SUBCLINICAL THYROID DISEASE: PRESENT KNOWLEDGE AND FUTURE DIRECTION

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SUBCLINICAL THYROID DISEASE: PRESENT KNOWLEDGE AND FUTURE DIRECTION

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Editorial: Subclinical thyroid disease: present knowledge and future direction

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Editorial on the Research Topic
Subclinical thyroid disease: present knowledge and future direction

For centuries, a wide spectrum of thyroid dysfunction has been described in the literature across different civilizations. Interestingly, our current understanding about the structural, functional, and pathophysiologic aspects underlying thyroid disease has only fundamentally changed in recent decades as new technologies are developed, in addition to the increasing amount of data from clinical trials. These discoveries have led to a paradigm change in the management of thyroid disease (1).

Mild to moderate thyroid dysfunction is commonly found during routine testing in clinical practice, affecting between 3-8% of the general population. There are numerous pathophysiological mechanisms described in the literature to establish a clear relationship between thyroid dysfunction and the development of various pathologies such as obesity, depression, cardiovascular disease, and dyslipidemia. Untreated subclinical hypothyroidism (SCH), for instance, has been linked with a number of deleterious outcomes, although its weight as a disease modifying factor is still subject of controversy in some specific scenarios (2).

Altogether, the emergence of subclinical thyroid disease as a significant contributor to other disease states has opened multiple lines of research and the expanding literature on this topic is a welcome addition to the existing body of knowledge available for the clinician, particularly in times when misinformation abounds among the general population regarding the definition of true thyroid illness (3). In the current Research Topic, different groups of

investigators explore various interesting questions and generate novel knowledge regarding this wide group of conditions.

One of the major challenges in subclinical thyroid disease is the need to establish a TSH cut-off point to define SCH. In this issue, Zheng et al. describe the association between thyroid autoantibodies distribution in relation to different TSH cut-off values in a large cohort of 145,015 patients. Another area of subject of intense research is the effect that SCH has in pregnancy related outcomes (4, 5). Meng et al. propose a nomogram that considers the effect of TSH and TPO antibodies and the interaction with other factors, such as mother age, that could predict an increased risk of preterm delivery. In the same pregnancy related topic, Zhou et al. describe the possible relationship between Free T4 levels in the first trimester and the risk of preterm delivery. Moreover, the benefit of treating antibody positive non-hypothyroid pregnant women with thyroid hormone replacement is an area of investigation that has not been studied extensively. A clinical trial by Li et al. demonstrated no difference in the incidence of hypertensive disorders during pregnancy, but a reduction in miscarriage occurrence was observed. In these reports several other materno-fetal outcomes are also investigated. Furthermore, a meta-analysis by Han et al. explores the effect of SCH in pregnant and non-pregnant women in the overall risk of developing hypertensive disorders.

Although the neurocognitive effects in the offspring of women with uncontrolled established hypothyroidism are well known, the effect of mild thyroid dysfunction in pregnant women without TPO antibodies is less understood. In the article by Wang et al. the presence of maternal mild thyroid dysfunction was associated to an impaired neurocognitive function, manifested as lower receptive communication score at one year of age when compared with children from women with normal thyroid function, at one year of age.

Cardiovascular disease remains the number one cause of death worldwide (6, 7). Thyroid dysfunction, specifically overt hypothyroidism is linked to a worse cardiovascular risk profile through several mechanisms, such as impaired lipid metabolism causing hypercholesterolemia (8). The effect of mild thyroid dysfunction, however, as a cardiovascular risk enhancer is less clear (9). In their paper, Li et al. compared a group of patients who presented with confirmed acute ST-segment elevation myocardial infarction, based on the presence of subclinical thyroid disease (both hyper and hypothyroid) and compared post-event outcomes with those individuals with normal thyroid function. After adjustments for other risk factors, there was an increment in hospital cardiovascular deaths in the group with subclinical hyperthyroidism. In the other hand, Meng et al. investigated the incidence of atrial fibrillation development in a group of patients with hypertrophic obstructive cardiomyopathy and low TSH. Given the complex and multifactorial pathogenesis of cardiovascular disease, it is frequently difficult to isolate the dominant factor leading to an excessive cardiac risk. An impaired coagulation is one of such risk factors. It is known that thyroid function also effects the coagulation and fibrinolytic system, and thyroid dysfunction is associated to a hypercoagulation state. The detail of this intricate relationship remains to be fully elucidated, but on systematic review by Xu et al. they analyzed data on 1325 patients from 12 observational studies and describe the pattern of disrupted homeostasis between hemostatic biomarkers in subjects with abnormal thyroid function.

Subclinical thyroid disease represents an important challenge in clinical medicine. Mounting evidence strongly indicates a pressing need for earlier and better screening in vulnerable populations likely to experience adverse outcomes, such as pregnant women and individuals with a high cardiovascular risk. Research is underway aiming to elucidate the specific mechanisms responsible for these interactions and to identify those patients more likely to benefit from early thyroid replacement and the optimal timing for intervention needed to reduce such outcomes.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be interpreted as a potential conflict of interest.

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A Novel Nomogram for Predicting the Risk of Premature Delivery Based on the Thyroid Function in Pregnant Women

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Background: Maternal thyroid dysfunction and autoantibodies were associated with preterm delivery. However, recommendations for cutoff values of thyroperoxidase antibody (TPOAb) positivity and thyroid-stimulating homone (TSH) associated with premature delivery are lacking.

Objective: To identify the pregnancy-specific cutoff values for TPOAb positivity and TSH associated with preterm delivery. To develop a nomogram for the risk prediction of premature delivery based on maternal thyroid function in singleton pregnant women without pre-pregnancy complications.

Methods: This study included data from the International Peace Maternity and Child Care Health Hospital (IPMCH) in Shanghai, China, between January 2013 and December 2016. Added data between September 2019 and November 2019 as the test cohort. Youden's index calculated the pregnancy-specific cutoff values for TPOAb positivity and TSH concentration. Univariate and multivariable logistic regression analysis were used to screen the risk factors of premature delivery. The nomogram was developed according to the regression coefficient of relevant variables. Discrimination and calibration of the model were assessed using the C-index, Hosmer-Lemeshow test, calibration curve and decision curve analysis.

Results: 45,467 pregnant women were divided into the training and validation cohorts according to the ratio of 7: 3. The testing cohort included 727 participants. The pregnancy-specific cutoff values associated with the risk of premature delivery during the first trimester were 5.14 IU/mL for TPOAb positivity and 1.33 mU/L for TSH concentration. Multivariable logistic regression analysis showed that maternal age, history of premature delivery, elevated TSH concentration and TPOAb positivity in the early pregnancy, preeclampsia and gestational diabetes mellitus were risk factors of premature delivery. The C-index was 0.62 of the nomogram. Hosmer-Lemeshow test showed that the Chi-square value was 2.64 ($P = 0.955 > 0.05$). Decision curve analysis showed a positive net benefit. The calibration curves of three cohorts were shown to be in good agreement.

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Conclusions: We identified the pregnancy-specific cutoff values for TPOAb positivity and TSH concentration associated with preterm delivery in singleton pregnant women without pre-pregnancy complications. We developed a nomogram to predict the occurrence of premature delivery based on thyroid function and other risk factors as a clinical decision-making tool.

Keywords: thyroperoxidase antibody, thyroid-stimulating hormone, premature delivery, nomogram, pregnancy trimester, first

INTRODUCTION

Premature delivery is defined as delivery before gestation week 37 (1). Every year, there are 15 million preterm births worldwide, responsible yearly for 965,000 neonatal and 125,000 toddlers and preschool children (aged 1 – 5 years) deaths (1, 2). The frequency of premature births is reported as 12 ~ 13% in America and 5 ~ 9% in the other developed countries (3). The causes of premature delivery are mostly unclear, and our knowledge of its pathophysiology is still limited. Despite the socio-demographic, environmental, obstetric, fetal and medical factors were reported to be associated with premature births, approximately two-thirds of premature births occur without an obvious risk factor (4–8).

Clinicians need a simple algorithm to identify pregnant women at the risk of premature delivery by applying it to all symptomatic or asymptomatic patients at any given gestational age, those with a singleton at high risk, and those at low risk (9). Unfortunately, it is unlikely that a single test could predict all premature deliveries. Recently, clinical risk prediction models are developed to predict the probability of preterm delivery in pre-pregnancy women or high risk populations (10–13). However, singleton pregnant women without any pre-pregnancy complications, as a low risk group, lack an individualized assessment or prediction model for the risk of premature birth.

Dysfunction of maternal thyroid is relatively common during pregnancy (14). Overt hyperthyroidism and hypothyroidism are well-known risk factors for premature delivery (15). Thyroid autoimmunity (TAI) is much more frequent in pregnant women than overt thyroid diseases, with a prevalence of 10% for thyroperoxidase antibody (TPOAb) positivity (16). Recent Studies showed that TPOAb-positive pregnant women had a significantly high risk of premature delivery (14). The pathophysiological mechanisms underlying this association are still unknown but are suspected to include subtly impaired thyroid function, a direct effect of thyroid autoantibodies on fetal tissue or an underlying more generalized autoimmune dysfunctions (17). Thyroid autoantibodies can reflect a generalized activation of the immune system and specifically a dysregulated activity of the immune system at the fetal-maternal interface (18). Dysregulation of the local placental-decidual environment can be associated with miscarriage and premature delivery (19). Thyroid function screening during pregnancy should include at least an assessment of thyroid-stimulating hormone (TSH) and TPOAb concentrations, regardless of the screening method (20). We hypothesized that TPOAb positivity and TSH concentration could be novel markers of premature delivery in pregnant women.

Taking into account the unique changes of maternal thyroid function in the first half of pregnancy, the latest American Thyroid Association (ATA) guidelines advocated to use pregnancy-specific and regional reference ranges for free thyroxine (FT4) and TSH based on euthyroid pregnant women (21). But the cutoff value for TPOAb positivity is usually provided by the assay manufacturer. However, it is unknown whether such a cutoff value could be generalized to the pregnant population. The determination of TPOAb positive cutoff value in previous studies did not fully consider the thyroid function changes in pregnancy, and usually has a wide threshold range (22). There are no data on reference ranges for pregnancy-specific TPOAb and TSH concentration in association with premature delivery.

This study aimed to determine the pregnancy-specific cutoff values for TPOAb-positive and TSH concentration association with the risk of premature delivery in singleton pregnant women without pre-pregnancy complications. Furthermore, we aimed to construct a nomogram to predict premature delivery based on thyroid function and other risk factors. The aim of our study was to develop a clinical decision-making tool for assessing the individual risk for premature delivery in pregnant women.

MATERIALS AND METHODS

Patient Enrollment

The retrospective study was performed at the International Peace Maternity and Child Health Hospital (IPMCH), a large public hospital providing tertiary care in Shanghai, China. The project was approved by the Ethics Committee of IPMCH (No. GKLW2019–16). From January 1, 2013, to December 31, 2016, a total of 52,027 pregnant women were enrolled the cohort. We added data from the same institution between September 2019 and November 2019 as the test cohort. Women who met the following criterias were included: participants who underwent a first prenatal screening during the first trimester at IPMCH and their FT4, TSH, and TPOAb data from the first presentation were available. Women with chronic diseases are known to cause adverse pregnancy outcomes and interventions are expected to be required before conception and during pregnancy. The exclusion criteria were as follows (1): women who had a history of thyroid diseases, diabetes mellitus, chronic

hypertension before pregnancy; (2) those using medication known to interfere with thyroid function before or after baseline measurements; (3) pregnant women with miscarriages or multiple births, induced abortions, or stillbirths, as the gestational age or birth weight were unavailable for these neonates. As a result, 45,467 pregnant women were enrolled in this study. Then randomly divide all the enrolled participants into the training cohort (n = 31,827) and validation cohort (n = 13,640) according to the ratio of 7: 3. 727 pregnant women were enrolled as the test cohort. The regional iodine status of pregnant women in Shanghai is considered adequate during the first trimester [urinary iodine concentration (UIC), 155.0 μg/L] and second trimester (UIC, 151.0 μg/L) (23).

Data Collection

The data came from the electronic medical record system of IPMCH. Data on maternal age, parity, last menstrual period (LMP), education levels, and previous diseases such as chronic hypertension, diabetes mellitus were collected through the first interview (about 9 – 13 weeks of pregnancy). Gestational age determination was estimated based on the date of LMP and confirmed by ultrasound. Fasting blood samples were drawn from the median cubital vein, and the serum was separated by centrifugation within six hours. The measurements of FT4, TSH and TPOAb concentrations were obtained in early pregnancy (9 – 13 weeks) and measured using the Architect i2000 immunoassay (Abbott, Chicago, IL, USA) according to the manufacturer's protocols. The intra- and inter-assay coefficient of variation ranged between 1.6 – 3.6% for TSH, 1.9 – 4.0% for FT4, and was 10.0% for TPOAb positivity (24). Information on pregnancy outcomes such as gestational age, birth weights and pregnancy complications was also obtained from the electronic medical records.

Diagnostic Criteria

Maternal pre-pregnancy body mass index (BMI) was calculated by dividing the pre-pregnancy weight (kg) by the squared height (m^2). Gestational hypertension was defined as new-onset hypertension without proteinuria, with blood pressure (BP) of ≥140/90 mmHg after week 20 of gestation; preeclampsia was defined by the same criteria and with proteinuria of 1+ on dipstick testing occurring when the BP was elevated (25). Gestational diabetes mellitus (GDM) was conducted with an abnormal oral glucose tolerance test (OGTT) at week 24 – 28 of gestation and defined following the standard diagnostic criterias that established by the American Diabetes Association (26). The main pregnancy outcome was the gestational age of the neonates. Premature delivery was defined as delivery before gestational week 37 or with a birth weight more than 1,000 g.

Statistical Analysis

The data were analyzed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA) and R 4.1.1. The measurement data were shown as mean ± standard deviation (SD) and statistically compared by the independent samples *t*-test. The categorical data were expressed as count and percentage and compared by the chi-squared test. The relationships between the risk factors and premature delivery were analyzed using the univariate and multivariable logistic regression analysis. Each independent variable was examined by a univariate model. Variables associated with the studied outcome ($P < 0.05$) would be included in the multivariate model. We used the maximum Youden's index for rating diagnostic tests to calculate the optimal cut-off point of TPOAb positivity and TSH concentration related to the prevalence of premature delivery. Then randomly divide all the enrolled participants into the training cohort (n = 31,827) and validation cohort (n = 13,640) according to the ratio of 7: 3. The test cohort included 727 pregnant women. The nomogram was developed based on the regression coefficients of the relevant variables in the training cohort. The values for model covariates were mapped to points in the range of 0 to 100. The total number of points obtained by the predictive model corresponded to the prevalence of premature delivery. Discrimination and calibration of the model were assessed using the C-index, Hosmer-Lemeshow test, calibration curve and decision curve analysis. Decision curve analysis was used to determine the clinical utility of the prediction model. The decision curve plots net benefits for a range of relevant risk thresholds. The performance of the nomogram was evaluated by the calibration curve in the validation cohort and test cohort. The closer the dots were to the diagonal dotted line, the better the prediction model was. Pregnancy outcomes included gestational week, birth weight of newborns, and premature delivery rate. The logistical regression model was used to estimate the odds ratios (ORs), hazard ratios (HRs) and 95% confidence intervals (CI) for the association between variables and preterm delivery. P value < 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Figure 1 showed the flow diagram for inclusion and exclusion of the study. Finally, 45,467 eligible pregnant women were enrolled in this study. Premature delivery occurred in 2,134 women (4.7%). The pregnant women were divided into two groups according to the gestational week of neonates. The patient characteristics in both groups are shown in **Table 1**. The minimum maternal age was 18 years and the maximum maternal age was 49 years. The mean maternal age was 30.68± 3.82 years in premature-delivery group and 30.01 ± 3.56 years in full-term group ($P < 0.001$). The median pre-pregnancy BMI was 21.18 ± 2.98 kg/m^2 in premature-delivery group and 20.99 ± 2.72 kg/m^2 in full-term group ($P = 0.023$). The proportion of multiparous women was higher in the premature delivery group (21.0% vs. 18.3%, $P = 0.001$). The proportion of previous history of premature delivery was higher in the premature-delivery group (1.7% vs. 0.3%, $P < 0.001$). Maternal education level and smoking were similar between two groups.

Assessment of the Pregnancy-Specific Cutoff Values for TPOAb Positivity and TSH Concentration Associated With Premature Delivery

The Youden's index was used to calculate the pregnancy-specific and regional cutoff values for TPOAb positivity and TSH

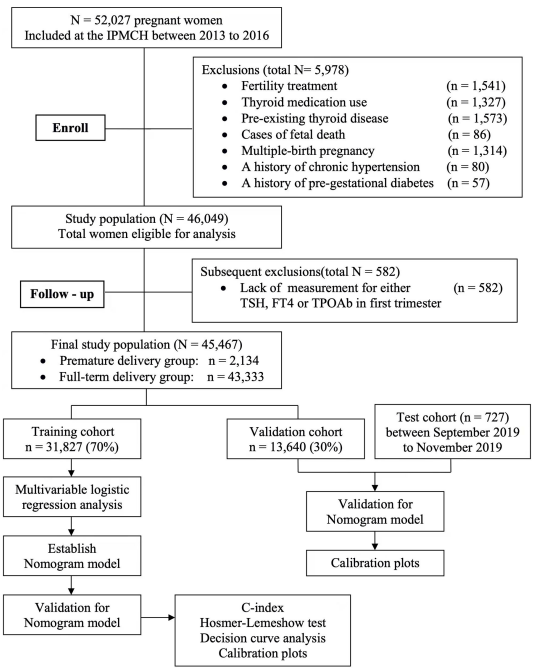

FIGURE 1 | Flowcharts illustrating study population selection and data availability.

concentration related to the prevalence of premature delivery. The cutoff value for TPOAb positive in the first trimester based on Youden's index maximum was 5.14 IU/mL, lower than the manufacturer's cutoff (5.61 IU/mL). The cutoff value for TSH concentration in the first trimester based on Youden's index maximum was 1.33 mU/L, significantly lower than the upper limit of normal threshold value for TSH in euthyroid pregnant women (3.52 mU/L).

