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Association between long-term exposure to $PM_{2.5}$ and thyroid nodules in school-aged children and adolescents: a cross-sectional study in Eastern China

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Abstract

Background Long-term exposure to particulate matter with aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$) are linked to thyroid nodules in adults, but epidemiological evidence in children and adolescents and adjustments for key confounders are lacking. This study aimed to explore the association between long-term exposure to $PM_{2.5}$ and the prevalence of thyroid nodules in school-aged children and adolescents.

Methods A cross-sectional study including 10,739 primary and junior high school students was conducted in Jiangsu Province, China, in 2021. Annual $PM_{2.5}$ concentrations were estimated by a satellite based space-time model based on machine learning. Individual exposure concentrations were assigned according to the school addresses of the participants. High-resolution diagnostic ultrasound imaging was used to detect the thyroid nodules. After adjustment for covariates, the link between the two-year (2019–2020) average $PM_{2.5}$ concentrations and thyroid nodules was estimated using a generalized linear mixed-effects model. The concentration-response (C-R) curves were smoothed using a restricted cubic spline function. Stratified analyses were performed to evaluate the modification effects of covariates on associations.

Results The average age of the 10,067 participants (51.9% boys) was 11 years, with a thyroid nodule prevalence of 30.5%. A non-linear positive correlation was found between the increase in prevalence of thyroid nodules and two-year average exposure concentration of $PM_{2.5}$. The C-R relationship curve between thyroid nodules and $PM_{2.5}$ had a J-shaped structure with a threshold value of 39.7 μg/m^3. Following covariates adjustment, the odds ratio (OR) and 95% confidence interval (CI) linked to thyroid nodules were 1.515 (1.199, 1.915) for per standard deviation (SD) increase in two-year average $PM_{2.5}$ concentrations (> 39.7 μg/m^3). The sex-specific associations found among adults were not observed in our stratified analyses.

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Conclusions Our findings demonstrated that long-term exposure to $PM_{2.5}$ was associated with a higher prevalence of thyroid nodules in children and adolescents. Strategies that consistently reduce $PM_{2.5}$ pollution levels to ease the burden of non-communicable diseases have important public health implications.

Keywords Children, Thyroid nodule, $PM_{2.5}$

Background

Thyroid nodules, which are discrete lesions inside thyroid gland [1], are becoming increasingly common in clinical practice [2]. Thyroid nodule detection is substantially improved by high-resolution ultrasound technology [3]. A substantial increase in the detection rate of thyroid nodules has been observed over the last 30 years [4]. Between 1985 and 2014, the prevalence of thyroid nodules in China rose from 11.0 to 24.4% [5, 6]. The incidence of malignant tumors in thyroid nodules among children is 2–3 times higher than that in adults, with malignant tumors typically accounting for 5 – 10% of adult thyroid nodules [7, 8]. Thyroid cancer in children is usually a more advanced disease, however, the long-term prognosis is better [9]. Therefore, it is critical to determine any possible risk factors for children thyroid nodules.

Thyroid nodule occurrence is influenced by multiple factors such as sex, age, obesity, smoking, iodine intake, stress, genetics and radiation exposure [10–18]. Globally, $PM_{2.5}$ is recognized as one of the environmental risk factors affecting public health [19]. Numerous epidemiological studies have confirmed the link between $PM_{2.5}$ and an increased risk of disease [20–23]. However, there is still little evidence on the association between $PM_{2.5}$ and thyroid nodules. Studies have indicated that ambient air pollution is a significant health burden in China [24–26]. To our knowledge, only a few articles have reported a link between air pollution and thyroid nodules, and that $PM_{2.5}$ may pose a considerable risk for thyroid nodules [27, 28]. However, these studies targeted adults over the age of 18 years and lacked adjustment for some important risk factors for thyroid nodules, such as psychological stress, sleep duration, individual urinary iodine concentration (UIC), and dietary iodine intake. Children are at a critical stage of growth and spend more time outdoors than adults. Owing to the critical function of the thyroid in body growth, children are more vulnerable to air pollution, especially long-term exposure $PM_{2.5}$ [29, 30]. Current research regarding on the impact of long-term $PM_{2.5}$ exposure on thyroid nodules in children and adolescents is limited.

Therefore, using a big sample of school-aged children and adolescents in Eastern China, our study aimed to explore the relationship between thyroid nodules prevalence and long-term $PM_{2.5}$ exposure in children and adolescents.

Methods

Participants

The participants were drawn from the cross-sectional investigation project on thyroid nodules in students in Jiangsu, Eastern China, in 2021. Jiangsu Province experiences a heavy burden of deaths caused by air pollution. A total of 10,739 students in the third grade of primary school and first grade of junior high school were drawn at 61 schools (both primary and junior high schools) from 17 districts of Jiangsu Province with the stratified whole-cluster multistage sampling method. Participants who suffer or have suffered from thyroid disease were excluded from the study. Participants with recent acute illness (including suspected or confirmed COVID-19 cases) were excluded. The study districts were located in the northern, central, and southern parts of Jiangsu, and the locations of the investigation sites are shown in Fig. 1. Signed informed permission was provided freely by all participants and their parents. Prior to recruiting participants for the survey, we conducted standardized training for school administrators and teachers to ensure that they understood the study objectives and ethical obligations. We released detailed study information, including questionnaires and procedures, through a parents-teachers-researchers WeChat group for interaction and clarification with researchers. At the same time, we obtained age-appropriate informed consent from students through classroom explanations emphasizing the right to voluntary participation and withdrawal without consequences. Only after resolving all participants' queries and obtaining signed informed consent in writing did we begin data collection. To enhance participation and show appreciation, we provided each student with a set of stationery (pens and rulers) as a small token. These incentives were designed to be modest and ethical to ensure that they did not influence the study results or participants' responses. The Ethical Committee of Jiangsu Provincial Center for Disease Control and Prevention (JSCDC) gave its approval to this investigation (JSJK2024-B033-01). We excluded 667 participants without thyroid test results and five participants without urinary iodine concentrations data. Finally, our study contained 10,067 surveys that were used in the analysis.

