid function measures (days); and season of blood collection (Spring (Apr-Jun), Summer (Jul-Sept), Autumn (Oct–Dec), and Winter (Jan–Mar).

TotalAdjusted for maternal age at pregnancy (years); gestational age of thyroid function measures (days); prepregnancy BMI (kg/m^2); parity (1 or 2); average family yearly income (<50,000, ≥ 50,000 Yuan or missing); maternal education levels (<9, 10-12, and ≥13 years); and season of blood collection (Spring (Apr-Jun), Summer (Jul-Sept), Autumn (Oct–Dec), and Winter (Jan–Mar)).

Table S2. Confounder assessment of associations between ambient PM_{10} exposure at the first trimester and maternal thyroid hormone levels measured for women between 10th and 17th week of gestation

PM_{10}										
	N*	**Unadjusted**			**Adjusted (1)**			**Adjusted (total)**		
		β	95%CI	P	β	95%CI	P	β	95%CI	P
FT4										
1st Tertile	307		Reference			Reference			Reference	
2nd Tertile	307	-0.59	-0.9, -0.28	<0.01	-0.31	-0.71, 0.09	0.13	-0.34	-0.74, 0.06	0.10
3rd Tertile	307	-0.48	-0.79, -0.16	<0.01	0.14	-0.39, 0.66	0.61	0.08	-0.44, 0.60	0.77
Per IQR		-0.31	-0.52, -0.11	<0.01	0.05	-0.37, 0.46	0.83	0.04	-0.38, 0.45	0.87
FT3										
1st Tertile	306		Reference			Reference			Reference	
2nd Tertile	284	-0.05	-0.14, 0.03	0.23	-0.04	-0.16, 0.07	0.43	-0.04	-0.15, 0.07	0.48
3rd Tertile	307	-0.01	-0.09, 0.08	0.89	0.02	-0.13, 0.16	0.80	0.03	-0.12, 0.17	0.71
Per IQR		0.01	-0.04, 0.07	0.69	0.07	-0.05, 0.18	0.25	0.07	-0.05, 0.18	0.26
FT4/FT3										
1st Tertile	306		Reference			Reference			Reference	
2nd Tertile	284	-0.08	-0.16, -0.01	0.03	-0.03	-0.13, 0.07	0.54	-0.04	-0.14, 0.05	0.38
3rd Tertile	307	-0.1	-0.18, -0.03	0.01	0.03	-0.10, 0.15	0.68	0.01	-0.11, 0.13	0.90
Per IQR		-0.08	-0.13, -0.04	<0.01	-0.04	-0.14, 0.06	0.40	-0.04	-0.14, 0.06	0.40
TSH										
1st Tertile	307		Reference			Reference			Reference	
2nd Tertile	306	-0.01	-0.2, 0.18	0.91	-0.04	-0.28, 0.21	0.76	-0.03	-0.28, 0.22	0.81
3rd Tertile	307	0.11	-0.08, 0.30	0.25	-0.05	-0.37, 0.27	0.77	-0.02	-0.34, 0.30	0.91
Per IQR		0.10	-0.02, 0.22	0.10	-0.02	-0.27, 0.23	0.87	0.00	-0.25, 0.26	0.98

(1)Adjusted for gestational age of thyroid function measures (days); and season of blood collection (Spring (Apr-Jun), Summer (Jul-Sept), Autumn (Oct–Dec), and Winter (Jan–Mar).

TotalAdjusted for maternal age at pregnancy (years); gestational age of thyroid function measures (days); prepregnancy BMI (kg/m^2); parity (1 or 2); average family yearly income (<50,000, ≥ 50,000 Yuan or missing); maternal education levels (<9, 10-12, and ≥13 years); and season of blood collection (Spring (Apr-Jun), Summer (Jul-Sept), Autumn (Oct–Dec), and Winter (Jan–Mar)).

Table S3. Associations between ambient $PM_{2.5}$ and PM_{10} exposure at the first trimester and maternal thyroid hormone levels measured for women between 10th and 17th week of gestation without passive smoking.