Logistic Regression Analysis and Development of a Nomogram Prediction Model

As shown in **Figure 2**, the univariate analysis showed that there were significant differences in maternal age, parity, history of preterm birth, pre-pregnancy BMI, preeclampsia, GDM, and TSH, FT4, and TPOAb concentrations in the first trimester between two groups. The multivariable logistic regression analysis demonstrated that maternal age, previous history of premature delivery, preeclampsia, GDM and TSH and TPOAb concentrations in the first trimester were independent risk factors for premature delivery in the training cohort (**Table 2**). The prediction model was developed based on these factors and presented as a nomogram (**Figure 3**).

Apparent Performance and Clincial Use of the Nomogram

The C-index was 0.62 and Hosmer-Lemeshow test for evaluation of calibration showed that the Chi-square value was 2.64 ($P = 0.955 > 0.05$) of the predictive model. Decision curve analysis indicated the net benefit of the nomogram was higher with the probability threshold ranging from 5% to 40% (**Figure 4**). The calibration curve of the training cohort was shown in **Figure 5A** (Mean absolute error = 0.002, Quantile of absolute error = 0.003). The calibration curve of the validation cohort was shown in **Figure 5B** (Mean absolute error = 0.002, Quantile of absolute error = 0.004) and the test cohort was shown in **Figure 5C** (Mean absolute error = 0.003, Quantile of absolute error = 0.007). The calibration curve of the nomogram for the prediction of premature delivery risk were proven to be in good agreement.

DISCUSSION

During recent decades, many studies on thyroid dysfunction and TAI in pregnant women have been published. A meta-analysis

TABLE 1 | Patient baseline characteristics.

Characteristics	Full-term delivery	Premature delivery	*P*-value
Number (%)	43,333 (95.3)	2,134 (4.7)	
Age[a] (years)	30.01 ± 3.56	30.68 ± 3.82	< 0.001
Pre-pregnancy BMI[a] (kg/m^2)	20.99 ± 2.72	21.18 ± 2.98	0.023
Parity[b] (n, %)			0.001
Primiparous	35,406 (81.7)	1,685 (79.0)	
Multiparous	7,927 (18.3)	449 (21.0)	
Smoking[b] (n, %)			0.651
No	43,301 (99.9)	2,133 (100.0)	
Yes	32 (0.1)	1 (0.0)	
Education level[b] (n, %)			0.063
Bachelor degree and below	35,331 (81.5)	1,774 (83.1)	
Master degree and above	8,002 (18.5)	360 (16.9)	
History of premature delivery[b] (n, %)			< 0.001
No	43,212 (99.7)	2,097 (98.3)	
Yes	121 (0.3)	37 (1.7)	

[a]*Mean ± SD, compared by independent-samples t-test.*
[b]*Compared by the chi-squared test.*
BMI, body mass index.

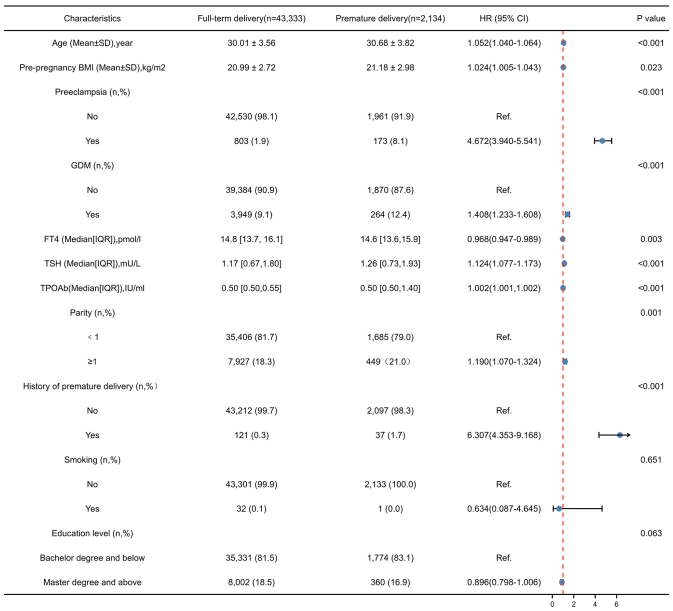

FIGURE 2 | Univariate analysis of risk factors for premature delivery.

on TPOAb-positive pregnant women from 2010 (27) and a systematic review with 3,043 TPOAb-positive cases from 2019 (14) indicated a 1.69-fold and 1.33-fold higher risk of preterm delivery, respectively, in comparison to TPOAb-negative pregnant women. These studies have demonstrated the importance of the underlying pathophysiological mechanisms. Compared with the non-pregnant population, TSH measurement declines in the early pregnancy and gradually increases throughout the later pregnancy, peaking just before delivery (28). TAI causes a gradual decrease in thyroid functional capacity and the adverse effects on thyroid function may be begun in the first trimester (20). TPOAb and its production might be a response to thyroid injury rather than a cause of it. The slightly abnormalities of maternal thyroid function might be related to the dysfunction of maternal-placental unit (29). The maternal-placental unit provides a stringently regulated endocrine and metabolic network for the fetus (30). Dysfunction of the maternal thyroid seems to be associated with an impairment of the placental-fetal glucose metabolism that might predispose the fetus to hypoglycemia and growth retardation by increasing the risk of low birth weight (31). The pathophysiological mechanism between maternal TAI and premature delivery needs further research.

Whether the metabolic control was achieved before and during pregnancy resulted in different pregnancy outcomes. However, studies on thyroid dysfunction and premature delivery have yielded mixed results. The exclusion or inclusion criterias used to select the pregnant women with thyroid disorders might be the major causes of heterogeneity in these studies (27). The 2017-ATA guidelines advocate using pregnancy-specific and regional reference ranges for FT4 and TSH measurements, but the definition of the regional and

TABLE 2 | Multivariable analysis of risk factors for premature delivery in the training group.

Characteristic	B	SE	Wald	P	OR	95%CI
Maternal age, year	0.022	0.006	13.447	< 0.001*	1.022	1.010 – 1.034
Pre-pregnancy BMI, kg/m^2	0.017	0.012	2.129	0.145	1.017	0.994 – 1.040
Preeclampisa	1.176	0.088	179.190	< 0.001*	3.241	2.728 – 3.850
GDM	0.279	0.093	8.971	0.003*	1.321	1.101 – 1.585
FT4[a], pmol/L	–0.001	0.017	0.002	0.996	0.999	0.966 – 1.034
TSH[a], mU/L	0.127	0.046	7.707	0.006*	1.135	1.038 – 1.242
TPOAb[a], IU/mL	0.576	0.055	15.900	< 0.001*	1.001	1.001 – 1.002
History of premature delivery	1.425	0.192	54.924	< 0.001*	4.157	2.852 – 6.060

**Significant variables.*

[a]the value was measured in the first trimester.

BMI, body mass index; GDM, gestational diabetes mellitus; FT4, free thyroxine; TSH, thyroid-stimulating hormone; TPOAb, thyroid peroxidase antibody; OR, odds ratio; CI, confidence Interval; SE, standard error.

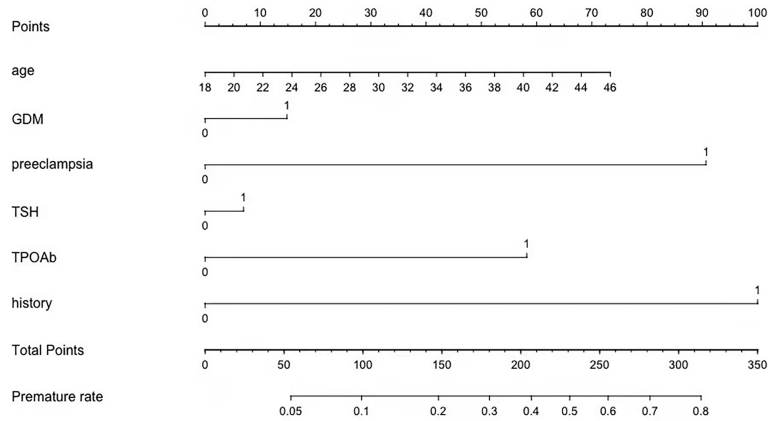

FIGURE 3 | A profile of a nomogram to estimate the risk of premature delivery in the training cohort. To calculate the probability of preterm delivery, draw a line perpendicular to the corresponding axis of each risk factor until it reaches the top line labeled "Points." Sum up the number of points for all risk factors, and then draw a line descending from the axis labeled "Total Points" until it intercepts with the lower line where the preterm birth probability is indicated. GDM, gestational diabetes mellitus; TSH, thyroid-stimulating hormone; TPOAb,thyroid peroxidase antibody; History, history of premature delivery. For Age, number=years. For binary variables, 0 = no and 1 = yes. For TPOAb positivity, 0= when TPOAb concentration less than 5.14 IU/mL and 1=when TPOAb concentration more than 5.14 IU/mL. For TSH concentration, 0= when TSH concentration less than 1.33 mU/L and 1= when TSH concentration more than 1.33 mU/L.

pregnancy-specific reference range for TPOAb positivity was not mentioned (20). Studies have reported various upper limits for TSH measurement (ranging from >2.5 to >6.0 mU/L) (14) and a wide range of cutoff values (ranging from 15 to 143 IU/mL) are used to define TPOAb positivity (22). The differences between assays and cutoffs used in various studies could contribute to the differences in the reported prevalence of thyroid antibodies, and differences in antibody associations with pregnancy outcomes (17). It was found that a dose-dependent relationship between TPOAb and thyroid function as well as the risk of premature delivery (22). In previous study, we have established a regional and pregnancy-specific thyroid function reference ranges for euthyroid pregnant women, 3.52 mU/L as an upper limit threshold value for TSH measurement in the first trimester (32). However, the regional pregnancy-specific cutoff value for TPOAb positivity has not been established yet. In our study, we investigated the association between maternal thyroid dysfunction and premature delivery. First, our study showed TPOAb-positive and TSH concentration during the first trimester was significantly associated with premature delivery. Furthermore, we investigated pregnancy-specific and regional cutoff values for TPOAb positivity and TSH concentration

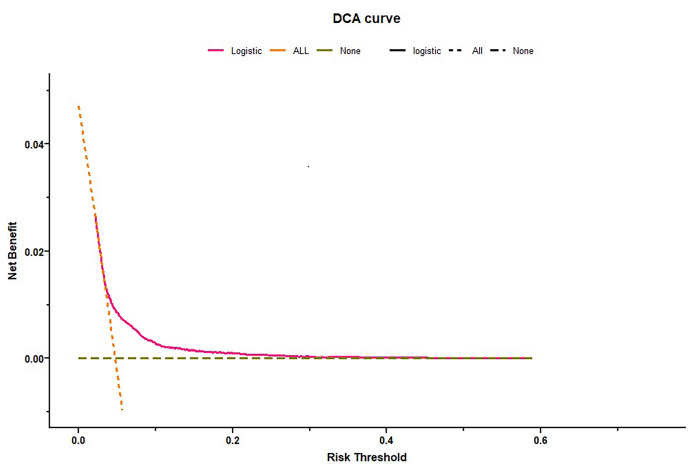

FIGURE 4 | Decision curve analysis for premature delivery. Dotted green line = net benefit when no one is at risk for premature delivery; Dotted orange line = net benefit when all are at risk for premature delivery. The y-axis measures the net benefit. The red line represents the nomogram. The decision curve showed that if the threshold probability is between 0.05–0.40, using the nomogram in the current study to predict premature delivery adds more benefit than the intervention-all-patients scheme or the intervention-none scheme.

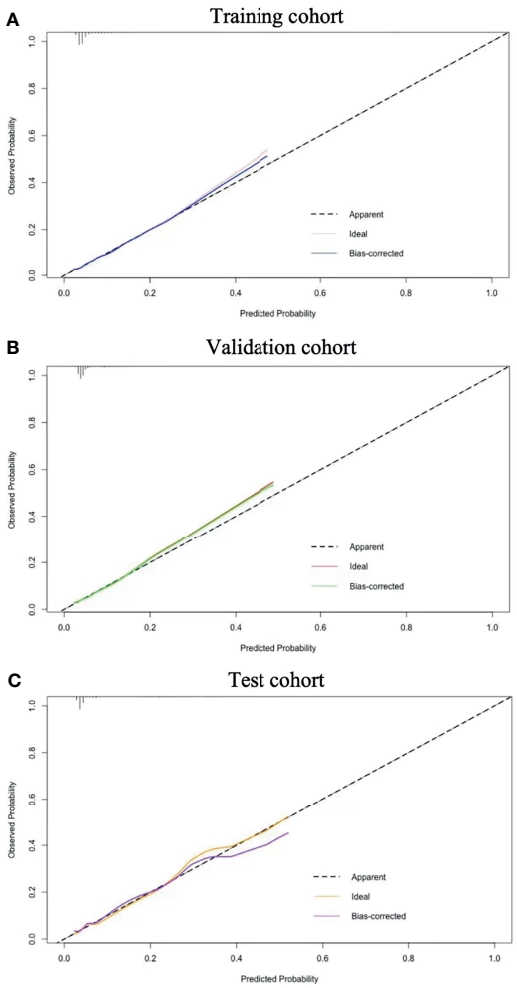

FIGURE 5 | Calibration results. Nomogram-predicted probability of premature delivery is plotted on the x-axis; actual probability of premature delivery is plotted on the y-axis. The diagonal dotted line represents a perfect prediction by an ideal model. The solid line represents the performance of the nomogram. The closer this line is to the diagonal dotted line, the better the prediction. Training cohort **(A)**; Validation cohort **(B)** and Test cohort **(C)**.

during the first trimester associated with premature delivery. The cutoff value for TPOAb positivity was lower than that provided by the assay manufacturer for the normal non-pregnant population (5.14 vs. 5.61 IU/mL). The cutoff value for TSH concentration was considerably lower than the upper limit of threshold value for TSH concentration in euthyroid pregnant women (1.33 vs. 3.52 mU/L). The risks indicated by these persisted even after adjusting for other confounding factors. Therefore, our study indicated that TPOAb positivity and TSH concentration in the early pengnancy were independent risk factors for premature delivery.

Our nomogram not only included the major well-known risk factors of preterm delivery, but also included other newly identified risk factors such as thyroid function, that had not been used in a nomogram associated with premature delivery before. Maternal history of premature delivery was commonly reported to confer a higher risk of preterm delivery in subsequent pregnancies (3, 8). Laughon et al. showed that previous history of premature birth was the most important risk factor for premature delivery, associated with a 32% high risk of a recurrent preterm birth (33). Previous preterm delivery in this study was one of the strongest predictors for premature delivery and then it was incorporated into the prediction model. Other variables such as preeclampsia and GDM were previously included in a risk-calculating nomogram and machine learning algorithm (10, 34). Hypertensive disorder was one of the known risk factors based on machine learning. Other risk factors included twin pregnancy, systemic lupus erythematosus and short cervical length (35). One of the benefits of machine learning model is the potential to identify risk for idiopathic or spontaneous premature delivery. And it can also consider a wide range of health conditions to infer patterns related to premature delivery (35). Han et al. found that thyroid autoantibodies in the first trimester were associated with an increased risk for hypertensive disorders of pregnancy, and theses associations were independent of thyroid dysfunction (36). In type 1 diabetes, the prevalence of TAI is higher than in healthy population (37). A meta-analysis showed that there was a significant but not strong association between thyroid antibodies and the risk of GDM (38). As indicated above, the pregnant women with TAI are at higher risk of developing preeclampsia and GDM.

To our knowledge, it was the first study that TPOAb positivity and TSH were enrolled in the prediction model of premature delivery. The final model included maternal age, history of premature birth, TPOAb and TSH concentrations in the first trimester, preeclampsia, and GDM. Using these findings, the nomogram was established. The nomogram prediction was supported by the C-index, Hosmer-Lemeshow test, calibration curve and decision curve analysis. The decision curve showed that using a threshold between 5% and 40% to identify pregnant women related with premature delivery would obtain a positive net benefit. The calibration curves of three cohorts were shown to be in good agreement. The strong predictive effect of these parameters was thought biologically plausible and clinically meaningful. Previous preterm delivery and thyroid functions are the most effective predictive factors in early pregnancy, providing important information to clinicians to assist in their decision-making. Preeclampsia and GDM, the main factors influencing pregnancy outcomes, were important variables for preterm birth prediction in this study. Our nomogram is a prediction model that combines preconception and antepartum factors. The dynamic changes in the variables should be noted. The total score of the nomogram will change when preeclampsia is diagnosed after week 20 of gestation or GDM after week 24.

Strengths and Limitations

Our study had some limitations. What needs to be emphasized is that observational research cannot prove causation, only association. There is currently no single test for predicting premature delivery. Tests such as cervical length and factors related to infection were not included in our model, even though

they were thought to be important for preterm birth prediction. Most nulliparous women in our study were considered as being at low risk, dispensing with routine cervical length screening. The sample size of the test cohort was smaller than that of the training and validation cohorts. Study on a large sample size is needed to confirm the effectiveness of a biomarker. We will expand the cohort and strive to validate the accuracy of our predictive tool in the future study.

This study had several strengths. First, we investigated pregnancy-specific cutoff values for TPOAb and TSH concentrations during early pregnancy association with premature delivery. To our knowledge, few studies were conducted to identify the pregnancy-specific cutoffs of TPOAb and the risk of premature delivery. Second, we have developed a nomogram that included new risk variables, such as thyroid function, that had not been used in a nomogram associated with premature delivery before. Third, our study was a large cohort and all variables in the study were based on available data from clinical obstetric history to facilitate the evaluation of pregnant women.