Thyroid nodule diagnosis

Two experienced radiologists performed thyroid ultrasonography on all the participants using a high-resolution diagnostic ultrasound machine (Myriad, USA). The

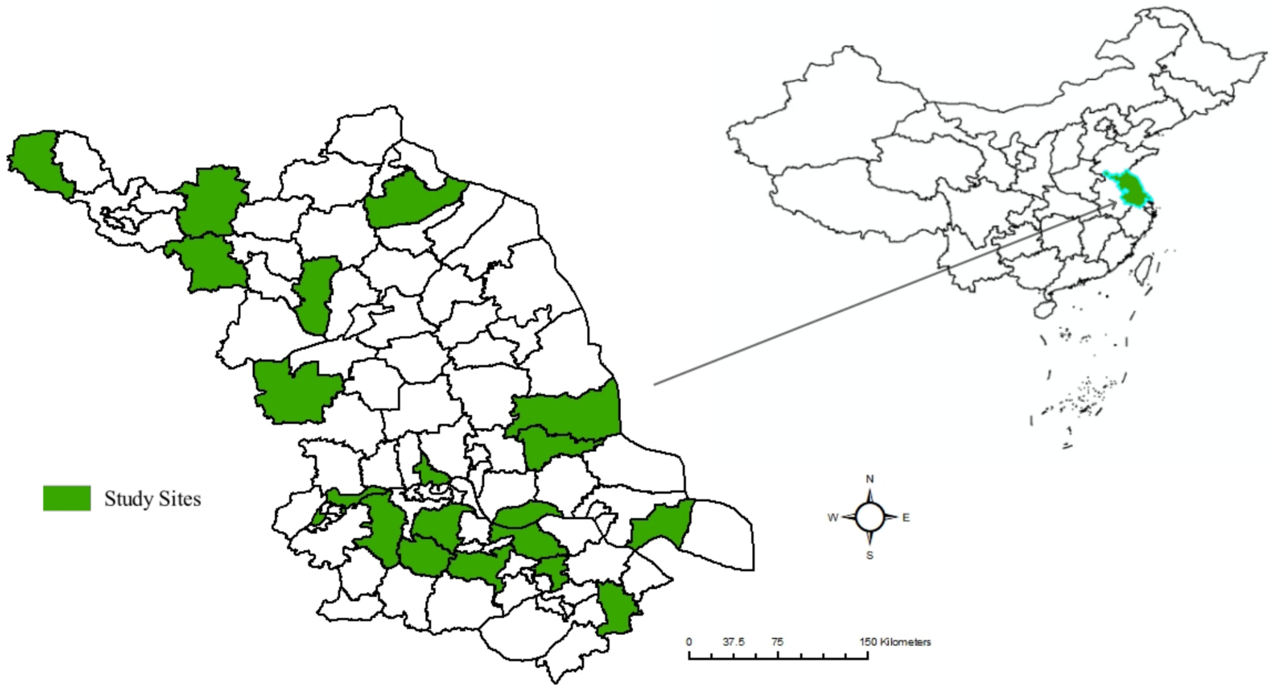

Fig. 1 Locations of the 17 investigation sites in Jiangsu Province, China

radiologists were asked to scan the left and right lobes of the thyroid of each participant in both transverse and longitudinal planes using a 7.5 MHz probe, while measuring and recording the size, number, echogenicity, location, and morphological characteristics of the thyroid nodules. Nodule size was defined as the maximum diameter of the nodule. If the maximum diameter is greater than 0 mm, it was recognized as a thyroid nodule.

Exposure to $PM_{2.5}$

We obtained annual gridded $PM_{2.5}$ data for Jiangsu Province for 2019–2020 using the China High Air Pollutants dataset (CHAP, available at https://weijing-rs.github.io/product.html), with a spatial resolution of 0.01° × 0.01°, or approximately 1 km × 1 km. As mentioned previously, the dataset was generated based on machine learning using an enhanced space–time extremely randomized tree model combined with satellite remote sensing [31, 32], which has been used in certain environmental epidemiological investigations in China [23, 33–35]. Tenfold cross-validation results confirmed the stability of the model, with coefficients of determination and root-mean-square-errors (RMSE) of 0.91 and 12.67 μg/m^3 (2013–2020), respectively. Annual outdoor $PM_{2.5}$ concentrations for 2019 and 2020 were assigned to each participant in this study according to the geocoding of the school address. We calculated the two-year average concentration as the long-term $PM_{2.5}$ exposure concentration of the participants [35, 36].