$PM_{2.5}$					**PM_{10}**				
	N*	**Adjusted†**				**N***	**Adjusted†**		
		β	95%CI	P			β	95%CI	P
FT4									
1st Tertile	230		Reference		1st Tertile	234		Reference	
2nd Tertile	246	-0.87	-1.23, -0.51	<0.01	2nd Tertile	242	-0.22	-0.65, 0.21	0.31
3rd Tertile	225	-0.58	-1.16, -0.01	0.05	3rd Tertile	225	0.14	-0.43, 0.71	0.62
IQR		-0.71	-1.25, -0.16	0.01	IQR		-0.01	-0.46, 0.43	0.96
FT3									
1st Tertile	230		Reference		1st Tertile	233		Reference	
2nd Tertile	224	-0.05	-0.15, 0.05	0.32	2nd Tertile	221	0.01	-0.11, 0.12	0.91
3rd Tertile	225	0.02	-0.14, 0.18	0.82	3rd Tertile	225	0.06	-0.09, 0.22	0.42
IQR		-0.00	-0.15, 0.15	0.10	IQR		0.05	-0.06, 0.17	0.36
FT4/FT3									
1st Tertile	230		Reference		1st Tertile	223		Reference	
2nd Tertile	224	-0.15	-0.24, -0.06	0.00	2nd Tertile	221	-0.05	-0.16, 0.06	0.35
3rd Tertile	225	-0.15	-0.30, -0.00	0.05	3rd Tertile	225	-0.02	-0.16, 0.13	0.81
IQR		-0.17	-0.31, -0.03	0.02	IQR		-0.05	-0.16, 0.06	0.35
TSH									
1st Tertile	230		Reference		1st Tertile	234		Reference	
2nd Tertile	245	0.07	-0.19, 0.33	0.59	2nd Tertile	241	-0.06	-0.36, 0.24	0.70
3rd Tertile	225	0.13	-0.28, 0.54	0.53	3rd Tertile	225	-0.01	-0.41, 0.39	0.97
IQR		0.21	-0.17, 0.60	0.27	IQR		0.01	-0.30, 0.32	0.96

†Adjusted for maternal age at pregnancy (years); gestational age of thyroid function measures (days); prepregnancy BMI (kg/m^2); parity (1 or 2); average family yearly income (<50,000, ≥ 50,000 Yuan or missing); maternal education levels (<9, 10-12, and ≥13 years); and season of blood collection (Spring (Apr-Jun), Summer (Jul-Sept), Autumn (Oct–Dec), and Winter (Jan–Mar)).

Table S4. Associations between ambient $PM_{2.5}$ and PM_{10} exposure at the first trimester and maternal thyroid hormone levels measured for women between 10th and 17th week of gestation without gestational hypertension.

$PM_{2.5}$					**PM_{10}**				
	N*	**Adjusted†**				**N***	**Adjusted†**		
		β	95%CI	P			β	95%CI	P
FT4									
1st Tertile	297		Reference		1st Tertile	298		Reference	
2nd Tertile	302	-0.84	-1.18, -0.50	<0.01	2nd Tertile	299	-0.30	-0.71, 0.11	0.16
3rd Tertile	299	-0.49	-1.02, 0.03	0.06	3rd Tertile	301	0.11	-0.42, 0.64	0.69
IQR		-0.57	-1.05, -0.09	0.02	IQR		0.06	-0.36, 0.48	0.79
FT3									
1st Tertile	297		Reference		1st Tertile	297		Reference	
2nd Tertile	278	-0.08	-0.17, 0.01	0.10	2nd Tertile	276	-0.07	-0.18, 0.05	0.26
3rd Tertile	299	0.01	-0.14, 0.16	0.90	3rd Tertile	301	0.01	-0.14, 0.15	0.92
IQR		-0.01	-0.14, 0.13	0.89	IQR		0.06	-0.06, 0.18	0.31
FT4/FT3									
1st Tertile	297		Reference		1st Tertile	297		Reference	
2nd Tertile	278	-0.12	-0.20, -0.05	0.00	2nd Tertile	276	-0.01	-0.11, 0.08	0.77
3rd Tertile	299	-0.11	-0.24, 0.01	0.07	3rd Tertile	301	0.03	-0.10, 0.15	0.66
IQR		-0.12	-0.24, -0.01	0.03	IQR		-0.03	-0.13, 0.06	0.49
TSH									
1st Tertile	297		Reference		1st Tertile	298		Reference	
2nd Tertile	301	0.05	-0.17, 0.26	0.67	2nd Tertile	298	-0.06	-0.31, 0.20	0.67
3rd Tertile	299	0.08	-0.25, 0.40	0.63	3rd Tertile	301	-0.05	-0.38, 0.28	0.78
IQR		0.18	-0.12, 0.48	0.24	IQR		-0.01	-0.27, 0.25	0.93

†Adjusted for maternal age at pregnancy (years); gestational age of thyroid function measures (days); prepregnancy BMI (kg/m^2); passive smoking (no or yes); parity (1 or 2); average family yearly income (<50,000, ≥ 50,000 Yuan or missing); maternal education levels (<9, 10-12, and ≥13 years); and season of blood collection (Spring (Apr-Jun), Summer (Jul-Sept), Autumn (Oct–Dec), and Winter (Jan–Mar)).

Table S5. Associations between ambient $PM_{2.5}$ and PM_{10} exposure at the first trimester and maternal thyroid hormone levels measured for women between 10th and 17th week of gestation without gestational diabetes.