CONCLUSION

This study identified the regional and pregnancy-specific cutoff values for TPOAb positivity and TSH concentration associated with premature delivery in singleton pregnant women without pre-pregnancy complications. We have developed a nomogram to predict premature delivery based on thyroid function and other risk factors. The risk calculation with this model was simple, could be used as a clinical decision-making tool.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study was approved by the Ethics Committee of the International Peace Maternity and Child Health Hospital, School of Medicine, Shanghai Jiaotong University (No. GKLW2019-16). The data analysis procedures followed the guidelines in the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

All the authors contributed to the work. This study was designed by JF, YM, and JL. YM and JL performed the statistical analysis and wrote the manuscript. JF reviewed and edited the manuscript. All authors read and approved the final version of this manuscript.

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Comparison of Five Different Criteria for Diagnosis of Subclinical Hypothyroidism in a Large-Scale Chinese Population

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Background: Several different criteria for subclinical hypothyroidism (SCH) have been used in the literature, but the performance of these criteria was unknown.

Objective: This retrospective study was to evaluate the diagnostic criteria for SCH.

Methods: Eligible participants were based on centration of thyroglobulin antibodies (TG-Ab), thyroid peroxidase antibodies (TPO-Ab), and five thyroid-related hormones including total thyroxine (TT4), total triiodothyronine (TT3), free thyroxine (FT4), free triiodothyronine (FT3), and thyroid-stimulating hormone (TSH). Euthyroid individuals were identified *via* specific criteria. Five different SCH diagnostic criteria were compared based on the distributions of those indicators. An appropriate TSH cut-off value was reconsidered.

Results: The study included 145,015 participants. The number of SCH cases diagnosed using criterion 5 was significantly different compared to the cases diagnosed using criteria 1-4 ($P<0.05$) and had the highest positive proportions of TG-Ab and TPO-Ab. Analysis of 60,515 subjects with normal other thyroid hormones revealed a median TSH concentration of 2.04 mIU/L, and the $P_{2.5}$–$P_{97.5}$ CI was 0.48-7.03 mIU/L. When the threshold for TSH elevation was elevated from ≥4.5 mIU/L to ≥6.50 mIU/L, the number of diagnosed SCH cases decreased from 7.30% to 2.09% and the proportions of positive TG-Ab and TPO-Ab increased from 23.69% and 24.07% to 33.75% and 35.06%, respectively ($P<0.01$).

Conclusions: Combination of an elevated TSH and normal TT3, TT4, FT3, and FT4 concentrations is a must for the diagnosis of SCH. A new TSH threshold should be identified for better patient monitoring and management, according to the real-world characteristics of TSH distribution in Chinese population.

Keywords: thyroid-associated hormones, hypothyroidism, subclinical hypothyroidism, diagnosis, criteria

INTRODUCTION

Subclinical hypothyroidism (SCH) is highly prevalent worldwide but remains challenging to diagnose. Individuals with SCH often do not have clinical symptoms and rarely seek medical care. However, several recent studies have shown that SCH is associated with coronary heart disease, hypertension, ischemic cerebrovascular disease, metabolic syndrome, osteoporosis, obstetric complications, and other diseases (1–3). Thus, attention has been drawn to identifying SCH, especially during physical examinations. It is generally accepted that SCH is characterized by elevated serum concentrations of thyroid-stimulating hormone (TSH) in the absence of clinical symptoms and thyroid hormone changes. However, due to technological limitations and the cost of screening, no consensus has been reached on how to diagnose SCH. For example, China's Guidelines for the Diagnosis and Treatment of Adult Hypothyroidism define SCH as an endocrine syndrome associated with elevated concentrations of TSH but normal concentrations of serum total thyroxine (TT4) and serum free thyroxine (FT4) in the absence of obvious signs and symptoms (4). Other studies have defined SCH as a condition with elevated serum concentrations of TSH but normal concentrations of FT4 and free triiodothyronine (FT3) (5, 6). Another study has suggested diagnosing SCH based on elevated TSH concentrations and normal FT4 concentrations (7), while still other studies have recommended diagnosing SCH based on elevated TSH concentrations and normal serum concentrations of TT4 and serum total triiodothyronine (TT3) (8–11). Moreover, there are substantial differences in the reported cut-off values for identifying elevated TSH concentrations to diagnose SCH (12). These discrepancies have generated controversies regarding the diagnosis and clinical significance of SCH, and it is important to determine how to best diagnose SCH based on five to seven thyroid function indicators. This study aimed to compare different criteria for diagnosing SCH based on thyroid function indicators.

MATERIALS AND METHODS

We evaluated individuals who underwent physical examinations in the Chinese People's Liberation Army General Hospital between March 2014 and November 2019. Subjects were considered eligible if they were ≥18yrs old and had undergone testing to evaluate thyroid function indicators. However, subjects were excluded based on missing data regarding sex, age, and laboratory findings for at least one of the five thyroid function indicators. In order to find out the real-world distribution characteristics of TSH in population with normal TT3, TT4, FT3, FT4, TSH, TG-Ab, and TPO-Ab, a specific group was identified with strict criteria, which was selected by excluding pregnant women; individuals with definite thyroid-related diseases or a history of thyroid-related surgeries; individuals with a thyroid nodule diameter of ≥1.0 cm; and individuals with abnormal results of thyroid-associated hormones except TSH, and with abnormal thyroglobulin antibodies (TG-Ab) and thyroid peroxidase antibodies (TPO-Ab), or thyroid ultrasonography.

The retrospective study protocol was approved (S2017-003-02) by the Chinese People's Liberation Army General Hospital ethics committee and complied with the principles of the Declaration of Helsinki and its contemporary amendments.

Data Collection

Data regarding age and sex were collected from the subjects' medical records. Medical histories were collected *via* face-to-face interviews. The height, weight, and blood pressure were measured by well-trained nurses and doctors. The body mass index (BMI) was calculated as the weight divided by the height squared. All blood samples were collected after the subjects fasted for 8–12 hr. According to the quality control and testing standards set by the Clinical Laboratory Department of the Clinical Laboratory Department of the Chinese People's Liberation Army General Hospital (13, 14), Fasting blood glucose, AST, triglyceride (TG), total cholesterol (TC), LDL-C and HDL-C levels were measured using a Roche C8000 automatic biochemical analyzer (Roche, Mannheim, Germany) with the corresponding reagents, calibrators, and quality control materials. The concentrations of TT4, TT3, FT4, FT3, TG-Ab, TPO-Ab, and TSH were determined using Roche Diagnostic reagents and the ACS:180 automatic chemiluminescence immunoassay system. The laboratory's results had an intra-assay difference of <5% and an inter-assay difference of <10%. The normal reference ranges were 66.00–181.00 nmol/L for TT4, 1.30–3.10 nmol/L for TT3, 3.10–6.80 pmol/L for FT3, 12.00–22.00 pmol/L for FT4, <115.00 IU/mL for TG-Ab, <34.00 IU/mL for TPO-Ab, and 0.10–4.50 mIU/L for TSH.

Thyroid ultrasonography was performed by trained operators who were not aware of the laboratory test results. Thyroid size and morphology were evaluated using a high-resolution 7–13 MHz linear transducer, with the subject seated and their neck slightly extended.

Age Grouping

We divided the subjects into three age-based groups: young subjects (<40yrs), middle-aged subjects (40–59yrs), and elderly subjects (≥60yrs). For some analyses, we created the following age stratification: <20yrs, 20–29yrs, 30–39yrs, 40–49yrs, 50–59yrs, 60–69yrs, 70–79yrs, and ≥80yrs.

Statistical Analysis

Data were collected and analyzed using Stata software (version 11.0). Continuous data were reported as mean ± SD and categorical data were reported as number (%). The laboratory data for the thyroid-associated hormones were used to calculate the median value and confidence intervals (CIs) spanning the 5th to 95th percentiles ($P_{5.0}$–P_{95} CIs) or the 2.5th to 97.5th percentiles ($P_{2.5}$–$P_{97.5}$ CIs). The variables were analyzed using the Kruskal-Wallis test, Wilcoxon rank-sum test, or chi-squared (χ^2) test, as appropriate. Differences were considered statistically significant at P-values of <0.05.

RESULTS

Demographic Characteristics

Between August 2013 and January 2018, a total of 150,035 subjects underwent physical examinations at the Chinese People's Liberation Army General Hospital and were considered eligible. However, 5,020 subjects were excluded because they fulfilled the exclusion criteria. Therefore, the study ultimately evaluated 145,015 participants, including 90,011 male subjects (62.07%) and 55,004 female subjects (37.93%) with a mean age of 47.96 ± 9.72 yrs. The subjects were from 34 province-level administrative regions, which consisted of provinces, autonomous regions, directly controlled municipalities, and special administrative regions.

Distributions of the Serological Thyroid Function Indicators

Normality tests indicated non-normal distributions for the concentrations of TT3, TT4, FT3, FT4, TSH, TG-Ab, and TPO-Ab. The median values and proportions of subjects with abnormal concentrations (relative to the reference ranges) were shown in **Table 1**. The highest abnormal rate was observed for TSH (10.21%), which was followed by TT3 (6.08%), FT4 (3.10%), TT4 (2.46%), and FT3 (1.01%). The median TSH concentration was 2.05 mIU/L, the $P_{5.0}$–$P_{95.0}$ CI was 0.78–5.42 mIU/L, and the $P_{2.5}$–$P_{97.5}$ CI was 0.21–9.35 mIU/L. TSH results above the normal reference value (>4.5 mIU/L) were observed for 8.69% of the subjects. There was no significant difference in the proportions of subjects who were TG-Ab-positive and TPO-Ab positive ($\chi^2 = 0.61$, $P = 0.43$).

Diagnosing SCH According to the Different Diagnostic Criteria

When an elevated TSH concentration was defined as ≥4.50 mIU/L, we compared the diagnosis of SCH based on five different criteria: (1) an elevated TSH concentration with a normal FT4 concentration, (2) an elevated TSH concentration with normal concentrations of FT3 and FT4, (3) an elevated TSH concentration with normal concentrations of TT3 and TT4, (4) an elevated TSH concentration with normal concentrations of FT4 and TT4, and (5) an elevated TSH concentration with normal concentrations of TT3, TT4, FT3, and FT4. The results of the SCH diagnoses using these criteria are summarized in **Table 2**. There were no significant differences in the numbers of SCH cases diagnosed using criteria 1–4 ($P > 0.05$), although a significantly different number of SCH cases was diagnosed using criterion 5 (vs. criteria 1–4, $P < 0.05$).

Relative to criterion 5, criterion 1 identified an additional 932 SCH cases, which included 35 cases with decreased FT3 concentrations, 31 cases with increased FT3 concentrations, 256 cases with decreased TT4 concentrations, 2 cases with increased TT4 concentrations, 778 cases with decreased TT3 concentrations, and 5 cases with increased TT3 concentrations. Relative to criterion 5, criterion 2 identified an additional 866 SCH cases, which included 747 cases with decreased TT3 concentrations, 3 cases with increased TT3 concentrations, 253 cases with decreased TT4 concentrations, and 2 cases with increased TT4 concentrations. Relative to criterion 5, criterion 3 identified an additional 767 SCH cases, which included 7 cases with decreased FT3 concentrations, 32 cases with increased FT3 concentrations, 690 cases with decreased FT4 concentrations, and 44 cases with increased FT4 concentrations. Relative to criterion 5, criterion 4 identified an additional 674 SCH cases, which included 33 cases with decreased FT3 concentrations, 30 cases with increased FT3 concentrations, 638 cases with decreased TT3 concentrations, and 3 cases with increased TT3 concentrations. Thus, using criteria 1–4 resulted in varying numbers of misdiagnosed SCH cases, relative to criterion 5 (i.e., normal TT3, TT4, FT3, and FT4 concentrations with elevated TSH concentrations). Regardless of the diagnostic criterion that was used, significantly higher proportions of TG-Ab positive and TPO-Ab positive individuals were observed among subjects who were diagnosed with SCH with criterion 5 ($P < 0.01$). Moreover, both of the positive proportions of TG-Ab and TPO-Ab in criteria 5 were significantly higher than those in criteria 1–4 ($P < 0.001$).

Identifying an Appropriate TSH Cut-Off Value

The strict criteria were fulfilled in 60,515 individuals, forming the specific group. Demographic characteristics of the individuals in this group were shown in **Table 3**. Those individuals showed normal concentrations of TT3, TT4, FT3, FT4, TG-Ab, TPO-Ab, and met other criteria, which included 43,357 males (71.65%) and 17,158 females (28.23%). The median TSH concentration was 2.04 mIU/L, the $P_{5.0}$–$P_{95.0}$ CI was 0.84–4.79 mIU/L, and the $P_{2.5}$–$P_{97.5}$ CI was 0.48-7.03 mIU/L in the special group. Thus, at least 5% of the 60,515 subjects had TSH concentrations that were

TABLE 1 | Distributions of serological thyroid function indicators for the 145,015 subjects.

Variables*	Median value ($P_{2.5}$-$P_{97.5}$ Cis)	Below the normal range (%)	In the normal range (%)	Above the normal range (%)
TT3 (nmol/L)	1.71 (1.11–2.60)	8,408 (5.80)	136,201 (93.92)	406 (0.28)
FT3 (pmol/L)	4.90 (3.48–6.67)	327 (0.23)	143,553 (98.99)	1,135 (0.78)
TT4 (nmol/L)	97.63 (60.47–149.60)	3,276 (2.26)	141,454 (97.54)	285 (0.20)
FT4 (pmol/L)	16.21 (11.43–22.59)	2,533 (1.75)	140,526 (96.90)	1,956 (1.35)
TSH (mIU/L)	2.05 (0.21–9.35)	2,205 (1.52)	130,210 (89.79)	12,600 (8.69)
TG-Ab (IU/mL)	14.60 (10.00–789.10)		130,822 (90.21)	14,193 (9.79)
TPO-A b (IU/mL)	9.80 (5.00–543.00)		131,000 (90.34)	14,015 (9.66)

**All indices are presented as the median (interquartile range); Normal range: referred by the Roche diagnostic reagents instructions.*

TT4, total thyroxine; TT3, total triiodothyronine; FT4, free thyroxine; FT3, free triiodothyronine; TSH, thyroid-stimulating hormone; TG-Ab, thyroglobulin antibodies; TPO-Ab, thyroid peroxidase antibodies.

TABLE 2 | The different criteria for diagnosing SCH based on TSH concentrations of ≥4.5 mIU/L.

	Diagnosed SCH cases (%)	TG-Ab Negative (%)	TG-Ab Positive (%)	TPO-Ab Negative (%)	TPO-Ab Positive (%)
Criterion 1	11,880 (7.92)	9,257 (77.92)	2,623 (22.08)*	9,214 (77.56)	2,666 (22.44)†
Criterion 2	11,814 (7.87)	9,204 (77.91)	2,610 (22.09)*	9,162 (77.55)	2,652 (22.45)†
Criterion 3	11,715 (7.81)	9,033 (77.11)	2,682 (22.89)*	9,068 (77.41)	2,647 (22.59)†
Criterion 4	11,622 (7.75)	9056 (77.92)	2,566 (22.08)*	9,021 (77.62)	2,601 (22.38)†
Criterion 5	10,948 (7.30)‡	8,354 (76.31)	2,594 (23.69)*‡	8,313 (75.93)	2,635 (24.07)†‡

**Significantly higher proportion of TG-Ab positivity relative to the normal reference range criteria (9.79%), (P<0.01).*

†Significantly higher proportion of TPO-Ab positivity relative to the normal reference range criteria (9.66%), (P<0.01).

‡Significantly different relative to the other diagnostic criteria (P<0.05).

SCH, subclinical hypothyroidism; TSH, thyroid-stimulating hormone; TG-Ab, thyroglobulin antibodies; TPO-Ab, thyroid peroxidase antibodies; Criteria 1, an elevated TSH concentration with a normal FT4 concentration; Criteria 2, an elevated TSH concentration with normal concentrations of FT3 and FT4; Criteria 3, an elevated TSH concentration with normal concentrations of TT3 and TT4; Criteria 4, an elevated TSH concentration with normal concentrations of FT4 and TT4; Criteria 5, an elevated TSH concentration with normal concentrations of TT3, TT4, FT3, and FT4.

≥4.79 mIU/L. The Wilcoxon rank-sum test revealed a significant difference in TSH concentrations between male and female subjects (Z = 28.44, $P < 0.001$) (**Table 4**).

The TSH concentration distributions for each age group were shown in **Table 4**. The Kruskal-Wallis test revealed significant differences in the TSH concentrations across the different age stratification ($\chi^2 = 62.42$, $P < 0.001$). Furthermore, there were significant differences when the subjects were grouped as young subjects, middle-aged subjects, and elderly subjects ($\chi^2 = 15.56$, $P < 0.001$). The Wilcoxon rank-sum test also revealed significant differences between young and middle-aged subjects (Z=1.99, P=0.046), between young and elderly subjects (Z = 4.69, $P < 0.001$), and between middle-aged and elderly subjects (Z = 6.82, $P < 0.001$).

The P95th upper limits for TSH concentration were >4.50 mIU/L in all age groups, increased according to age, and reached 12.26 mIU/L for subjects who were ≥80yrs old. The $P_{2.5}$–$P_{97.5}$ CI values were 0.57–6.49 mIU/L for young subjects, 0.45–7.09 mIU/L for middle-aged subjects, and 0.43–8.96 mIU/L for elderly subjects. Thus, at least 2.5% of the 60,515 subjects with normal thyroid function and no thyroid-related diseases had TSH concentrations of ≥6.49 mIU/L.

There is general consensus that SCH patients with TSH concentrations of <10.00 mIU/L do not require clinical intervention (4, 15, 16), and that overdiagnosis could cause unnecessary psychological and economic burden. But the SCH patients with TSH concentrations of <10.00 mIU/L could develop clinical thyroid diseases every year, which means they could not be ignored and need monitoring. Therefore, although sex and age stratification were significant, we defined the TSH threshold for diagnosing SCH as 6.50 mIU/L as a clear, easily remembered, and practical cut-off value, according to the real TSH distribution in Chinese population, especially based on the Roche platform.