Covariates

The study collected detailed demographic characteristics of the participants as well as associated behavioral and lifestyle factors with a questionnaire designed by JSCDC. Participants were requested to complete the questionnaire independently. Potential covariates for adjustment in our analyses were selected through a systematic approach, incorporating evidence from prior studies and employing a directed acyclic graph (DAG) constructed using the DAGitty web-based platform (www.dagitty.net) [37–40] (Figure S1). This study included the following covariates: sex (male, female), age, frequency of intake of iodine-rich foods (less than twice a month, more than twice a week, middle portion), hours of sleep per night (≤8 h, 8–9 h, 9–9.5 h, >9.5 h, according to quartiles), time spent per day to complete homework (≤1 h, 1–2 h, 2–2.5 h, >2.5 h, according to quartiles), attending tutorial classes outside of school (yes, no), and parental smoking status (either parent: yes, no). We explicitly provided visual references and text descriptions of regionally relevant high-iodine foods during questionnaire administration based on The Chinese Dietary Guidelines for Iodine Supplementation and local dietary patterns in Jiangsu Province. Specifically, we included: (1) seaweed products (nori, kelp, wakame), (2) shellfish (dried shrimp, swimming crabs, razor clams, scallops), (3) marine fish (hairtail, yellow croaker, eel, squid), and (4) eggs (quail eggs, goose eggs).

A standardized measuring tool was used to measure height and weight of each participant, during which participants were instructed to remove shoes and wear light clothing. The formula for calculating body mass index (BMI) was weight (kilograms) divided by height (meters) squared. Based on the Chinese national standards, BMI cutoff values by age and sex were used to define obesity among school-aged children and adolescents in this study [41]. UIC was measured by collecting the first urine sample from the participants in the morning. Samples were transferred to the laboratories at low temperatures (2–8 °C), and all laboratories passed Chinese Center for Disease Control and Prevention quality control test. UIC was categorized into four groups (< 100 μg/L, 100–199 μg/L, 199–300 μg/L, > 300 μg/L). Drinking water consumed by students was also collected from school to measure its iodine concentration. Drinking water iodine concentrations were divided into three categories (< 40 μg/L, 40–100 μg/L, > 100 μg/L).

Statistical analyses

Continuous variables were presented as mean (standard deviation, SD) and categorical variables as frequency (percentage). We used a generalized linear mixed-effects model (GLMEM) to assess the association between long-term $PM_{2.5}$ exposure (per SD increment) and thyroid nodules, in which school was considered to be a random effect [42]. To assess the effects of covariates on the estimated associations, we used the sequential adjustment method to construct three GLMEMs: unadjusted, age- and sex- adjusted and multivariate-adjusted. To explore the concentration-response (C-R) relationship between $PM_{2.5}$ concentrations and prevalence of thyroid nodules, $PM_{2.5}$ was fitted as a smooth term in age- and sex-adjusted models using a restricted cubic spline (RCS) with three knots at the 10th, 50th, and 90th percentiles [43]. A likelihood ratio test was used to verify the non-linearity of the C-R curves, and a p-value of less than 0.05 revealed a substantial departure from the assumption of linearity [44, 45]. If the C-R relationship between $PM_{2.5}$ concentrations and the prevalence of thyroid nodules significantly deviates from the linear assumption, we would identify a threshold to categorize the participants based on the threshold. Subsequently, we will perform piecewise fitting using GLMEMs to estimate the association between $PM_{2.5}$ concentration and the prevalence of thyroid nodules [46, 47]. Stratified analyses were made to investigate the modification of potential effects by variables: sex (male, female), age (9 years old, 13 years old), UIC (< 100, 100–199, 199–300, > 300 μg/L), daily sleep time (≤ 8, 8–9, 9-9.5, > 9.5 h), daily time spent completing homework (≤ 1, 1–2, 2-2.5, > 2.5 h), parental smoking status (yes, no), frequency of iodine-rich food consumption (low (less than twice a month), middle portion, high (more than twice a week)), obesity (yes, no), and attending tutorial classes outside of school (yes, no). Participants were nine years old in the third grade of primary school and thirteen years old in the first grade of junior high school, which was consistent with the distribution of school type, consequently, the school type (primary school, junior high school) was not included in the stratified analysis. Briefly, we added a multiplicative interaction term between $PM_{2.5}$ and the stratification variables in the multivariate adjustment model.

Furthermore, three sensitivity analyses were conducted to evaluate the robustness of our findings. First, we defined nodules with a maximum diameter greater than 3 mm in the ultrasound images as thyroid nodules in the analysis, based on experience of clinicians in risk stratification of thyroid nodules during clinical practice [48]. Second, we used one-year annual concentrations (2020) as the exposure level of $PM_{2.5}$ for participants in the models to explore the short-term exposure effects of $PM_{2.5}$. Since the average $PM_{2.5}$ concentrations in 2020, as the most recent complete annual record prior to the survey, scientifically reflects the short-term exposure prior to the survey, it is more consistent with the time frame of the study and ensures the validity of the short-term exposure assessment. Third, psychological factors may play a crucial role in the development of thyroid nodules [49]. Thyroid dysfunction was closely associated with psychological problems such as anxiety, depression and sleep disorders [50]. Anxiety disorders, one of the most common psychiatric disorders, have their first onset in childhood and adolescence [51]. Negative emotions in children and adolescents due to school and life stress may adversely affect thyroid health. We made additional adjustments for attitudes of children toward learning and school anxiety symptoms in multivariate adjustment models. Symptoms of anxiety were assessed in school-aged children using the Screen for Child Anxiety Related Emotional Disorders (SCARED), and we collected attitudes of children toward learning by the question "Do you enjoy learning?".