$PM_{2.5}$					**PM_{10}**				
	N*	**Adjusted†**				**N***	**Adjusted†**		
		β	95%CI	P			β	95%CI	P
FT4									
1st Tertile	292		Reference		1st Tertile	295		Reference	
2nd Tertile	289	-0.84	-1.18, -0.49	<.001	2nd Tertile	284	-0.35	-0.76, 0.07	0.10
3rd Tertile	284	-0.51	-1.06, 0.03	0.06	3rd Tertile	286	0.07	-0.47, 0.61	0.80
IQR		-0.56	-1.04, -0.07	0.02	IQR		0.03	-0.40, 0.46	0.90
FT3									
1st Tertile	292		Reference		1st Tertile	294		Reference	
2nd Tertile	265	-0.07	-0.17, 0.02	0.14	2nd Tertile	261	-0.04	-0.16, 0.07	0.47
3rd Tertile	284	0.01	-0.15, 0.16	0.92	3rd Tertile	286	0.03	-0.12, 0.18	0.72
IQR		0.00	-0.13, 0.14	0.98	IQR		0.06	-0.06, 0.18	0.32
FT4/FT3									
1st Tertile	292		Reference		1st Tertile	294		Reference	
2nd Tertile	265	-0.12	-0.21, -0.04	0.00	2nd Tertile	261	-0.04	-0.14, 0.06	0.41
3rd Tertile	284	-0.11	-0.24, 0.02	0.09	3rd Tertile	286	0.01	-0.12, 0.13	0.89
IQR		-0.12	-0.24, -0.01	0.03	IQR		-0.04	-0.14, 0.06	0.46
TSH									
1st Tertile	292		Reference		1st Tertile	295		Reference	
2nd Tertile	288	0.06	-0.15, 0.28	0.57	2nd Tertile	283	-0.03	-0.28, 0.23	0.83
3rd Tertile	284	0.09	-0.25, 0.43	0.60	3rd Tertile	286	0.00	-0.33, 0.33	0.99
IQR		0.19	-0.11, 0.49	0.21	IQR		0.00	-0.26, 0.26	0.26

†Adjusted for maternal age at pregnancy (years); gestational age of thyroid function measures (days); prepregnancy BMI (kg/m^2); passive smoking (no or yes); parity (1 or 2); average family yearly income (<50,000, ≥ 50,000 Yuan or missing); maternal education levels (<9, 10-12, and ≥13 years); and season of blood collection (Spring (Apr-Jun), Summer (Jul-Sept), Autumn (Oct–Dec), and Winter (Jan–Mar)).

Table S6. Associations between ambient $PM_{2.5}$ and PM_{10} exposure at the first trimester and maternal thyroid hormone levels measured for women between 10th and 17th week of gestation without passive smoking, gestational hypertension, and gestational diabetes.

$PM_{2.5}$					**PM_{10}**				
	N*	**Adjusted†**				**N***	**Adjusted†**		
		β	95%CI	P			β	95%CI	P
FT4									
1st Tertile	211		Reference		1st Tertile	218		Reference	
2nd Tertile	225	-0.81	-1.19, -0.43	<.001	2nd Tertile	217	-0.20	-0.65, 0.26	0.39
3rd Tertile	208	-0.58	-1.19, 0.02	0.06	3rd Tertile	209	0.16	-0.43, 0.75	0.60
IQR		-0.59	-1.13, -0.05	0.03	IQR		0.03	-0.43, 0.49	0.91
FT3									
1st Tertile	211		Reference		1st Tertile	217		Reference	
2nd Tertile	203	-0.04	-0.14, 0.06	0.41	2nd Tertile	196	-0.02	-0.14, 0.10	0.73
3rd Tertile	208	0.02	-0.15, 0.19	0.82	3rd Tertile	209	0.05	-0.11, 0.20	0.56
IQR		-0.01	-0.15, 0.13	0.90	IQR		0.04	-0.08, 0.16	0.49
FT4/FT3									
1st Tertile	211		Reference		1st Tertile	217		Reference	
2nd Tertile	203	-0.14	-0.24, -0.05	0.00	2nd Tertile	196	-0.02	-0.14, 0.09	0.67
3rd Tertile	208	-0.15	-0.31, 0.00	0.05	3rd Tertile	209	0.00	-0.15, 0.15	0.97
IQR		-0.14	-0.27, 0.00	0.05	IQR		-0.04	-0.15, 0.08	0.54
TSH									
1st Tertile	211		Reference		1st Tertile	218		Reference	
2nd Tertile	224	0.08	-0.19, 0.36	0.56	2nd Tertile	216	-0.07	-0.39, 0.26	0.69
3rd Tertile	208	0.12	-0.31, 0.56	0.58	3rd Tertile	209	0.01	-0.42, 0.43	0.98
IQR		0.17	-0.21, 0.55	0.38	IQR		0.00	-0.33, 0.33	1.00

†Adjusted for maternal age at pregnancy (years); gestational age of thyroid function measures (days); prepregnancy BMI (kg/m^2); parity (1 or 2); average family yearly income (<50,000, ≥ 50,000 Yuan or missing); maternal education levels (<9, 10-12, and ≥13 years); and season of blood collection (Spring (Apr-Jun), Summer (Jul-Sept), Autumn (Oct–Dec), and Winter (Jan–Mar)).