Re-Diagnosis According to the New TSH Cut-Off Value

The new cut-off value for elevated TSH concentrations was applied to diagnostic criteria 1–5 in order to re-diagnose SCH and the results were summarized in **Table 5**. There were still no

TABLE 3 | Demographic characteristics of the individuals included in the specific group (n=60,515).

Variables	Total	Female (n=17,158)	Male (n=43,357)	Female vs Male
Age (yrs)	45.37 ± 9.23	44.15 ± 10.25	45.86 ± 8.75	z = 18.60, P = 0.009
BMI (kg/m^2)	24.98 ± 3.54	22.83 ± 3.31	25.83 ± 3.25	z = 97.08, *P* <0.001
SBP (mmHg)	120.44 ± 16.59	112.81 ± 16.55	123.45 ± 15.61	z = 81.94, *P* <0.001
DBP (mmHg)	79.78 ± 11.69	75.44 ± 10.48	82.07 ± 11.43	z = 88.89, *P* <0.001
Hb (g/L)	149.22 ± 15.31	132.19 ± 11.77	155.47 ± 10.72	z = 232.75, *P* <0.001
AST(U/L)	21.04 ± 13.62	18.57 ± 8.76	21.79 ± 13.96	z = 73.70, *P* <0.001
TC (mmol/L)	4.76 ± 0.91	4.75 ± 0.91	4.76 ± 0.93	z = 4.42, *P* <0.001
TG (mmol/L)	1.82 ± 1.54	1.27 ± 0.89	2.04 ± 1.64	z = 113.03, *P* <0.001
HDL-C(mmol/L)	1.25 ± 0.34	1.46 ± 0.35	1.16 ± 0.28	z = 134.31, *P* <0.001
LDL-C(mmol/L)	3.03 ± 0.80	2.99 ± 0.81	3.07 ± 0.81	z = 17.82, *P* <0.001
FBG (mmol/L)	5.68 ± 1.35	5.39 ± 1.07	5.89 ± 1.51	z = 76.30, *P* <0.001
Smoke				χ2 = 12,000, *P* <0.001
No	34,248	15,851 (92.38%)	18,397 (42.43%)	
yes	26,267	1,307 (7.62%)	24,960 (57.57%)	
Hypertension				χ2 = 3,200, *P* <0.001
No	40,748	14,472 (84.35%)	26,276 (60.60%)	
yes	19,767	2686 (15.65%)	17,081 (39.40%)	

BMI, Body mass index; SBP, systolic blood pressure; DBP, Diastolic pressure; TC, Total cholesterol; TG, Triglyceride; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; FBG, Fasting blood glucose.

TABLE 4 | Distributions of TSH concentrations in the different stratification in the specific group (n=60,515).

	N	Median TSH (mIU/L)	TSH (mIU/L) ($P_{5.0}$-$P_{95.0}$ CIs)	TSH (mIU/L) ($P_{2.5}$-$P_{97.5}$ CIs)	
age stratification					
<20yrs	115	2.17	0.98–5.37	0.65–6.01	$\chi2 = 62.42$, $P < 0.001$
20–29yrs	3,465	2.15	0.92–4.76	0.61–6.69	
30–39yrs	10,554	1.98	0.87–4.49	0.55–6.34	
40–49yrs	27,049	2.03	0.85–4.73	0.47–6.90	
50–59yrs	15,862	2.05	0.81–4.96	0.41–7.39	
60–69yrs	3,030	2.11	0.78–5.35	0.43–8.56	
70–79yrs	421	2.11	0.76–6.29	0.44–9.23	
≥80yrs	19	2.19	0.75–12.26	0.76–12.26	
Age subgroups					$\chi2 = 15.56$, $P <0.001$
Young subjects (<40yrs)	14,134	2.04	0.88–4.55	0.57–6.49	
Middle-aged subjects (40–59yrs)	42,911	2.03*	0.83–4.82	0.45–7.09	
Elderly subjects (≥60yrs)	3,470	2.11*†	0.78–5.44	0.43–8.96	
Sex stratification					$Z = 28.44$, $P <0.001$
males	43,357	1.97	0.83-4.51	0.51-6.54	
females	17,158	2.26	0.88-5.44	0.37-8.09	
Total	60,515	2.04	0.84–4.79	0.48-7.03	

**Compared with young subjects; †Compared with middle-aged subjects.*
TSH, thyroid-stimulating hormone; Cis, confidence intervals.

statistically significant differences in the number of SCH cases diagnosed using criteria 1–4 ($P > 0.05$), although a significantly different number of SCH cases was diagnosed using criterion 5 (vs. criteria 1–4, $P < 0.05$). Similarly, both of the positive proportions of TG-Ab and TPO-Ab in criteria 5 were significantly higher than those in criteria 1–4 ($P < 0.01$). Furthermore, the number of SCH based on criterion 5 and the new TSH threshold (≥6.50 mIU/L) was significantly less than that a diagnosis was based on a frequently-used TSH threshold of ≥4.50 mIU/L (2.09% vs. 7.30%; $\chi^2 = 4{,}600$, $P < 0.001$). Moreover, relative to a diagnosis using a TSH threshold of ≥ 4.50 mIU/L, SCH cases diagnosed using criteria 1–5 and the new threshold (≥ 6.50 mIU/L) had significantly higher proportions of TG-Ab-positive and TPO-Ab-positive cases ($P < 0.01$).

DISCUSSION

There is significant controversy regarding the diagnosis and management of SCH (17, 18). Although an increasing number of studies have demonstrated that SCH has adverse effects on various physical functions, there are inconsistent diagnostic criteria for SCH. This has generated confusion in and unnecessary burden on the medical community (19). Our study compared five commonly used criteria for diagnosing SCH and revealed that criteria 1–4 were basically equivalent in terms of the number of diagnosed SCH cases, in which included some cases that obviously did not meet the definition of SCH. However, a significantly different number of cases was diagnosed using criterion 5 and the positive proportions of TG-Ab and TPO-Ab were significantly higher than those in criteria 1–4 ($P < 0.001$). Our results indicate that criterion 5 was stricter and avoided misdiagnosis of SCH. Therefore, we recommend using criterion 5 in the clinical setting based on the Roche platform, despite it being associated with an increased cost of SCH screening.

Clinical laboratories typically use the reference ranges that are proposed by test manufacturers. However, those ranges are generally based on data from non-Chinese populations and

TABLE 5 | Diagnosis of SCH based on the diagnostic criteria and TSH concentration threshold of ≥6.5 mIU/L.

	Diagnosed SCH cases (%)	TG-Ab Negative (%)	TG-Ab Positive (%)	TPO-Ab Negative (%)	TPO-Ab Positive (%)
Criterion 1	3,466 (2.31)	2,421 (69.85)	1,045 (30.15)*	2,387 (68.87)	1,079 (31.13)*
Criterion 2	3,444 (2.30)	2,405 (69.83)	1,039 (30.17)*	2,371 (68.84)	1,073 (31.16)*
Criterion 3	3,594 (2.4)	2,380 (66.22)	1,214 (33.78)*	2,471 (68.75)	1,123 (31.25)*
Criterion 4	3,367 (2.24)	2,354 (69.91)	1,013 (30.09)*	2,321 (68.93)	1,046 (31.07)*
Criterion 5	3,132 (2.09)†	2,075 (66.25)	1057 (33.75)*‡	2,034 (64.94)	1098 (35.06)*‡

**Significantly different relative to a TSH concentration threshold of ≥4.5 mIU/L (P<0.01).*
†Significantly different relative to the other diagnostic criteria (P<0.05).
‡Significantly different relative to the other diagnostic criteria (P<0.001).
SCH, subclinical hypothyroidism; TSH, thyroid-stimulating hormone; TG-Ab, thyroglobulin antibodies; TPO-Ab, thyroid peroxidase antibodies; Criteria 1, an elevated TSH concentration with a normal FT4 concentration; Criteria 2, an elevated TSH concentration with normal concentrations of FT3 and FT4; Criteria 3, an elevated TSH concentration with normal concentrations of TT3 and TT4; Criteria 4, an elevated TSH concentration with normal concentrations of FT4 and TT4; Criteria 5, an elevated TSH concentration with normal concentrations of TT3, TT4, FT3, and FT4.

there has been no comprehensive assessment of the five thyroid-associated hormones and their relationships with thyroid disease in a large cohort of healthy Chinese individuals (11). Our study revealed that at least 5% of the Chinese population with completely normal TT3, TT4, FT3, FT4, TG-Ab, TPO-Ab and no thyroid-related diseases would be expected to have TSH concentrations of ≥4.50 mIU/L (the upper limit of the normal reference range). Moreover, both the upper 95.0^{th} and 97.5^{th} percentile values for TSH concentration increased with age and reached 12.26 mIU/L among individuals who were ≥80 yrs. As the purpose of a clinical diagnosis is to guide careful monitoring or intervention for the patient, a diagnosis that does not prompt additional steps has limited clinical significance and may increase the economic and psychological burden on the patient. Most recent studies indicate that drug intervention is not necessary for patients with SCH until they have TSH concentrations of ≥10.00 mIU/L. Therefore, we set the TSH threshold to ≥6.50 mIU/L. In Korea, also in Asia, park WR, et al. (20) found that when SCH was more predictive of overt hypothyroidism, the cut off value was TSH > 7.45 μIU/ml and higher prevalence positive anti-thyroid peroxidase (anti-TPO Ab) and anti-thyroglobulin antibody (anti-Tg Ab). But their study enrolled only 197 patients.

Interestingly, a diagnosis of SCH based on criterion 5 and the new TSH threshold (≥6.50 mIU/L) was made in a significantly smaller proportion of the study population, relative to when the diagnosis was based on a threshold of ≥4.50 mIU/L. However, the higher TSH threshold identified SCH in a smaller proportion of subjects, these cases had significantly higher proportions of TG-Ab and TPO-Ab positivity, relative to cases that were identified using the lower threshold. Previous studies have also shown that the incidences of clinical hypothyroidism and SCH are significantly higher when subjects have high titers of TPO-Ab (20) or test positive for both TG-Ab and TPO-Ab (21). Therefore, given that individuals who were diagnosed with SCH using the new TSH threshold (≥6.50 mIU/L) are more likely to clinically progress, they are more suitable for clinical monitoring or intervention. In Huber's study (22), it was considered that TSH≥6 was more predictive in patients with SCH. In another neighboring Asian country, a cohort study in Japan found that TSH level >8 mIU/L was a predictive value for development of overt hypothyroidism (23). While a study in South Korea, which is also located in East Asia, found that the TSH threshold of 6.86 is more suitable for the diagnosis of SCH (24). TSH could vary in different countries or ethnic groups (25, 26). Therefore, our results at TSH were slightly different from those of other studies.

One limitation of our study is that it was a single-center study of Chinese adults. Thus, the results cannot be generalized to other racial and ethnic groups. In addition, TSH secretions are theoretically sensitive to very small changes in serum FT4, which means that TSH changes could occur during early-stage hypothyroidism even before FT4 abnormalities are detectable (27). However, in practice, TSH concentrations are influenced by numerous factors, including age, race, sex (28), acute illness, renal insufficiency, medications (29), pregnancy (30), depression (31), and anorexia nervosa (32). Meanwhile, between-assay differences and variations in reference ranges can directly impact the diagnosis and management of subclinical hypothyroidism (33). Therefore, changes in the TSH concentrations for our study may not have always been directly related to changes in the concentrations of TT3, TT4, FT3, or FT4, and may have even exhibited inverse relationships. However, our study also had several strengths. First, we used broad inclusion criteria, without excluding patients with unrelated diseases or medications, which presumably allowed us to capture both healthy people and people with subclinical thyroid disease. Therefore, our study sample is likely representative. Our study also used an ultra-sensitive TSH measurement technique to minimize the risk of indirect changes in TSH concentrations.

In conclusion, our study revealed that the diagnosis of SCH can be made based on elevated TSH concentrations in the presence of normal TT3, TT4, FT3, and FT4 concentrations (criterion 5). Other commonly used simplified criteria (criteria 1–4) were associated with an increased risk of misdiagnosis, based on the Roche platform. We found that increasing the TSH threshold from ≥4.50 mIU/L to ≥6.50 mIU/L might improve the accuracy of SCH diagnosis and thus possibly guide better patient monitoring and management, which means a new TSH threshold should be identified according to the real TSH distribution characteristics in Chinese population.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Chinese People's Liberation Army General Hospital ethics committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

QZ designed this study. Y-sZ wrote the original drafts. S-yD reviewed and edited the manuscript. YG acquired and analyzed the data. J-hW and FW wrote the review and prepared the tables. Y-sZ and S-yD contributed equally as co-first authors. All authors read and approved the final manuscript. We agree to the terms of the BioMed Central Copyright and License Agreement.

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Identifying Non-Linear Association Between Maternal Free Thyroxine and Risk of Preterm Delivery by a Machine Learning Model

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Objective: Preterm delivery (PTD) is the primary cause of mortality in infants. Mounting evidence indicates that thyroid dysfunction might be associated with an increased risk of PTD, but the dose-dependent association between the continuous spectrum maternal free thyroxine (FT4) and PTD is still not well-defined. This study aimed to further investigate this relationship using a machine learning-based model.

Methods: A hospital-based cohort study was conducted from January 2014 to December 2018 in Shanghai, China. Pregnant women who delivered singleton live births and had first-trimester thyroid function data available were included. The generalized additive models with penalized cubic regression spline were applied to explore the non-linear association between maternal FT4 and risk of PTD and also subtypes of PTD. The time-to-event method and multivariable Cox proportional hazard model were further applied to analyze the association of abnormally high and low maternal FT4 concentrations with the timing of PTD.

Results: A total of 65,565 singleton pregnancies with completed medical records and no known thyroid disease before pregnancy were included for final analyses. There was a U-shaped dose-dependent relationship between maternal FT4 in the first trimester and PTD (p <0.001). Compared with the normal range of maternal FT4, increased risk of PTD was identified in both low maternal FT4 (<11.7 pmol/L; adjusted hazard ratio [HR] 1.34, 95% CI [1.13–1.59]) and high maternal FT4 (>19.7 pmol/L; HR 1.41, 95% CI [1.13–1.76]). The association between isolated hypothyroxinemia and PTD was mainly associated with spontaneous PTD (HR 1.33, 95% CI [1.11–1.59]) while overt hyperthyroidism may be attributable to iatrogenic PTD (HR 1.51, 95% CI [1.18–1.92]) when compared with euthyroid women. Additionally, mediation analysis identified that an estimated 11.80% of the association between overt hyperthyroidism and iatrogenic PTD risk was mediated *via* the occurrence of hypertensive disorders in pregnancy (p <0.001).

Conclusions: We revealed a U-shaped association between maternal FT4 and PTD for the first time, exceeding the clinical definition of maternal thyroid function test abnormalities. Our findings provide insights towards the need to establish optimal range of maternal FT4 concentrations for preventing adverse outcomes in pregnancy.

Keywords: free thyroxine, spontaneous preterm delivery, iatrogenic preterm delivery, Isolated hypothyroxinemia, overt hyperthyroidism, generalized additive model

INTRODUCTION

Preterm delivery (PTD, also acknowledged as preterm birth) is the primary cause of mortality in neonates, infants, and also younger children, and is defined as any live birth before 37 completed weeks of pregnancy (1–3). PTD annually affects ~15 million newborns globally with 1.2 million (7.8%) in China (4). Furthermore, preterm birth children are at increased risk of serious illness (e.g., lung immaturity, infection) and are susceptive to neurodevelopmental, cognitive, cardiovascular, and metabolic disorders in adulthood (5–9). Although several risk factors for PTD have been reported (e.g., history of PTD, advanced maternal age, low socioeconomic status, exposure to smoking or narcotics) (1, 10), the mechanisms that lead to PTD is still not understood. Moreover, the relationship between maternal thyroid function and PTD has not been fully elucidated.

Maternal thyroid hormones (namely, thyroxine or tetraiodothyronine [T4] and triiodothyronine [T3]) in early pregnancy are associated with intra-uterine inflammation, placentation functions, and adverse pregnancy complications (e.g., intrauterine growth retardation and pre-eclampsia) (11, 12). There is mounting evidence indicating that an increased risk of PTD might be related to both maternal hyper- and hypothyroidism (13, 14). A study in 2015 demonstrated a statistically significant incremental risk of PTD among pregnant women with overt hyper- and hypothyroidism while not in women with mild thyroid dysfunction (e.g., subclinical hypothyroidism or isolated hypothyroxinemia) (15). Moreover, it was revealed that women with isolated hypothyroxinemia in early pregnancy had a higher risk of spontaneous PTD (16). In contrast, recent research illustrated that higher maternal free thyroxine (FT4) concentration was associated with a reduced risk of PTD under a linear regression model (17). In this study, we proposed that there might be a non-linear shape of the dose–response relationship between FT4 and the risk of PTD, which have not been established until recently.

Therefore, the primary goal of this study was to evaluate the non-linear association between the continuous spectrum of maternal FT4 concentrations with the risk of PTD and its subtypes by a machine learning-based model.

MATERIALS AND METHODS

Study Population

Pregnant women who delivered between January 2014 and December 2018, with records of first-trimester antenatal screening and regular antenatal visits at the International Peace Maternity and Child Health Hospital (IPMCH), a tertiary university-attached maternity center in Shanghai, China, were included. Written informed consent was obtained from all participants when they registered in the hospital. Exclusion criteria were: fetal chromosome abnormality, multiple pregnancies, *in vitro* fertilization, miscarriage, fetal death, diabetes or hypertension before pregnancy, or a history of either thyroid disease or thyroid treatment. Women without available records of thyroid function measurements in the first trimester were also excluded. The study protocol was approved by the Institutional Medical Ethics Committee of IPMCH (GKLW2019-43) and registered at the Chinese Clinical Trial Registry (ChiCTR2000034742).