All statistical analyses were completed using R software version 4.3.0, and a two-tailed p-value < 0.05 was defined as statistically significant.

Design

This study was a cross-sectional survey, which was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (Table S1).

Results

Descriptive analysis

Table 1 summarizes the characteristics of the participants. The average age of the 10,067 participants was 11

Table 1 General characteristics of participants in the study

	Non- Thyroid Nodule	Thyroid Nodule	All
	(*n* = 6998)	**(*n* = 3069)**	**(*n* = 10067)**
Sex, male, *n* (%)	3751 (53.6%)	1478 (48.2%)	5229 (51.9%)
Age (years), mean (SD)	10.8 (1.99)	11.2 (1.99)	11.0 (2.00)
BMI (kg/m^2), mean (SD)	19.0 (4.12)	19.2 (3.75)	19.1 (4.01)
Obesity	1167(16.7%)	472(15.4%)	1639(16.3%)
UIC (μg/L)			
< 100	636 (9.1%)	257 (8.4%)	893 (8.9%)
[100, 199]	2075 (29.7%)	895 (29.2%)	2970 (29.5%)
(199, 300)	2138 (30.6%)	1002 (32.6%)	3140 (31.2%)
≥ 300	2149 (30.7%)	915 (29.8%)	3064 (30.4%)
WIC (μg/L)			
< 40	6895 (98.5%)	3012 (98.1%)	9907 (98.4%)
[40, 100]	103 (1.5%)	57 (1.9%)	160 (1.6%)
Frequency of iodine-rich food intake			
Less than twice per month	1852 (26.5%)	820 (26.7%)	2672 (26.5%)
Middle portion	2847 (40.7%)	1313 (42.8%)	4160 (41.3%)
More than twice per week	2299 (32.9%)	936 (30.5%)	3235 (32.1%)
School			
Primary school	3783 (54.1%)	1361 (44.3%)	5144 (51.1%)
Junior high school	3215 (45.9%)	1708 (55.7%)	4923 (48.9%)
Daily sleep time (hours)			
Q1, ≤8	2012 (28.8%)	992 (32.3%)	3004 (29.8%)
Q2, (8,9]	2194 (31.4%)	1059 (34.5%)	3253 (32.3%)
Q3, (9,9.5]	975 (13.9%)	357 (11.6%)	1332 (13.2%)
Q4, > 9.5	1817 (26.0%)	661 (21.5%)	2478 (24.6%)
Time spent per day to complete homework (hours)			
Q1, ≤1	2727 (39.0%)	1086 (35.4%)	3813 (37.9%)
Q2, (1,2]	2496 (35.7%)	1149 (37.4%)	3645 (36.2%)
Q3, (2,2.5]	237 (3.4%)	111 (3.6%)	348 (3.5%)
Q4, > 2.5	1538 (22.0%)	723 (23.6%)	2261 (22.5%)
Attending tutorial classes outside of school			
No	3506 (50.1%)	1365 (44.5%)	4871 (48.4%)
Yes	3492 (49.9%)	1704 (55.5%)	5196 (51.6%)
Parental smoking status			
No	5544 (79.2%)	2461 (80.2%)	8005 (79.5%)
Yes	1454 (20.8%)	608 (19.8%)	2062 (20.5%)

Abbreviations: SD, standard deviation; BMI, body mass index; UIC, urinary iodine concentration; WIC, drinking water iodine concentration

Table 2 Annual average $PM_{2.5}$ exposure concentrations of participants in 2019–2020

Time	Mean	SD	Median	Rang	IQR
Annual average concentration in 2019 (μg/m^3)	45.1	4.4	44.1	39.0-57.3	4.1
Annual average concentration in 2020 (μg/m^3)	38.9	4.6	37.6	31.0-50.5	3.2
Two-year average concentration (μg/m^3)	42	4.5	40.8	36.6–53.9	3.7

Abbreviations: SD, standard deviation; IQR, interquartile range

years, with a thyroid nodule prevalence of 30.5%. Almost half of the participants were boys (51.9%), came from primary schools (51.1%), and were required to attend tutorial classes outside of school (51.6%). A minority of the participants were in obesity (16.3%) and had experienced passive smoking (20. 5%). In addition, 37.4% of the participants had to spend 1–2 h per day completing homework for school, and 34.5% of the participants got 8–9 h of sleep per night.

Table 2 shows the distribution of annual $PM_{2.5}$ exposure concentrations of participants for 2019–2020. The median (interquartile range, IQR) $PM_{2.5}$ exposure concentration was 44.1 μg/m^3 (4.1 μg/m^3) in 2019 and 37.6 μg/m^3 (3.2 μg/m^3) in 2020. The range of two-year average $PM_{2.5}$ exposure concentrations for participants was 36.6–53.9 μg/m^3.

Association between $PM_{2.5}$ exposure and thyroid nodules

The association between $PM_{2.5}$ and thyroid nodules is shown in Table 3. Increased two-year average $PM_{2.5}$ exposure concentrations were strongly linked with a higher frequency of thyroid nodules. In the unadjusted, age- and sex-adjusted and multivariate-adjusted models, the odds ratios (ORs) and 95% confidence intervals (CIs) associated with thyroid nodules for per SD increment in two-year average $PM_{2.5}$ exposure concentration(SD:4.5 μg/m^3) were 1.260 (1.023, 1.522), 1.265(1.037, 1.544), and 1.270(1.027,1.570). Figure 2 demonstrates the C-R relationship between long-term $PM_{2.5}$ exposure and thyroid nodules. We observed that the OR of thyroid nodules steadily rose with the increase of $PM_{2.5}$ concentration (P for overall < 0.001). After adjustment for sex and age, the C-R curve for long-term $PM_{2.5}$ exposure associated with thyroid nodules was J-shaped (P for nonlinear = 0.001). We selected the lowest point of the curve (39.7 μg/m^3) as the threshold value. For $PM_{2.5}$ concentration below the threshold value, the OR (95% CI) of thyroid nodules for per SD increment in $PM_{2.5}$ exposure concentration(SD:0.68 μg/m^3) was 1.112 (0.807, 1.533). For $PM_{2.5}$ concentration above the threshold value, the OR (95% CI) of thyroid nodules for per SD increment in $PM_{2.5}$ exposure concentration(SD:4.18 μg/m^3) was 1.515 (1.199, 1.915).

Stratified analysis

As shown in Fig. 3, we investigated the potential effects of all covariates on the association between $PM_{2.5}$ and thyroid nodules with $PM_{2.5}$ concentrations greater than the threshold value. We found a positive correlation between $PM_{2.5}$ and thyroid nodules across all subgroups. However, no significant differences in effect sizes were observed between the subgroups when comparing the estimated effects.

Sensitivity analysis

The estimated association between $PM_{2.5}$ concentrations and thyroid nodules remained robust in our sensitivity analysis. The positive correlation between $PM_{2.5}$ and thyroid nodules remained significant when additional adjustments were made for attitudes of children toward learning and school anxiety symptoms. After adjusting the definition of thyroid nodules, the association between $PM_{2.5}$ and thyroid nodules ≥ 3 mm in maximum diameter was similar to the results of our primary analysis. Similarly, as described above, significant positive association was also observed when we used one-year annual $PM_{2.5}$ concentrations.

Discussion

To our knowledge, this study is the first comprehensive epidemiological investigation to show a link between long-term exposure to $PM_{2.5}$ and thyroid nodules among school-aged children and adolescents. Our study demonstrated that long-term exposure to higher $PM_{2.5}$ concentrations was linked to a higher prevalence of

Table 3 Association between long-term exposure to $PM_{2.5}$ and thyroid nodules in children and adolescents

Methods of analysis	Model	All			< threshold value			> threshold value		
		OR	95% CI	*P*-value	OR	95% CI	*P*-value	OR	95% CI	*P*-value
GLMEM	Crude model	1.673	(1.063,2.632)	0.026	1.132	(0.796,1.611)	0.490	1.466	(1.164–1.846)	0.001
	Model 1	1.688	(1.084,2.627)	0.020	1.107	(0.797,1.537)	0.545	1.483	(1.189,1.849)	< 0.001
	Model 2	1.700	(1.062,2.721)	0.027	1.112	(0.807,1.533)	0.518	1.515	(1.199,1.915)	0.001
Sensitivity analysis I [a]	Crude model	1.790	(0.966,3.364)	0.064	1.131	(0.789,1.620)	0.504	1.503	(1.049,2.153)	0.026
	Model 1	1.800	(1.066,3.083)	0.028	1.077	(0.817,1.420	0.598	1.513	(1.103,2.074)	0.010
	Model 2	1.861	(1.064,3.253)	0.030	1.088	(0.821,1.442)	0.558	1.554	(1.107,2.180)	0.011
Sensitivity analysis II [b]	Crude model	1.652	(1.054,2.590)	0.029	0.813	(0.581,1.138)	0.228	1.515	(1.210,1.897)	< 0.001
	Model 1	1.665	(1.069,2.594)	0.024	0.795	(0.586,1.078)	0.140	1.533	(1.237,1.900)	< 0.001
	Model 2	1.669	(1.058,2.633)	0.028	0.812	(0.602,1.096)	0.174	1.568	(1.251,1.966)	< 0.001
Sensitivity analysis III [c]	Model 2 + AL + SA	1.710	(1.069,2.734)	0.025	1.100	(0.806,1.500)	0.548	1.532	(1.200,1.956)	0.001

[a] We defined nodules with a maximum diameter > 3 mm in the ultrasound images as thyroid nodules in the analysis

[b] We used one-year annual concentrations (2020) as the exposure level of $PM_{2.5}$ for participants in the models

[c] We made additional adjustments for attitudes of children toward learning and school anxiety symptoms in multivariate adjustment models

Abbreviations: GLMEM, generalized linear mixed-effects model; OR, odds ratio; CI, confidence interval; AL, attitudes of children toward learning; SA, school anxiety symptoms

Crude model: no adjustment

Model 1: adjusted for sex-, age-

Model 2: adjusted for sex, age, urinary iodine concentration, drinking water iodine concentration, obesity, frequency of iodine-rich food intake, daily sleep time, time spent completing homework per day, attending tutorial classes outside school, and parental smoking status