Data Collection and Measurement

Data were collected by nurses and gynecologists during routine prenatal pregnancy examinations. This included maternal age, education level, last menstrual period (LMP), parity, and medical history routinely gathered *via* face-to-face interviews during the first antenatal visit. The calculation of pre-pregnant body mass index (BMI) was obtained by dividing the self-reported weight of the patient before pregnancy (in kg) by the square of their height measured by the nurses (in m). Gestational age was estimated by LMP and later adjusted in accordance with ultrasonography results in early pregnancy. Alcohol consumption and smoking status were not included in the analysis as their use were rare (<1%) among pregnant women in our study population.

Quantitative analyses of FT4, thyrotropin (also known as thyroid-stimulating hormone, TSH), and thyroid peroxidase antibody (TPO-Ab) concentrations in fasting blood samples were determined with kits (ARCHITECT i2000; Abbott, Chicago, IL, USA) in accordance with the manufacturer's protocol in the standardized clinical laboratory of the hospital. The intra- and inter-assay coefficients of variation were, respectively, 1.6 and 3.59% for TSH; 1.9 and 4.01% for FT4; and both 10% for TPO-Ab. TPO-Ab concentrations exceeding 5.6 IU/ml was considered positive per the cut-off value defined by the manufacturer. Data were extracted from the medical record system of the hospital by experienced information engineers.

Diagnostic Criteria and Outcomes

The local population-based reference range (P2.5–P97.5) of FT4 and TSH in early pregnancy is 11.7–19.7 pmol/L and 0.03–3.64 mIU/L, respectively. According to the reference ranges, we defined overt hypothyroidism as FT4 <P2.5 with TSH >P97.5; isolated hypothyroxinemia as FT4 <P2.5 with TSH within normal range; overt hyperthyroidism as FT4 >P97.5 with TSH <P2.5; subclinical hyperthyroidism as TSH <P2.5 with

FT4 within the normal range; subclinical hypothyroidism as TSH >P97.5 with FT4 within the normal range; and isolated hyperthyroxinemia as FT4 >P97.5 with TSH within the normal range.

Gestational diabetes mellitus (GDM) was diagnosed in a 2-h 75 g oral glucose tolerance test at 24–28 weeks of pregnancy according to the criteria of the American Diabetes Association (18).

Hypertensive disorders in pregnancy (HDP) included gestational hypertension and pre-eclampsia, diagnosed by blood pressure measurements ≥140 mmHg systolic or 90 mmHg diastolic at least twice within 4–6 h, with or without proteinuria. The proteinuria was defined as ≥300 mg protein in a 24-h urine sample or a urine dipstick positive test (19).

The primary outcome was PTD, defined as birth before 37 weeks of pregnancy. The secondary outcomes were the PTD subtypes, namely, spontaneous PTD (defined as the spontaneous onset of labor with intact membranes or after preterm premature rupture of the membranes) and iatrogenic PTD (defined as labor induction with intact membranes or by C-section delivery without labor due to maternal or fetal indications) (1).

Statistical Analyses

Continuous variables with normal distribution were presented as mean ± standard deviation (SD), and non-normally distributed variables were shown as medians with interquartile range (IQR). Categorical variables were demonstrated as numbers (percentages) for baseline characteristics.

The generalized additive model (GAM) with penalized cubic regression spline (k = 5) were applied to explore a smooth, potential non-linear association between maternal FT4 and risk of PTD and the duration of gestation, allowing a better fit than models assuming a strict linear association (20, 21). For GAM analyses, continuous TSH and FT4 concentrations were analyzed after the removal of outliners (0.5%).

For time-to-event analyses, time was determined as the gestational weeks at delivery, PTD as an event, and a term or post-term delivery was censored at delivery. To estimate the adjusted accumulative incidence of PTD, a three-category maternal FT4-categorized Kaplan–Meier estimate of the probability of PTD was appraised with variances reported from log-rank tests overall and pairwise between subgroups, after adjustment for multiple comparisons *via* the Benjamini & Hochberg method.

To further compare the risk of PTD across different types of thyroid test abnormalities, a multivariable Cox proportional hazards regression model was conducted after adjusting for maternal age, education level, medical insurance status, parity, fetal sex, pre-pregnant BMI, and TPO-Ab. The potential confounders were chosen based on the biological plausibility, the selection of confounders in the previous studies, and changes of the effect estimate of interest. Mediation analysis was employed to determine potential mediation effects of HDP on the association of FT4 with iatrogenic PTD. The total effect of FT4 on iatrogenic PTD was divided into average direct effects (ADEs) and the average causal mediation effects (ACMEs)—the effect mediated *via* the development of HDP (22). The mediation proportion was estimated as the ACMEs divided by the total effect.

Based on previous studies concerning the risk factors for PTD (2, 10, 17), their association with FT4 (23–25), and also their clinical relevance, we further stratified pregnant women into the following subgroups: (1) age <35- or ≥35-year-old groups; (2) pre-pregnant BMI <18.5, 18.5–23.9, or ≥24 kg/m^2 groups in accordance with the Chinses Working Group on Obesity (26); (3) TPO-Ab positive or -negative groups; and (4) nulliparity or multiparity groups—to assess whether the findings were affected by advanced age, abnormal BMI, thyroid autoimmunity, or multiparity. Sensitivity analyses were conducted to assess the robustness of results excluding women with either a history of PTD, thyroid medication use during pregnancy, GDM, or HDP.

All analyses were conducted with R Software v3.6.3 (R Project for Statistical Computing; with packages *mgcv*, *ggplot2*, *forestplot*, *survminer*, *survival*, and *mediation*). Statistical significance was set at p <0.05 (all tests were 2-sided).

RESULTS

Population Characteristics

The final study population comprised 65,565 pregnant women (**Figure 1**). The baseline population characteristics are presented in **Table 1**. The mean maternal age was 30.5 ± 3.77 years. The median of gestational weeks at delivery was 39.1 (38.4–40.0) weeks. The study population was mainly primiparous 48,383 (73.8%), mostly normal weight 47,833 (73.0%) with a pre-pregnant BMI of 18.5–23.9 kg/m^2, and a low ratio of PTD history 771 (1.18%). The median weeks of maternal thyroid function examined was 12.1 (11.7–12.6). The median of TSH and FT4 in the first trimester were 1.18 (0.65–1.84) mIU/L and 14.3 (13.3–15.5) pmol/L, respectively. The percentage of TPO-Ab positivity was 7,097 (10.8%). The missing variables included 528 (0.8%) entries of education level, which was missing at random.

Non-Linear Association of Maternal FT4 With Risk of PTD

Using GAM models, we identified an inverted U-shaped association between maternal FT4 and gestational age at delivery (**Figure 2A**) while no such association was identified between maternal TSH and gestational weeks at birth (**Figure 3A**). The estimated smooth effect curves demonstrating the associations between maternal FT4 and PTD (p <0.001), spontaneous PTD (p = 0.06), and iatrogenic PTD (p <0.001) are shown respectively in **Figures 2B–C**. The fully adjusted smooth curve fitting demonstrated a non-linear U-shaped association between FT4 and PTD (**Figure 2B**), while no such association was observed between maternal TSH and PTD (**Figures 3B–D**).

A significantly increased probability of overall PTD (**Figure 2B**) was observed at both abnormally high and low FT4 concentrations (estimated prevalence of PTD for participants with low FT4 of 10 pmol/L: 6.88%; 95% confidence interval (CI) [6.82–6.94%]; and high FT4 levels of 25 pmol/L: 7.82%; 95% CI [7.67–7.98%]; while the estimated probability of PTD reaches its lowest point at FT4

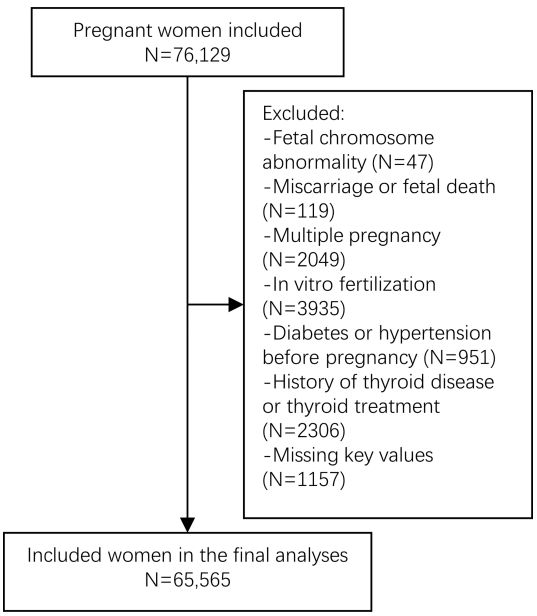

FIGURE 1 | Flow chart of the study population.

TABLE 1 | Demographic data of the study population (N = 65,565).

Characteristics	Participants, No. (%)
Maternal characteristics	
Age, mean (SD), y	30.5 (3.77)
Prepregnant BMI[a]	
<18.5	9,794 (14.9%)
18.5–23.9	47,833 (73.0%)
≥24	7,938 (12.1%)
Primiparous	48,383 (73.8%)
Education Level	
High school and below	4,445 (6.8%)
College	47,882 (73.0%)
Postgraduate	12,710 (19.4%)
Missing	528 (0.8%)
Insurance	51,202 (78.1%)
History of preterm delivery	771 (1.18%)
Hypertensive disorders in pregnancy	2,961 (4.5%)
Gestational diabetes	8,004 (12.2%)
FT4, median (IQR), pmol/Lb	14.3 (13.3, 15.5)
TSH, median (IQR), mIU/L	1.18 (0.65, 1.84)
TPOAb positive	7,097 (10.8%)
Gestational age for thyroid function test, median (IQR), wk	12.1 (11.7, 12.6)
Fetal characteristics	
Gestational age at birth, median (IQR), wk	39.1 (38.4, 40.0)
Preterm birth (gestational age <37 wk)	3176 (4.8%)
Spontaneous preterm birth	2,127 (3.2%)
Iatrogenic preterm birth	1,049 (1.6%)
Birth weight, mean (SD), g	3,340 (431)
Male sex	33,826 (51.6%)
Female sex	31,739 (48.4%)

Gestational weeks for TBA/thyroid function screening were 9–13 weeks in early pregnancy. BMI, body mass index; IQR, interquartile range; TSH, thyroid-stimulating hormone or thyrotropin; FT4, free thyroxine; TPO-Ab, thyroid peroxidase antibody; SD, Standard deviation.

[a]*Calculated as weight in kilograms divided by height in meters squared.*

concentration of 17 pmol/L: 4.38%; 95% CI [4.36–40%]). **Figures 2C, D** further demonstrated the estimated smooth effect curves of the estimated risk of spontaneous and iatrogenic PTD, respectively. In **Figure 2C**, participants with low FT4 of 10 pmol/L tend to have higher estimated risk of spontaneous PTD (4.38%; 95% CI [4.34–4.42%]) when compared with participants with higher FT4. **Figure 2D** showed a steep increase in the estimated risk of iatrogenic PTD among participants of high FT4 of 25 pmol/L (5.21%; 95% CI [5.12–5.29%]) when compared with participants with low FT4 of 10 pmol/L (2.36%; 95% CI [2.33–2.39%]).

Both High and Low Levels of Maternal FT4 Were Associated With Increased Risk of PTD

A time-to-event analysis by gestational week for different FT4 categories showed that the hazard ratio (HR) for PTD in women with FT4 <11.7 and >19.7 pmol/L were significant when compared to women with normal range FT4 concentrations in **Figure 4**. Compared with the normal range of maternal FT4, both low FT4 (<11.7 pmol/L) and high maternal FT4 (>19.7 pmol/L) were significantly associated with 34 and 41% increased risk of PTD, respectively (for low FT4: HR 1.34, 95% CI [1.13–1.59]; for high FT4: HR 1.41, 95% CI [1.13–1.76]). Increasing HRs for spontaneous PTD by gestational week were seen in women with low FT4 (HR 1.42, 95% CI [1.16–1.74]) while the prevalence of iatrogenic PTD was high among women with high FT4 (HR 2.02, 95% CI [1.46–2.80]) after adjusting for confounders. These results were further verified in the stratified analyses, showing 36% (HR 1.36; 95% CI [1.11–1.65]) and 29% (HR 1.29; 95% CI [1.05–1.58]) reduction of PTD risk in women with FT4 <P2.5 and FT4 >P97.5, respectively (**Figure 5**).

The Association Between Maternal Thyroid Test Abnormalities and Risk of PTD

We further explored the association between maternal thyroid test abnormalities and PTD (**Figure 6**). Compared with euthyroid women, an incremental risk of overall PTD was observed among pregnant women with isolated hypothyroxinemia (HR 1.33, 95% CI [1.11–1.59]) and overt hyperthyroidism (HR 1.51, 95% CI [1.18–1.92]) in early pregnancy. Consistent with the results of three groups categorized by maternal FT4, we also found there was a significant association between isolated hypothyroxinemia and spontaneous PTD (HR 1.43, 95% CI [1.15–1.76]), while overt hyperthyroidism and iatrogenic PTD (HR 2.16, 95% CI [1.51–3.07]).

The Mediating Effect of HDP on the Association Between High FT4 or Overt Hyperthyroidism

The mediation analysis unraveled potential mediating effects of HDP on the association between either high FT4 or overt hyperthyroidism and iatrogenic PTD (**Table 2** and **Figure 7**).

The total effect of overt hyperthyroidism on iatrogenic PTD was 0.0177 (95% CI [0.0077–0.0325], p <0.001), including a direct mean effect of 0.0156 (95% CI [0.0061–0.0300] p <0.001). A mediation effect of overt hyperthyroidism associated with iatrogenic PTD (mean causal mediation effect, 0.0021; 95% CI

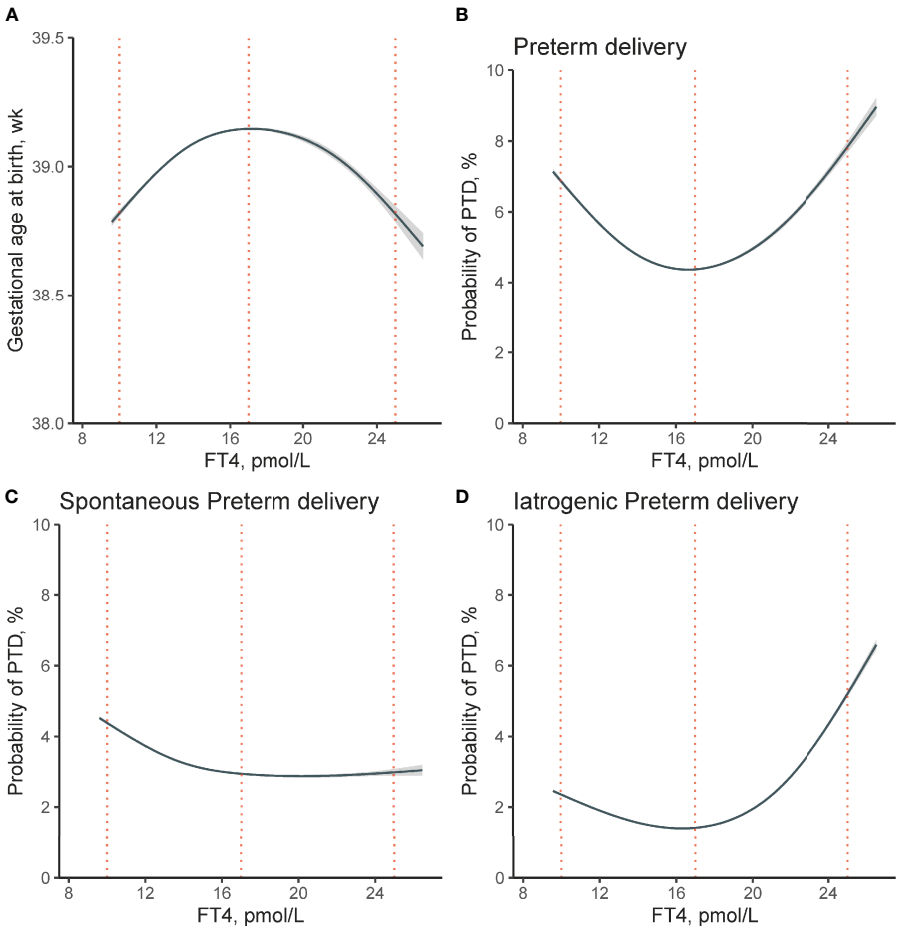

FIGURE 2 | Non-linear association between maternal FT4 concentration in early pregnancy and risk of PTD. Non-linear association between maternal FT4 concentrations and **(A)** gestational age at birth (χ^2 = 5.18, p <0.001), **(B)** the risk of overall PTD (χ^2 = 16.36, p <0.001), **(C)** spontaneous PTD (χ^2 = 6.32, p = 0.06), and **(D)** iatrogenic PTD (χ^2 = 24.9, p <0.001) were analyzed, respectively. The generalized additive models were conducted by adjusting for maternal age, pre-pregnant body mass index, parity, education levels, insurance, TPO-Ab status, and fetal sex. The solid lines and shaded areas represent the estimated mean risk and 95% confidence intervals; dashed vertical lines indicate FT4 concentrations at 10, 17, and 25 pmol/L respectively. FT4, free thyroxine; PTD, preterm delivery; TPO-Ab, thyroid peroxidase antibody.

[0.0006–0.0038], p <0.001) through HDP was found, and the estimated proportion of mediation effect was 11.80% (95% CI [3.98–25.89%], p <0.001). No mediation effect of HDP was identified in the association between low FT4 or isolated hypothyroxinemia and spontaneous PTD.

We also explored the mediating effect of ICP and placental abruption on the association between maternal FT4 and PTD, and found no such effect (p >0.05, data not shown).

Subgroup and Sensitivity Analyses

We further conducted subgroup analysis stratified by maternal age, pre-pregnant BMI, TPO-Ab status, and parity (**Table 3** and **Figure 8**). We found stronger associations of low FT4 in early pregnancy with PTD risk among those who had a younger maternal age (<35 years old), higher maternal pre-pregnancy BMI (≥24 kg/m^2), TPO-Ab negative and nulliparity (**Table 4**). We also identified a stronger association of high FT4 in early pregnancy with PTD risk among those who had a lower maternal pre-pregnancy BMI (<18.5 kg/m^2) and the association did not differ in other subgroups (**Table 4**).