School was fitted as a random effect in model

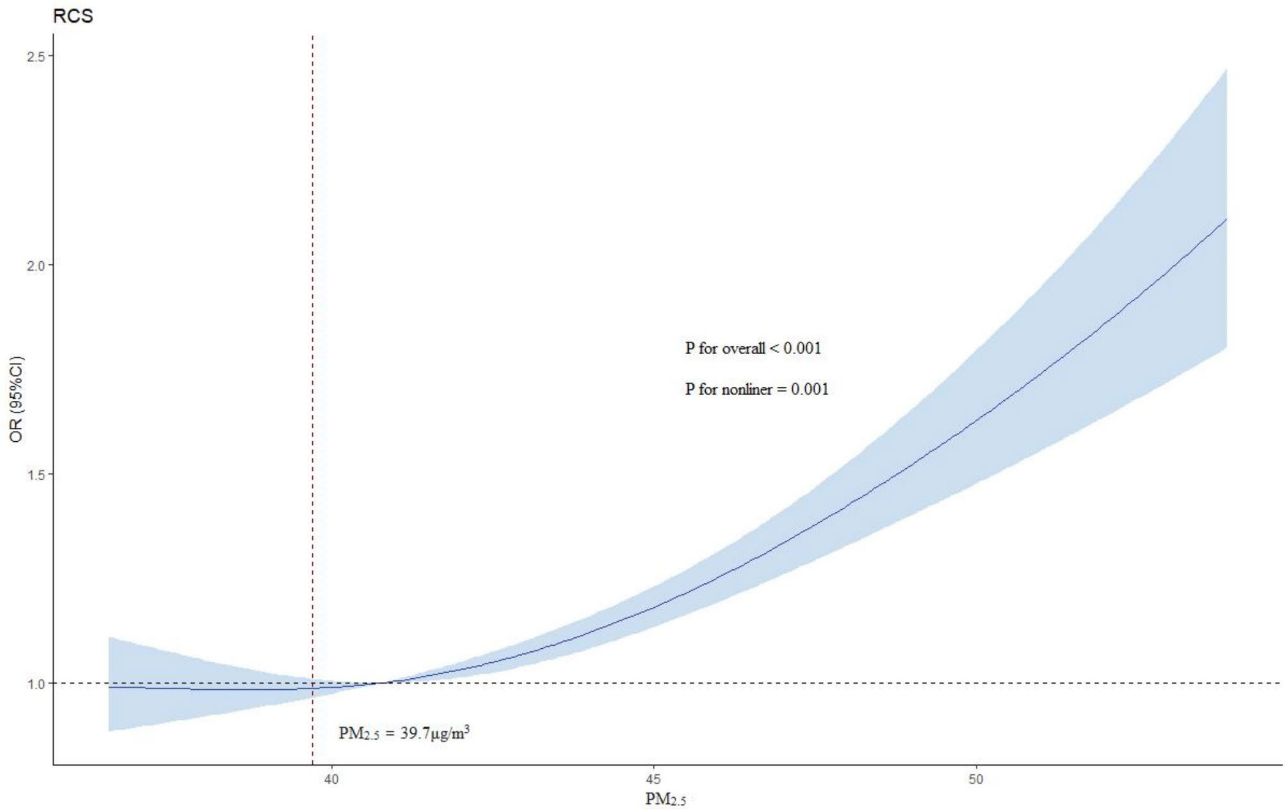

Fig. 2 The concentration–response relationship between long-term $PM_{2.5}$ exposure and thyroid nodules. The solid blue line represents the effect estimates. The 95% confidence intervals are shown by the gray areas. The inflection point for the risk associated with thyroid nodules is shown by the red dotted line. Abbreviations: $PM_{2.5}$, particulate matter ≤ 2.5 μm in aerodynamic diameter; OR, odds ratio; CI, confidence interval

thyroid nodules in school-aged children and adolescents in Jiangsu. This association remained significant in most of the subgroups. The shape of the C-R relationship curve between $PM_{2.5}$ and thyroid nodules was J-shaped with a threshold value of 39.7 μg/m^3.

The prevalence of thyroid nodules observed in this study (30.5%) was higher than the overall prevalence of 11-24% of 1985–2014 in China reported in the meta-analysis. We attributed this difference to the combined effects of regional differences in survey areas, upgraded study methods, policy adjustments in salt iodine content, and large sample size surveys [6, 39, 52–55]. Although many studies have investigated the factors affecting thyroid nodules, the association between $PM_{2.5}$ and thyroid nodules has rarely been reported, and studies on this topic have been conducted mainly among adults [55–59]. A study conducted in China examined the connection between six air pollutants and thyroid nodules among adults undergoing health examinations [28]. This study reported a significant non-linear association between $PM_{2.5}$ and risk of thyroid nodules. Exposure to six air pollutants was observed to increase the risk of thyroid nodules even when air pollutant concentrations were below the annual average limits recommended by the WHO. The study found that each 10-μg/m^3 increase in $PM_{2.5}$ led to a 6.1% rise in thyroid nodules. Potential associations were estimated in the study using annual $PM_{2.5}$ concentrations of the city of the participants as the exposure, with adjustment for covariates such as age, sex, UIC, smoking, BMI, and education. However, some covariates used in the study such as educational level, smoking, and UIC was estimated using the provincial averages calculated in previous national cross-sectional surveys, which provided rough estimates. The study estimated the association between $PM_{2.5}$ and thyroid nodules using a multivariate logistic regression model that assumed independence among covariates for each participant, but this was not always the case.

Compared with these studies, we had more precise data regarding long-term $PM_{2.5}$ exposure concentrations for participants, expanded the range of potential covariates, and used more advanced association estimation models; therefore, the associations estimated in our study were more precise. The observed decline in annual average $PM_{2.5}$ concentrations within our study area between 2019 and 2020 may be attributed to the synergistic effects of sustained air quality management policies and the implementation of unprecedented COVID-19 containment

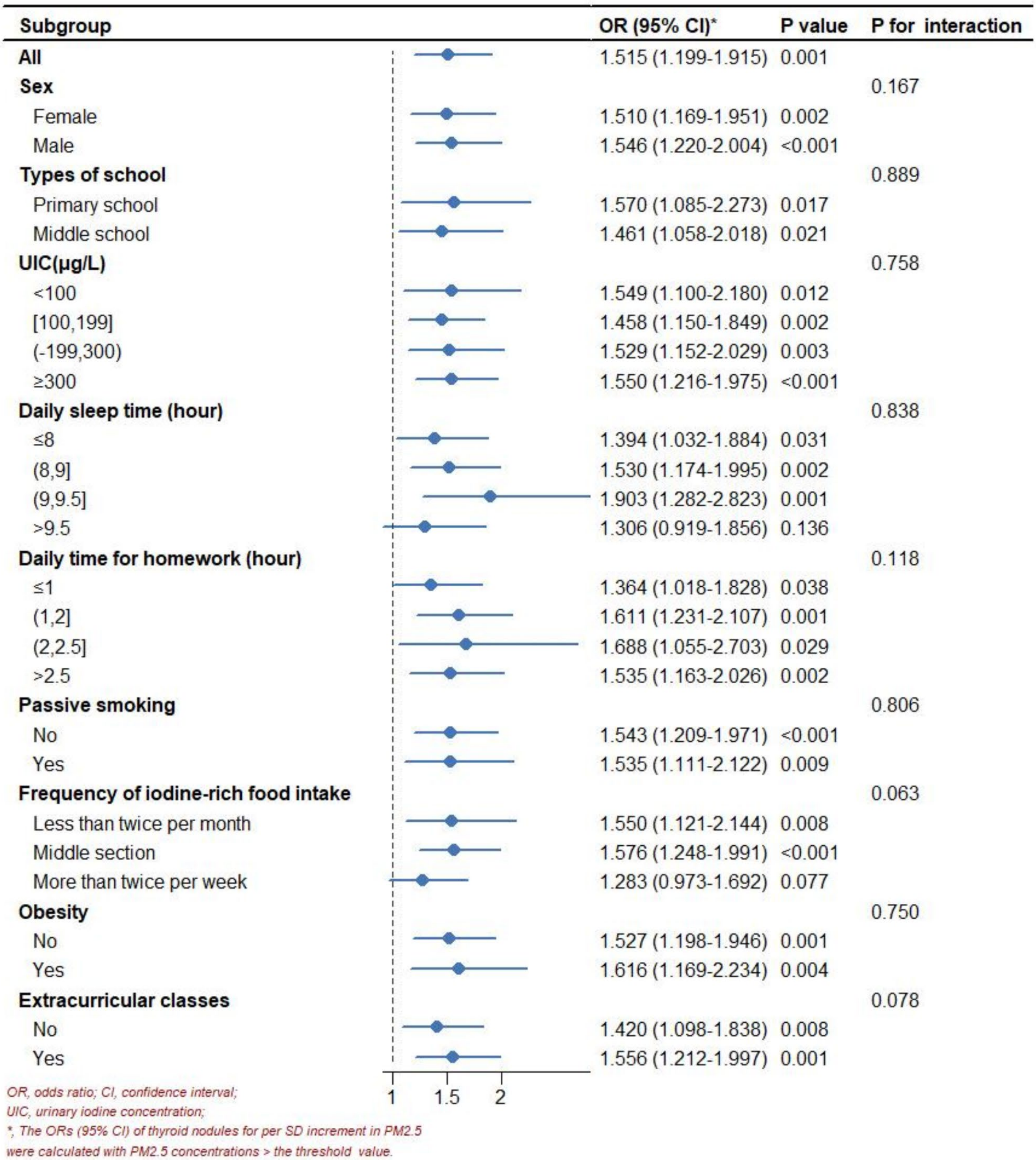

Fig. 3 Association between per SD increase in $PM_{2.5}$ and the OR (95% CI) of thyroid nodules among all subgroups with $PM_{2.5}$ concentrations > the threshold value