For sensitivity analysis, the associations between low/high FT4 and risk of PTD were still robust after exclusion of women with PTD history, taking thyroid medication during pregnancy, GDM, and HDP (**Table 4**).

DISCUSSION

To the best of our knowledge, our findings revealed a U-shaped association between continuous spectrum maternal FT4 and PTD for the first time, providing a better fit for real-world clinical data. Our study further indicated both low and high maternal FT4 concentrations as risk factors for PTD. Moreover, the positive association of isolated hypothyroxinemia with PTD

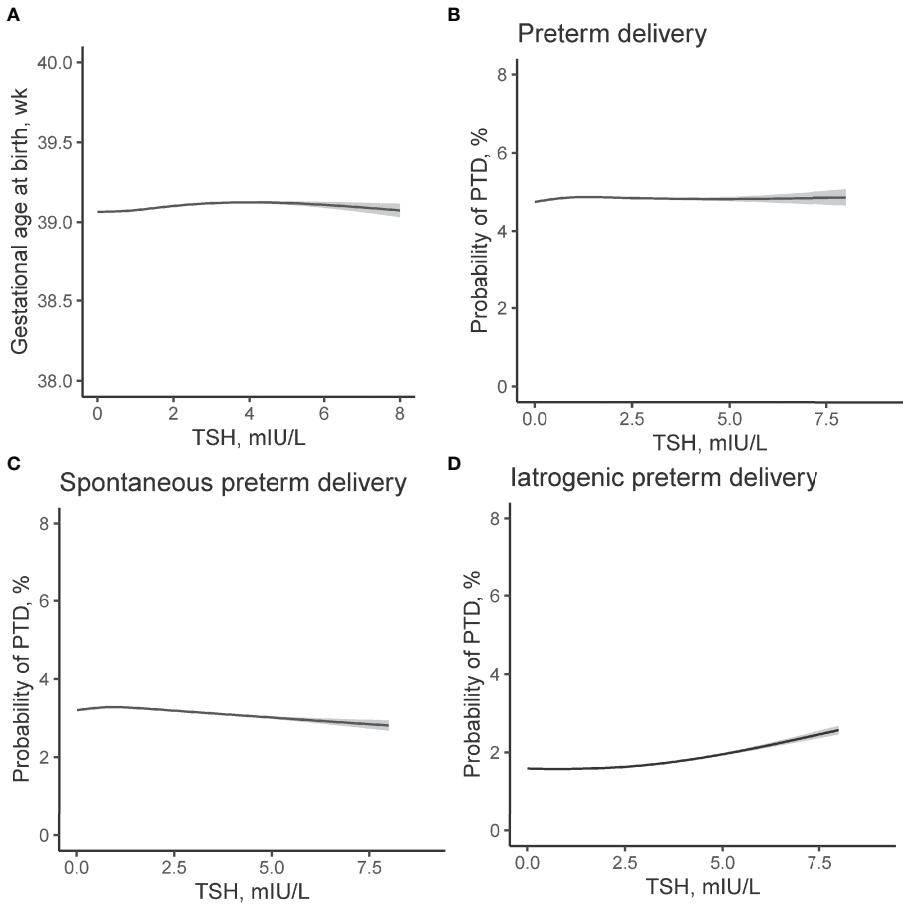

FIGURE 3 | Non-linear association between TSH concentrations in early pregnancy and risk of PTD. Association between maternal TSH concentrations and **(A)** gestational age at birth (χ^2 = 3.17, p = 0.044), **(B)** overall PTD (χ^2 = 0.001, p = 0.996), **(C)** spontaneous PTD (χ^2 = 0.57, p = 0.46), and **(D)** iatrogenic PTD (χ^2 = 1.67, p = 0.34) were evaluated by generalized additive models. The models have 4 *df* and were adjusted for maternal age, fetal sex, pre-pregnant body mass index, parity, education levels, TPO-Ab status, and insurance. The solid lines and shaded areas represent the estimated values and their corresponding 95% confidence intervals. TSH, thyroid-stimulating hormone; PTD, preterm delivery; TPO-Ab, thyroid peroxidase antibody.

was mainly driven by spontaneous PTD while women with overt hyperthyroidism were more susceptive to iatrogenic PTD. We also illustrated that the association of high FT4 or overt hyperthyroidism with iatrogenic PTD was partially mediated through the development of HDP.

Our results demonstrated that abnormal maternal FT4 concentrations might attribute to a higher risk of PTD. Maternal thyroid hormone concentrations in the first trimester are pivotal for fetal growth (24, 27) and neurodevelopment (5, 7, 28) when the fetus depends solely on maternal thyroid hormones *via* transplacental transition (29). However, epidemiological research has shown inconsistent evidence concerning mild alterations of maternal thyroid function during pregnancy and PTD (15–17). Furthermore, limited research has looked into the association of thyroid dysfunction with subtypes of PTD (16, 30, 31). Most observational studies studied maternal thyroid test abnormalities with widely different definitions. This type of categorization of continuous variables might obscure important information, and few studies have evaluated the risk of PTD across the full spectrum of maternal FT4 concentrations. Therefore, taking advantage of an intrinsically interpretable machine learning model, our study is the first to analyze the non-linear dose-dependent relationship between maternal FT4 and PTD. Our results demonstrated that both low and high maternal FT4 is associated with a higher risk for PTD—indicating a beneficial role of early maternal thyroid function screening to identify high-risk PTD in pregnant women. In addition, isolated hypothyroxinemia and overt hyperthyroidism were identified as risk factors for spontaneous and iatrogenic PTD, respectively. Therefore, these results might provide new evidence towards the significance of timely clinical management concerning women with isolated hypothyroxinemia and overt hyperthyroidism identified in the first trimester. Furthermore, these results also encourage future research toward early management to maintain maternal FT4 in an optimal range for the prevention of adverse pregnancy outcomes.

The mechanisms behind the U-shaped relationship between maternal FT4 and PTD might be explained *via* several potential pathways and our mediation analyses underlined a differentiated

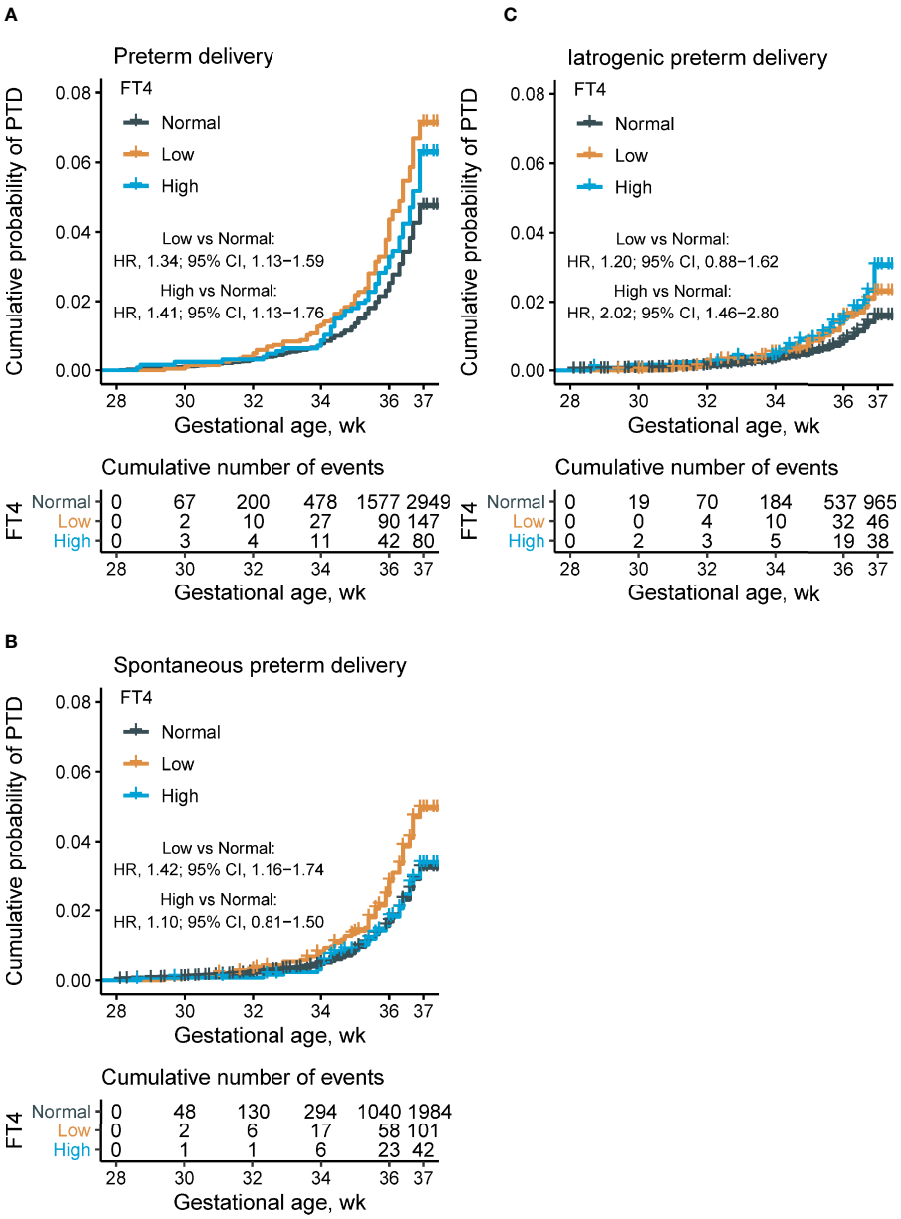

FIGURE 4 | Proportions of overall, spontaneous, and iatrogenic PTD, and time-to-event analysis, by maternal FT4 concentrations. Kaplan–Meier plots showing the proportion of overall PTD **(A)**, spontaneous PTD **(B)**, and iatrogenic PTD **(C)** by different maternal FT4 concentrations categories (low maternal FT4 (<11.7 pmol/L), *n* = 62,227; normal maternal FT4 (11.7–19.7 pmol/L), *n* = 2,064; and high maternal FT4 (>19.7 pmol/L), *n* = 1,274). Cox multivariant analysis was conducted to calculate the hazard ratio by adjusting for maternal age, pre-pregnant body mass index, parity, education levels, insurance, TPO-Ab status, and fetal sex. FT4, free thyroxine; PTD, preterm delivery; TPO-Ab, thyroid peroxidase antibody.

PTD pathogenesis mechanism of high and low maternal FT4. First, the full compensatory mechanisms needed to improve the maternal–fetal transfer of thyroid hormones might be absent in the placenta of patients with pathological maternal thyroid hormone deficiency during gestation (32). In addition, disrupted endocrine factors, namely, vasopressin, under maternal thyroid hypofunction (33), and the inflammation process at the maternal–fetal interface triggered by oxidative stress (34–36), might be both related to the early onset of spontaneous PTD. Moreover, maternal thyroid hormone deficiency could also lead to insufficient trophoblast cell invasion, which might further lead to abnormal placentation and PTD (12, 37, 38). Importantly, maternal hyperthyroidism may accelerate the degradation of proteins and lipids which results in chronic maternal caloric deficiency and further adversely affects fetal growth (39). Overt hyperthyroidism is a well-acknowledged risk factor for HDP

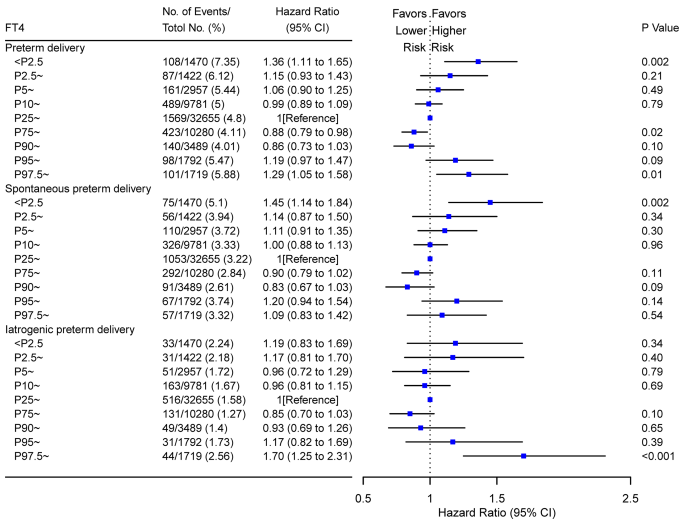

FIGURE 5 | Forest plots for risk of PTD in women with different FT4 percentile at early pregnancy. Hazard ratios of overall PTD, spontaneous PTD, and iatrogenic PTD were shown for FT4 at different percentiles (from low to high). Women with P25–P75 of FT4 were used as the reference control. Model adjusted for maternal age, fetal sex, prepregnant BMI, parity, education levels, TPO-Ab status and insurance; PTD, preterm delivery. FT4, free thyroxine; PTD, preterm delivery; TPO-Ab, thyroid peroxidase antibody.

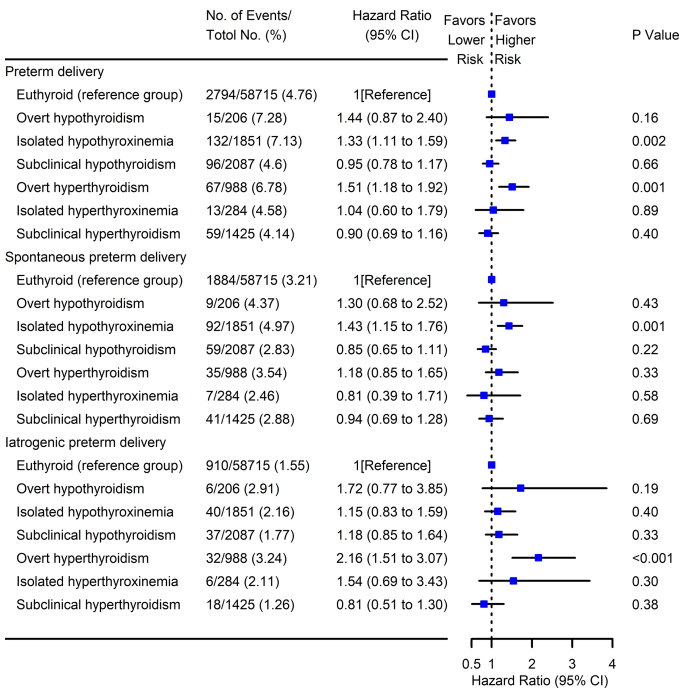

FIGURE 6 | Forest plots for risk of PTD with maternal thyroid test abnormalities. Cox multivariant analysis was conducted for the risk of PTD subtypes (overall, spontaneous, and iatrogenic) with different maternal thyroid test abnormalities by adjusting for maternal age, pre-pregnant body mass index, parity, education levels, insurance, TPO-Ab status, and fetal sex. Pregnancies with euthyroid were used as the reference group. PTD, preterm delivery; TPO-Ab, thyroid peroxidase antibody.

TABLE 2 | Mediation effect of hypertensive disorders in pregnancy on the association of high-low FT4 concentrations/thyroid dysfunction with iatrogenic/spontaneous PTD.

Total effect (95% CI)	ADE (95% CI)	ACME (95% CI)	Proportion of Mediation (%)
High FT4, HDP and iatrogenic PTD			
0.0169 (0.0063, 0.0300)***	0.0152 (0.0048, 0.0275)***	0.0017 (0.0005, 0.0031)***	10.71 (3.72,19.53)***
Overt hyperthyroidism, HDP and iatrogenic PTD			
0.0177 (0.0077, 0.0325)***	0.0156 (0.0061, 0.0300)***	0.0021 (0.0006, 0.0038)***	11.80 (3.98,25.89)***
Low FT4, HDP, and spontaneous PTD			
0.0127 (0.0049, 0.0200)***	0.0128 (0.005 0.0200)***	–0.0001 (–0.0003, 0.00)	–0.74 (–2.35,0.00)
Isolated hypothyroxinemia, HDP and spontaneous PTD			
0.0137 (0.0051, 0.0200)***	0.0138 (0.0053, 0.0200)***	0.0001 (0.0003, 0.00)	–0.90 (–3.44,0.00)

FT4, free thyroxine; PTD, preterm delivery; ACME, average causal mediation effects; ADE, average direct effects.
FT4 >19.7 pmol/L was categorized as high FT4 and low FT4 was diagnosed with <11.7 pmol/L. Multivariable logistic models were adjusted for maternal age, fetal sex, pre-pregnancy BMI, parity, education levels, TPO-Ab status and insurance.
****p-value <0.001.*

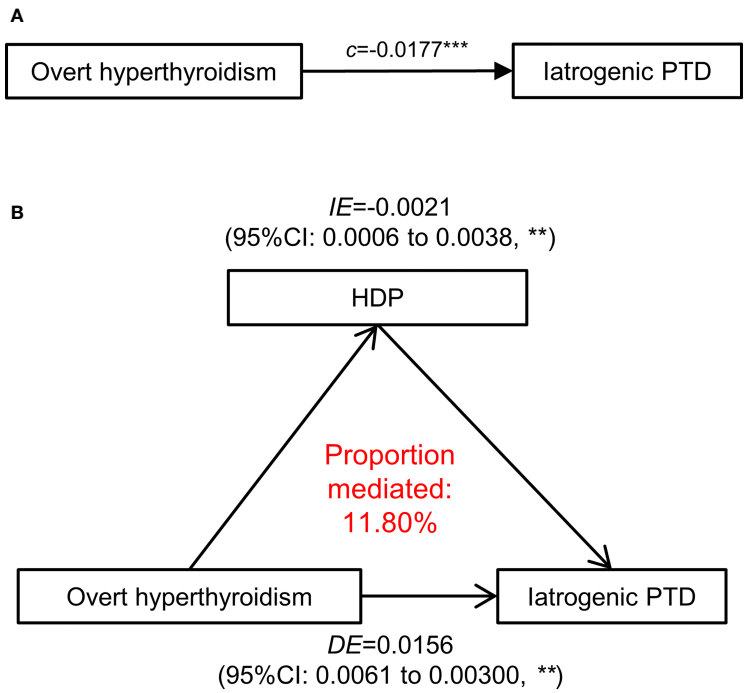

FIGURE 7 | Mediation effect of hypertensive disorders in pregnancy on the association of overt hyperthyroidism with iatrogenic PTD. **(A)** The total effect of maternal overt hyperthyroidism (defined as FT4 >19.7 pmol/L)-iatrogenic PTD relationship was presented as path (c). **(B)** The direct effect in a mediation model is presented and measures the effect of overt hyperthyroidism on the iatrogenic PTD through independent of HDP (the mediator). The difference between Indirect effect and direct effect indicates the effect of maternal overt hyperthyroidism on iatrogenic PTD that operates through development of HDP. HDP, Hypertensive disorders in pregnancy; PTD, preterm delivery; ACME, average causal mediation effects; ADE, average direct effects. All the association adjusted for maternal age, fetal sex, pre-pregnancy BMI, parity, education levels, TPO-Ab status and insurance. The p-values were adjusted for multiple comparisons using the Benjamini & Hochberg method. **p-value < 0.01, ***p-value <0.001.