measures [60–63]. Students spent a longer part of the day participating in learning activities at school, including the morning of the day when air pollution was at its worst; consequently, we collected the average $PM_{2.5}$ concentrations from the location of the school as the exposure concentration of the students [64, 65]. Data on UIC, drinking water iodine concentration, and the frequency of intake of iodine-rich foods were collected from each school-aged child to evaluate individual dietary iodine intake levels. Psychological stress is an important factor of influencing the development of thyroid nodules, and we collected information about the learning-related stress of each participant, which included the time spent completing homework, the time spent sleeping per day, and whether they attended tutorial classes outside of school. Given the similarity of diets and learning tasks among students in the same school, we used a GLMEM to calculate the correlation between $PM_{2.5}$ and thyroid nodules, with school used as a random-effects term. We found a significant non-linear relationship between long-term exposure to $PM_{2.5}$ and thyroid nodules in school-aged children and adolescents, which was consistent with findings among adults. In contrast to findings of Zhang et al., our studies found that long-term exposure to $PM_{2.5}$ concentrations exceeding 39.7 μg/m^3 increased the probability of thyroid nodules, and the threshold of 39.7 μg/m^3 was significantly higher than the annual average value recommended by the WHO. Smoking can accelerate iodine efflux from the body and inhibit iodine transport, which may increase the risk of thyroid nodules [66]. However, this association was not found in our study, which may be related to the living environment of the students, as only 20.5% of the children had a history of passive smoking. Two definitions are commonly used in high-resolution ultrasound to identify thyroid nodules: maximum diameter > 0 mm or maximum diameter ≥ 3 mm in epidemiological studies on thyroid nodules [16, 59]. The results of our sensitivity analysis, in which we analyzed both cases, confirmed the robustness of our findings. The previously reported potential modifying effects of sex and UIC on the association of $PM_{2.5}$ concentrations with thyroid nodules were not observed in our stratified analyses. We believe that this is because school-aged girls have not yet reached the estrogen levels of adult women. Studies have indicated that the increased occurrence of thyroid nodules in adult women is related to estrogen levels and receptors [67]. The risk of thyroid nodules is similar for boys and girls among young children, but the girls have a higher risk in late adolescence [68]. The modifying effect of UIC reported in previous studies may not be robust because provincial averages were used as estimates of the UIC of participants.

While our study primarily focused on the association between long-term $PM_{2.5}$ exposure and thyroid nodules, we have taken into account the potential influence of the COVID-19 pandemic on thyroid health. COVID-19 may affect thyroid function through multiple mechanisms, including direct viral effects on thyroid cells, immune-mediated thyroid dysfunction, and systemic inflammation-induced alterations in thyroid hormone metabolism [69]. During our study period, COVID-19 prevalence in Jiangsu Province was relatively low due to stringent public health measures. Additionally, we excluded participants with recent acute illnesses, including suspected or confirmed COVID-19 cases, to minimize the impact of acute infections on thyroid function. We acknowledge that the pandemic may have indirectly affected thyroid health through factors such as stress, changes in healthcare access, or delayed diagnoses [70], which could not be fully accounted for in the current study. We plan to incorporate serological testing for SARS-CoV-2 antibodies in future research to better elucidate the potential role of COVID-19 in thyroid disease development. This approach will allow us to further explore the complex interplay between environmental exposures and infectious factors in thyroid health.

Although our study confirmed the association between $PM_{2.5}$ and thyroid nodules in school-aged children and adolescents, the exact mechanism remains unclear. We hypothesize that this association may be related to inflammation or oxidative stress, which is consistent with an existing hypothesis that oxidative stress may be one of the mechanisms underlying the pathogenesis of several thyroid diseases [71]. Multiple studies have shown that exposure to air pollution can induce inflammation and oxidative stress [72–74]. This association may raise the risk of autoimmune thyroiditis, which has been linked to an increased incidence of thyroid nodules [75]. Compared to adults, the incidence of malignant tumors is higher in thyroid nodules in children [7, 8], but we did not find ultrasound images of thyroid tumors in our study. We are fully aware of the scientific significance regarding the association between $PM_{2.5}$ exposure and thyroid cancer. However, we were unable to directly analyze this relationship in the current cross-sectional study. To explore this relationship, we are actively working on a follow-up longitudinal study in collaboration with a pediatric hospital.

Our study had some pertinent limitations. First, as a cross-sectional survey study, our study was not able to confirm a causal association between long-term $PM_{2.5}$ exposure and thyroid nodules. Second, although we used the more precise school-address-based $PM_{2.5}$ concentrations as exposure estimates, these are not exact individual exposures, which could cause misclassification of exposures and result in biased estimates of potential associations. Third, complex correlations have been found between other air pollutants and $PM_{2.5}$, and we have not yet considered the potential effects that other pollutants may have on the associations found in our study. Fourth, we recruited only students in the third grade of primary school and the first grade of junior high school, who were less pressured to advance to a higher educational level. Students from other grades were not included among the participants, which may have reduced the prevalence of the associations of interest among school-aged children and adolescents. Finally, questionnaires were used to collect information about the lifestyles and study habits of participants, which may have created a recall bias.

Conclusions

Our study is the first comprehensive epidemiological investigation to show a link between long-term exposure to $PM_{2.5}$ and thyroid nodules in school-aged children and adolescents. This study demonstrated that $PM_{2.5}$ exhibited a nonlinear relationship with the prevalence of thyroid nodules. Long-term exposure to higher $PM_{2.5}$ concentrations was related to a higher prevalence of thyroid nodules in school-aged children and adolescents in Jiangsu, Eastern China. The potential modifying effects of covariates on associations among children and adolescents were not observed in this study. Based on the above findings, further longitudinal cohort studies are required to confirm the causal association between $PM_{2.5}$ and thyroid nodules.

Abbreviations

GLMEM	Generalized linear mixed-effects model
OR	Odds ratio
CI	Confidence interval
AL	Attitudes of children toward learning
SA	School anxiety symptoms

Supplementary Information

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Supplementary Material 1

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Author contributions

ML performed the data analyses and wrote the original draft. PHW, YJY, LS, YTX, and YW collected the data. YX provided funding and supervision throughout the project. ZD revised the original draft. All authors read and approved the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The Ethical Committee of Jiangsu Provincial Center for Disease Control and Prevention (JSJK2024-B033-01) gave its approval to this investigation. All participants provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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