(40–44) and current clinical management of HDP includes timely termination of pregnancy under the more severe form of the disease in need of iatrogenic PTD. Our data indicated that the subsequent development of HDP might act as a bridge between high FT4 or overt hyperthyroidism and iatrogenic PTD, while no mediation effect of HDP was identified in the association between low FT4 or isolated hypothyroxinemia and spontaneous PTD.

GAM is an intrinsically interpretable machine learning model to reduce the mean squared error for the exposure effect after adjustment, and circumvent the increase of the type I error for testing the exposure effect (20). With no assumption of a specific priori functional association (e.g., linearity) between maternal FT4 and PTD, GAM enables the exploration of a smooth, possibly non-linear association that is determined by the data rather than the modeler. Moreover, the time-to-event (for PTD)

TABLE 3 | Hazard ratios of preterm delivery with different FT4 categories in subgroup analysis.

Variables	FT4 categories	No. of Events/Total No. (%)	HR (95% CI)[a]	P-value
Maternal age, y				
<35	Normal	2,378/52,957 (4.49)	1 (reference)	
	Low	97/1,452 (6.68)	1.42 (1.15 to 1.74)	<0.001
	High	63/1,119 (5.63)	1.32 (1.03 to 1.69)	0.03
≥35	Normal	571/9,270 (6.16)	1 (reference)	
	Low	50/612 (8.17)	1.29 (0.96 to 1.73)	0.09
	High	17/155 (10.97)	1.86 (1.15 to 3.02)	0.01
Pre-pregnancy BMI				
<18.5	Normal	437/9,329 (4.68)	1 (reference)	
	Low	8/159 (5.03)	0.99 (0.49 to 2.01)	0.99
	High	24/306 (7.84)	1.75 (1.16 to 2.64)	0.008
18.523.9	Normal	2,072/45,551 (4.55)	1 (reference)	
	Low	91/1,371 (6.64)	1.33 (1.08 to 1.65)	0.008
	High	49/911 (5.38)	1.23 (0.93 to 1.64)	0.15
≥24	Normal	440/7,347 (5.99)	1 (reference)	
	Low	48/534 (8.99)	1.46 (1.08 to 1.98)	0.01
	High	7/57 (12.28)	2.02 (0.96 to 4.27)	0.06
TPO-Ab				
Negative	Normal	2,633/55,597 (4.74)	1 (reference)	
	Low	129/1,737 (7.43)	1.40 (1.17 to 1.67)	<0.001
	High	66/1,116 (5.91)	1.32 (1.03 to 1.69)	0.03
Positive	Normal	316/6,613 (4.78)	1 (reference)	
	Low	18/327 (5.5)	1.07 (0.66 to 1.73)	0.79
	High	14/157 (8.92)	1.97 (1.15 to 3.38)	0.01
Parity				
nulliparity	Normal	2,088/46,170 (4.52)	1 (reference)	
	Low	84/1,214 (6.92)	1.39 (1.11 to 1.74)	0.003
	High	57/999 (5.71)	1.33 (1.02 to 1.73)	0.04
multiparity	Normal	861/16,057 (5.36)	1 (reference)	
	Low	63/850 (7.41)	1.28 (0.99 to 1.66)	0.06
	High	23/275 (8.36)	1.65 (1.09 to 2.51)	0.02

Gestational weeks for thyroid function screening were 9–13 weeks in early pregnancy. Low maternal FT4 defined as FT4 <11.7 pmol/L, normal maternal FT4 as FT4 between 11.7–19.7 pmol/L and high maternal FT4 as FT4 >19.7 pmol/L. Model adjusted for age, fetal sex, pre-pregnancy BMI, parity, education status, TPO-Ab status and insurance.
FT4, free thyroxine; TPO-Ab, thyroid peroxidase antibody; HR, hazard ratio, CI, confidence interval; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

method and multivariable Cox proportional hazard models were further applied to analyze the association of abnormally high and low maternal FT4 concentrations with the timing of PTD. We also differentiated the subtypes of PTD (including spontaneous and iatrogenic PTD) and explored which subtype primarily attributed to the association between different maternal thyroid dysfunctions and PTD. Taking advantage of this method, we further proved that isolated hypothyroxinemia pregnant women might have an incremental risk of spontaneous PTD while women with hyperthyroidism were more susceptive to iatrogenic PTD. Lastly, we also identified a potential mediating effect of HDP on the association between high FT4 concentration and PTD—the mechanism of which should be further studied in future.

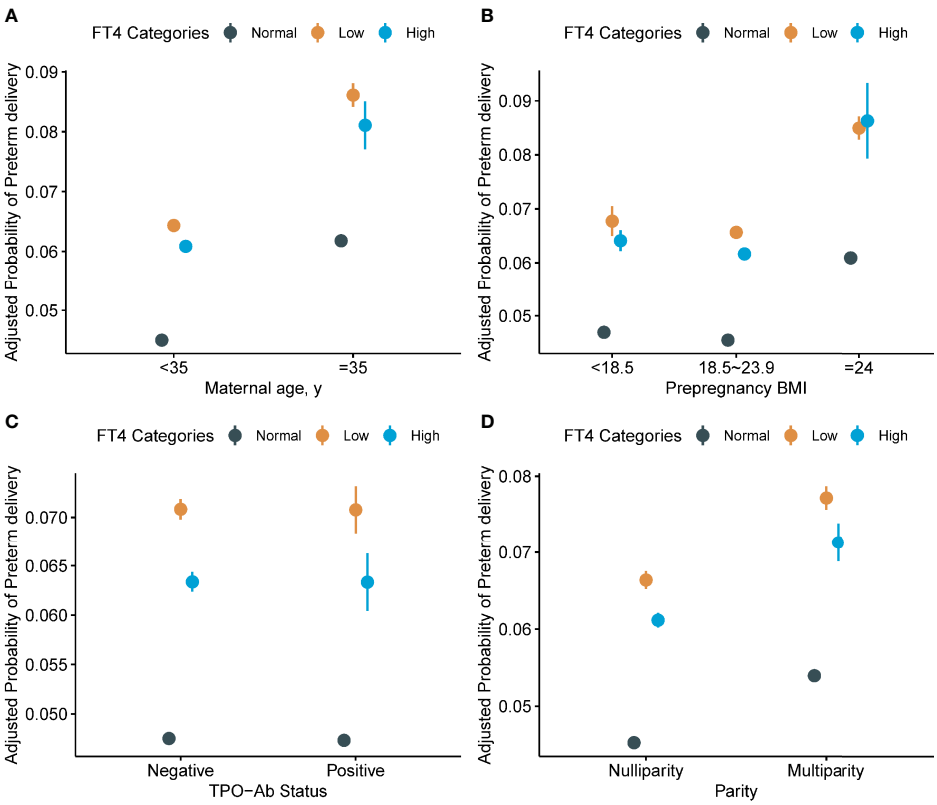

FIGURE 8 | Adjusted probability of preterm delivery (PTD) in different free thyroxine (FT4) level categories stratified by potential modifiers. **(A)** Model adjusted for fetal sex, prepregnant BMI, parity, education levels, TPO-Ab status and insurance; **(B)** Model adjusted for maternal age, fetal sex, parity, education levels, TPO-Ab status and insurance; **(C)** Model adjusted for maternal age, fetal sex, prepregnant BMI, parity, education levels, and insurance; **(D)** Model adjusted for maternal age, fetal sex, prepregnant BMI, education levels, TPO-Ab status and insurance. Maternal FT4 categories: Normal FT4 (11.7–19.7 pmol/L); Low FT4 (<11.7 pmol/L); and High FT4 (>19.7 pmol/L). FT4, free thyroxine; TPO-Ab, thyroid peroxidase antibody; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); PTD, preterm delivery.

TABLE 4 | Sensitivity analysis for association of FT4 with PTD.

FT4	No. of events/Total No. (%)	HR 95% CI	P-Value
Exclude history of preterm delivery			
Normal	2,746/61,516 (4.46)	1 [Reference]	
Low	135/2,019 (6.69)	1.35 (1.13 to 1.60)	<0.001
High	73/1,259 (5.8)	1.37 (1.09 to 1.73)	0.008
Exclude thyroid medication during pregnancy			
Normal	2,893/61,201 (4.73)	1 [Reference]	
Low	138/1,975 (6.99)	1.32 (1.11 to 1.57)	0.002
High	72/1,224 (5.88)	1.32 (1.04 to 1.67)	0.02
Exclude HDP and GDM			
Normal	2,227/52,534 (4.24)	1 [Reference]	
Low	93/1,525 (6.1)	1.34 (1.09 to 1.66)	0.006
High	62/1,084 (5.72)	1.41 (1.10 to 1.82)	0.007

Models were adjusted for age, fetal sex, pre-pregnancy BMI, parity, education levels, TPO-Ab status and insurance.
FT4, free thyroxine; HR, hazard ratio; CI, confidence intervals; PTD, preterm delivery; HDP, hypertensive disorders during pregnancy; GDM, gestational diabetes mellitus.

Regardless, this study also has several limitations. First, selection bias might be present because it was a cohort study based on a single center; hence, multiple obstetric centers should be considered in future. Second, because maternal thyrotropin receptor antibodies (TRAb) were not available in the current study, we could not fully exclude the impact of a small number of undiagnosed Grave's hyperthyroidism (TRAb-positive) even though we excluded women with pre-existing thyroid disease and thyroid medication. Third,

although a series of potential confounders were adjusted, the possibility of residual confounding could not be completely ruled out. For example, the blood and urine iodine were not assessed during the routine pregnancy examinations. Although the city of Shanghai is not an iodine-deficient area (45), we could not fully eliminate the influence of the iodine status. Finally, this is an observational study, and our findings are warranted to be validated by future large, multi-center randomized control trials.

In conclusion, there is a U-shaped dose-dependent relationship between maternal FT4 in the first trimester and PTD. The association between isolated hypothyroxinemia and PTD was mainly associated with spontaneous PTD while overt hyperthyroidism may be attributable to iatrogenic PTD. Therefore, the early monitoring of maternal thyroid function during pregnancy could be important to identify high-risk PTDs. Future research into early management to maintain maternal FT4 in an optimal range are warranted for the prevention of adverse pregnancy outcomes.

DATA AVAILABILITY STATEMENT

Data available on reasonable request. Requests to access the datasets should be directed to fanjianxia122@126.com.

AUTHOR CONTRIBUTIONS

YulZ: Conceptualization, Methodology, Investigation, Form analysis, Writing—Original draft preparation. YL: Methodology, Writing—Original draft preparation & Review & Editing. YuaZ: Writing—Original draft preparation & Review & Editing. YoZ: Project Administration. JF: Conceptualization, Resources, Writing—Reviewing and Editing, Supervision, Funding acquisition, data interpretation and revision. WW: Conceptualization, Methodology, Software, Data curation, Writing—Review & Editing, Supervision, Funding acquisition. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Relationship Between Subclinical Hypothyroidism in Pregnancy and Hypertensive Disorder of Pregnancy: A Systematic Review and Meta-Analysis

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Objective: Studies have shown a high incidence of subclinical hypothyroidism in pregnancy, but the adverse pregnancy outcomes caused by it are not clear. Therefore, we conducted a systematic review and meta-analysis to evaluate the relationship between subclinical hypothyroidism in pregnancy and hypertensive disorders of pregnancy(HDP) to guide clinical practice.

Method: We searched the MEDLINE (PubMed), Cochrane Central, EMBASE, Web of Science, and SCOPUS databases and screened all studies evaluating the relationship between subclinical hypothyroidism in pregnancy and hypertensive disorders of pregnancy. Two researchers independently evaluated the quality of all eligible original studies using the Newcastle-Ottawa Scale (NOS). We also performed a meta-analysis using STATA15.1. Sensitivity analyses were also performed by examining the effects of individual studies as well as using different effect models and detecting any publication bias using the harbord test.

Results: Twenty-two studies were included in the final meta-analysis. Our results indicated that pregnant women with subclinical hypothyroidism had an increased risk of HDP (OR = 1.54(95% CI: 1.21-1.96) I^2=67.1%), compared with euthyroidism. Subclinical hypothyroidism in pregnancy was not associated with hypertensive disorders of pregnancy at TSH diagnostic cut-off of less than 3.0 mIU/L (P = 0.077). Curiously, the risk of HDP increases when the TSH diagnostic cut-off value is higher or lower than 4 mIU/L. Although only 9 studies were above the threshold, the risk of developing HDP was still 1.69 times, which was highest in all subgroup analyses. This is consistent with the newly recommended diagnostic cut-off value of 4 mIU/L for TSH by the ATA. Our results consider that the risk of hypertensive disorder complicating pregnancy is increased regardless of the diagnosis of subclinical hypothyroidism at any stage of pregnancy. Unfortunately, there is insufficient evidence to support that patients can benefit from treatment with levothyroxine.

Conclusion: The results of this meta-analysis indicate that subclinical hypothyroidism in pregnancy is associated with an increased risk of developing HDP, and this association exists regardless of the gestational period. However, the available evidence cannot support these patients receiving thyroxine intervention can benefit from it, so routine screening is only recommended for pregnant women with risk factors for hypothyroidism. Further research is needed to validate more scientific and rigorous clinical studies to clarify the relationship between subclinical hypothyroidism and HDP to improve patient prognosis.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/, PROSPERO (CRD42021286405)

Keywords: subclinical hypothyroidism, hypertensive disorders of pregnancy (HDP), levothyroxine alone, thyroid-stimulating hormone (TSH), pregnancy

INTRODUCTION

As one of the most important endocrine diseases in pregnant women, thyroid disease during pregnancy has gradually become a hot spot in clinical and basic research in the field of maternal-fetal medicine with the publication of the results of more than ten large-sample clinical trials in recent years. Among them, subclinical hypothyroidism as a population with a large number of patients has also attracted countless attention. Subclinical hypothyroidism (SCH) refers to elevated serum TSH levels with normal fT4 or TT4 values (1). According to incomplete statistics, 10% of adults, as well as 3.47% of pregnant women are currently afflicted (2, 3). However, individual differences and the presence of other confounding factors (such as iodine intake, thyroid antibody status, etc.) make the establishment of an appropriate reference range an important challenge for researchers (1). HDP is one of the important causes of maternal and neonatal-perinatal death and other serious adverse pregnancy outcomes worldwide and has been a focus of attention for clinicians for many years because of its wide range of effects as well as high medical expenditure. A variety of studies have investigated the relationship between maternal subclinical hypothyroidism and a variety of obstetric as well as neonatal outcomes including HDP (4–7). Studies have shown impaired endothelium-associated vasodilation in patients with subclinical hypothyroidism (8), suggesting that subclinical hypothyroidism may be a risk factor for HDP. However, some existing clinical studies have conflicting conclusions and no uniform consensus has been reached.

In 2011, the American Thyroid Association (ATA) developed a unified standard for the diagnosis and treatment of thyroid disease during pregnancy (9). The guidelines recommend that every effort should be made to establish pregnancy-based reference ranges for serum TSH to accurately screen for SCH. When pregnancy and assay-specific TSH reference ranges are not available, the upper limit of 2.5 mIU/L in the first trimester and 3.0 mIU/L in the second trimester can be used. Based on the study of sample and ethnicity, the ATA guideline was revised in 2017 to include 4 mIU/L as the upper limit of normal for serum TSH values in early pregnancy (1).

Up to now, there are various studies on whether maternal subclinical hypothyroidism is associated with HDP. Some studies believe that women with subclinical hypothyroidism in pregnancy are at risk of HDP compared with euthyroid pregnant women during pregnancy (10, 11). However, the results of a META analysis showed no correlation between subclinical hypothyroidism in pregnancy and HDP (12). More importantly, since the ATA guidelines were revised in 2017, several studies have been published successively. Therefore, the purpose of this study was to systematically review the published eligible studies to determine the correlation between subclinical hypothyroidism during pregnancy and HDP, and to perform a more detailed analysis according to the difference in TSH cut-off values and different pregnancy periods, to provide a basis for clinical diagnosis and prognosis of the disease.

MATERIALS AND METHODS

Search Strategy

Two reviewers were assigned to assess the eligibility of the literature search in the MEDLINE (PubMed), Cochrane Central, EMBASE, Web of Science, and SCOPUS databases between January 1949 and October 2021. Additionally, each reviewer re-assessed the relevance of the studies found for inclusion in the present study. We used the terms "pregnancy induced hypertension" [All Fields] OR "gestational hypertension" [All Fields]) OR "pregnancy transient hypertension" [All Fields]) OR "Preeclampsia" [All Fields]) OR "hypertensive disorder of pregnancy". These previously mentioned terms were combined with AND ("subclinical hypothyroidism" [All Fields] OR "subclinical thyroid dysfunction" [All Fields]) OR "untreated subclinical hypothyroidism" [All Fields]) OR "maternal subclinical hypothyroidism" [All Fields] OR "thyrotropin "[Mesh Term]) OR "thyroid-stimulating hormone" [All Fields]) OR "thyroid

stimulating hormon" [All Fields]) OR "TSH" [All Fields]) OR ldquo; thyreotropin" [All Fields]) OR "thyrotropic hormone" [All Fields]) OR "maternal TSH level" [All Fields]). The references of all included original articles were also determined by two researchers for their eligibility. All controversial original articles were decided in consultation with a third study person.

Study Selection and Eligibility Criteria

The inclusion criteria comprised of the following conditions: 1) articles that were published in English and were clinical cohort studies were eligible 2) studies needed to describe the specific gestational age and blood sample collection information 3) studies needed to provide the normal reference range of TSH and FT4, thyroglobulin status (if tested) and the kits used for detection 4) Studies needed to offer diagnostic criteria for gestational hypertension and preeclampsia. The exclusion criteria included: 1) randomized controlled study, cross-sectional studies, case-control studies, randomized controlled study case reports or reviews 2) full text not available. **Figure 1** is the flow chart of literature screening. Subclinical hypothyroidism during pregnancy was defined as serum TSH greater than the upper limit of the pregnancy-specific reference range and serum FT4 within the pregnancy-specific reference range. Gestational hypertension was defined as systolic blood pressure ≥ 140 mmhg and/or diastolic blood pressure ≥ 90 mmhg found after 20 weeks of gestation and required at least two blood pressure measurements in the same arm before diagnosis. Preeclampsia was defined as the presence of positive random urine protein or 24-hour urine protein ≥ 0.3g in addition to the above findings.

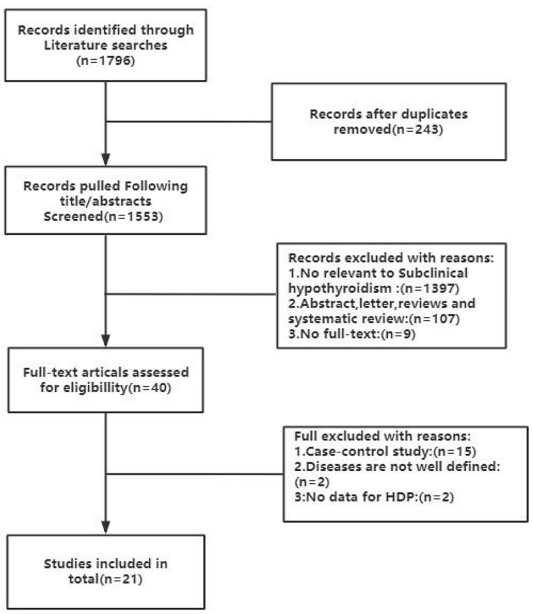

FIGURE 1 | Flow chart of the literature search and selection process in the MEDLINE (PubMed), EMBASE, Cochrane Central, Web of Science and SCOPUS.

Quality Assessment

The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the literature in all finally included studies (13). The Newcastle-Ottawa Scale (NOS) mainly contains three parts, which are selectivity, comparability and outcome, with a maximum score of 9 stars. In the evaluation process, the objection shall be jointly decided by negotiation with a third party.

Statistical Analysis

All statistical analyses were performed by STATA15.1. Random effects models were applied to calculate odds ratios (ORs) and 95% confidence intervals (CIs) to determine the association between subclinical hypothyroidism during pregnancy and HDP. The I^2statistic was applied to test for heterogeneity between studies (14). When I^2 was less than 25%, it was considered that the heterogeneity between studies was low, and when I^2 value was greater than 75%, it indicated that the heterogeneity between studies was high. Subgroup analysis was used to investigate the source of heterogeneity between studies. First, without considering gestational age, TSH cut-off values of 3 mIU/L, and 4 mIU/L were used for analysis, respectively. Subsequently, different pregnancy periods (first trimester (T1):≤12weeks, second trimester (T2): ≤28weeks and third trimester(T3):>28weeks) were analyzed. When the original study tested serum TSH values separately in different pregnancy periods, if the TSH diagnostic threshold used was similar (i.e., TSH diagnostic cut-off values were > 3 mIU/L or < 3 mIU/L, and TSH diagnostic threshold values were > 4 mIU/L or < 4 mIU/L), the comparisons were performed according to the individual studies, otherwise the comparisons were performed separately. Sensitivity analyses were performed by examining the effects of individual studies as well as by employing different effect models. Publication bias was detected by the harbord test (15). This study follows PRISMA2009.

RESULTS

Search Results

The literature screening process is summarised in **Figure 1**. Eventually, a total of 1796 articles were retrieved in the database according to the established search strategy, 243 articles were removed due to duplication. Subsequently, during screening through the abstract, 1397 studies unrelated to subclinical hypothyroidism were found, 107 reviews, letters and abstracts were excluded, and the other 9 original studies could not be obtained in full text and were eliminated. We then further searched the full texts of 40 articles to assess their eligibility, of which 15 were case-control studies, 2 studies were poorly defined for disease, and 2 studies that did not provide HDP-related data were excluded. Eventually, we included 22 original studies to investigate the relationship between subclinical hypothyroidism in pregnancy and HDP (7, 10, 11, 16–33).

Characteristics of Qualified Literatures

Table 1 depicts the basic features of the included articles. A total of 108831 patients from 10 countries from 2005 to 2020 were finally analyzed in this study. A total of 4808 patients with subclinical hypothyroidism, 94306 with euthyroidism, and the rest with other thyroid diseases [there is a part of the repeated population because Li, M.F., et al. and his colleagues assessed the same population with different diagnostic criteria, respectively (10)].There were 15 prospective cohort studies (16–20, 22–29, 31, 32) and 7 retrospective cohort studies (4, 7, 10, 11, 21, 30, 33). In addition, due to slight differences in thyroid parameters during different pregnancy periods, there were 10, 6, and 1 studies evaluating the relationship between subclinical hypothyroidism in pregnancy and HDP in the first, second, and third trimesters, respectively. However, only 2 studies have assessed the relationship between subclinical hypothyroidism and HDP in different TPOAb status (7, 25). Only five studies provided data on the development of HDP after treatment with levothyroxine in patients with subclinical hypothyroidism (11). Due to differences in sample size and study population, the incidence of subclinical hypothyroidism varied from 2.2% to 45.4%. In this study, the incidence of clinical hypothyroidism was 4.42%, the incidence in the first trimester was 8.17%, and the incidence in the second and third trimesters was 3.27% [calculated using the data obtained according to the 2017ATA guideline as the diagnostic criteria in the study by Li, M.F., et al. and his colleagues (10)]. The upper normal cut-off for TSH in this study was between 2.5 mIU/L and 5.78 mIU/L. Curiously, TSH values between 2.5 mIU/L and 4.08 mIU/L were defined as "mildly elevated TSH" in the study by Zhang et al, so they were analyzed separately in this study (7). The results of the quality evaluation of the included studies are presented in **Supplementary Table 1**. The results showed that all studies achieved high scores, suggesting high confidence in the meta-analysis results.

Meta-Analysis

Fifty percent of the 22 studies included in this paper believed that subclinical hypothyroidism in pregnancy was associated with HDP, and the rest were considered unrelated. As shown in **Figure 2**, compared with euthyroidism, pregnant women with subclinical hypothyroidism had an increased risk of HDP [OR = 1.54(95% CI: 1.21-1.96) I^2=67.1%]. Disappointingly, five studies further investigated these patients treated with levothyroxine did not have a reduced risk of HDP compared with patients with subclinical hypothyroidism who were not treated with levothyroxine (p = 0.241) (7, 11, 30, 34, 35), however, due to the limited number of current studies, the credibility of the conclusions is limited.

Subgroup Analysis

According to the 2017ATA guideline, 4.0 mIU/L can be used as the upper limit of TSH in the first trimester when the specific TSH reference range is not available, and 3.0 mIU/L can be used as the upper limit of TSH in the second and third trimesters according to the 2011ATA guideline. Therefore, in this study, 3.0 mIU/L and 4.0 mIU/L were used as TSH diagnostic cut-off values to complete the grouping analysis, respectively, regardless of the effect of gestational age. As shown in **Figures 3**, **4**, when a meta-analysis was performed at a TSH diagnostic cut-off above or below 3.0 mIU/L(Because the study subjects were not clearly distinguished by a TSH diagnostic cut-off of 3 mIU/L in the study by Gupta, R (23), this study was excluded from the subgroup analysis.), SCH was not associated with HDP at TSH diagnostic cut-off of less than 3.0 (P = 0.077), and the risk of developing HDP was increased 1.67-fold (95% CI: 1.17 – 2.37) at TSH diagnostic cut-off of more than 3.0 mIU/L. Curiously, when a meta-analysis was performed using a TSH diagnostic cut-off of 4.0 mIU/L as a grouping basis, patients with subclinical hypothyroidism in pregnancy had a 1.69-fold (95% CI: 1.02 – 2.81) increased risk of HDP above this threshold compared with euthyroid pregnant women, and a 1.45-fold (95% CI: 1.12 – 1.86) increased risk below this threshold (**Table 2**).

However, the effect of different pregnancy periods on thyroid parameters cannot be ignored either. Therefore, we further investigated the relationship between screening diagnosis of subclinical hypothyroidism in the first or second and third trimester of pregnancy and the development of HDP(**Figure 5**). The results suggest that the risk of HDP is increased by 1.79-fold (95% CI: 1.04 – 3.07) after screening in the first trimester for the diagnosis of subclinical hypothyroidism and by 1.58-fold (95% CI: 1.03 – 2.42) during the second and third trimesters of pregnancy (**Table 2**). Only 2 studies provided data on the effect of TPOAb status on the development of HDP and were not analyzed in this meta-analysis.

Sensitivity Analysis and Publication Bias

First, in this study, model stability was judged by different effect models. Second, the stability of the conclusions was judged by investigating the effects of individual studies one by one according to different effect scales, and the above results suggested that the conclusions of this study were stable and credible (results shown in **Supplementary Figure 1** and **Figure 2**). We used the harbord test to detect publication bias and found no significant publication bias (P = 0.081).

DISCUSSION

Up to now, a total of 22 articles have explored the relationship between subclinical hypothyroidism during pregnancy and HDP, but the findings are not consistent. To our knowledge, the results of a meta-analysis by Maraka, S., et al. suggested that subclinical hypothyroidism during pregnancy was not associated with gestational hypertension and preeclampsia (12). However, some relevant studies have been published recently, proposing some new conclusions. The results of two recently completed prospective cohort studies indicate that subclinical hypothyroidism in pregnancy is associated with an increased risk of developing HDP and is a risk factor for HDP (26–31). Similarly, the study by Cakmak and Wu, M.Q reached the same conclusion (4, 11). Therefore, we reviewed a total of 108831 patients involved in 10 countries in the relevant published

TABLE 1 | The general characteristics of the 22 included studies.

Author	Year	Study type	Country	Sample size	The prevalence of SCH	Time points of assessment of thyroid parameters	The cut-off for TSH in SCH (mIU/L)
Sitoris G. et al. (3)	2020	prospective cohort study	Belgium	1521	10.45%	<G20w	>2.51
Li M.F. et al. (10)	2020	retrospective cohort study	China	1556	37.6% (2011ATA), 9.77% (2017ATA)	T1	>2.5 (2011ATA), >4 (2017ATA)
Lai H., Z.Y. et al. (26)	2020	prospective cohort study	China	1226	5.79%	T1	>3.0
Wu M.Q. et al. (11)	2019	retrospective cohort study	China	6157	2.68%	T1, T2	>4.432 (T1),>4.053(T2)
Cakmak et al. (4)	2019	retrospective cohort study	Turkey	8916	10.43%	T1	>2.5
Gupta R. et al. (23)	2018	prospective cohort study	India	1268	11.20%	<G20w	T1:>2.5 T2:>3.0
Furukawa S. et al. (21)	2017	retrospective cohort study	Japan	745	22.41%	<G20w	>3
Hebbar S. et al. (24)	2017	prospective cohort study	India	171	45.40%	T1	>2.5
Zhang et al. (7)	2016	retrospective cohort study	China	3562	1.67%	T1	>4.08
Kishore R. N.et al. (32)	2015	prospective cohort study	India	263	6.08%	T1	>2.5
Ajmani S.N. et al. (16)	2014	prospective cohort study	India	400	9.00%	T2	>3.0
Chen L.M. et al. (19)	2014	prospective cohort study	China	8012	4.63%	T1,T2,T3	>3.47 (T1),>3.81(T2), >4.99(T3)
Saki F. et al. (29)	2014	prospective cohort study	Iran	600	11.30%	T2	>3
Breathnach F.M. et al. (17)	2013	prospective cohort study	Ireland	904	1.77%	<G20w	>4.1
Goel P. et al. (22)	2012	prospective cohort study	India	1005	3.40%	T1,T2,T3	T1>5.0,T2>5.78,T3:5.7
Wang S. et al. (30)	2012	retrospective cohort study	China	756	26.49%	T1	>2.5
Karakosta P. et al. (25)	2012	prospective cohort study	Greece	1170	6.92%	<G20w	T1:>2.53 T2:>2.73
Wilson K.L. et al. (33)	2012	retrospective cohort study	USA	24883	2.12%	<G20w	>4.13
Mannisto et al. (27)	2010	prospective cohort study	Finland	5805	3.90%	<G20w	>3.6
Sahu M.T. et al. (28)	2010	prospective cohort study	India	633	6.47%	T2	>5.5
Cleary-Goldman J. et al. (20)	2008	prospective cohort study	USA	21980	2.20%	T1,T2	>4.29 (T1),>3.94(T2)
Casey B.M. et al. (18)	2005	prospective cohort study	USA	17298	2.33%	<G20w	>2.74

literature to re-evaluate the correlation between subclinical hypothyroidism during pregnancy and HDP, so as to guide clinical practice and improve adverse pregnancy outcomes in perinatal pregnant women.

Due to differences in diagnostic cut-off selection, race, iodine intake, etc., the prevalence of subclinical hypothyroidism during pregnancy ranges from 1.5% to 42.9% (3), and the incidence is about 10 times that of overt hypothyroidism (36). Therefore, the huge sick population has also gained the attention of the majority of researchers and become a hot spot and frontier of current clinical and basic research. Compared with overt hypothyroidism, the effect of subclinical hypothyroidism during pregnancy on adverse pregnancy outcomes is not clear. Existing research suggests that patients with subclinical hypothyroidism in pregnancy may have an increased risk of gestational diabetes, spontaneous abortion, and preterm delivery compared with euthyroid pregnant women (37–39). In addition, short-term neurodevelopment as well as long-term mental development, and motor development may also be affected in offspring (40, 41). Previous studies have suggested that thyroid hormone has a profound effect on the cardiovascular system through cardiac contraction, systemic vascular resistance, and cholesterol metabolism (42–44), which induces the production of NO under the action of ion channels, which in turn produces impaired endothelium-dependent vasodilation and the formation of hypertensive disorders (8). However, HDP is a common complication that seriously threatens maternal and child health and safety is one of the important causes of maternal death. It has become a disease that obstetricians focus on screening and treatment. Therefore, it is of great practical significance to clarify

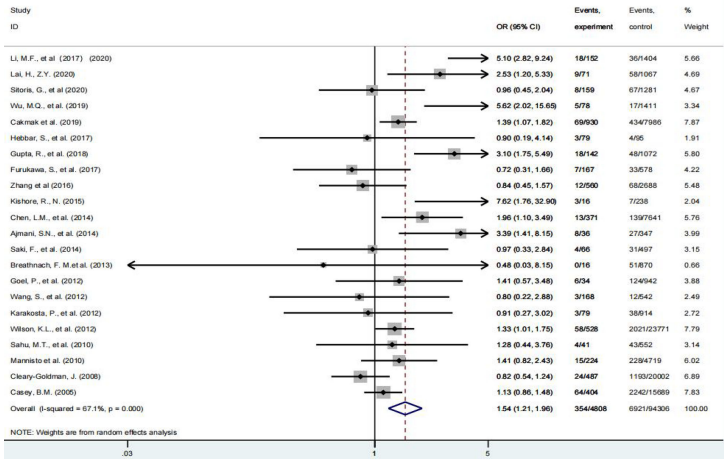

FIGURE 2 | Forest plot of relative risk and 95% confidence interval (CI) of pooled studies comparing pregnant women with subclinical hypothyroidism to euthyroid pregnant women for risk of HDP.

the relationship between subclinical hypothyroidism in pregnancy and HDP to standardize pregnancy management and reduce adverse pregnancy outcomes in pregnant women.

Of the 22 articles included in this study, about 50% of the studies considered subclinical hypothyroidism in pregnancy to be unrelated to HDP. Ultimately, our findings showed a 1.54-fold increased risk of HDP in pregnant women with subclinical hypothyroidism compared to euthyroid pregnant women. Considering the heterogeneity among studies caused by different diagnostic cut-off values selected in different studies, we further used TSH diagnostic cut-off values of 3.0 mIU/L and 4.0 mIU/L as a grouping basis for analysis. The results showed that when the diagnostic cut-off value of TSH was less than 3 mIU/L, subclinical hypothyroidism in pregnancy was not associated with HDP, and when it was more than 3 mIU/L, the risk of HDP increased by 1.67 times. When the TSH diagnostic cut-off value is 4 mIU/L, above or below this threshold, the risk of developing HDP increases. Although only 9 studies were above the threshold, the risk of developing HDP was still 1.69 times, which was highest in all subgroup analyses. This is consistent with the newly recommended diagnostic cut-off value of 4 mIU/L for TSH by the ATA. This conclusion may be more supported as more clinical studies are conducted in the future.

Pregnancy status profoundly affects thyroid function as well as the metabolism of thyroid hormones, making them significantly different from non-pregnant periods. Because human chorionic gonadotropin and TSH have similar chemical structures, they have partial TSH function, which in

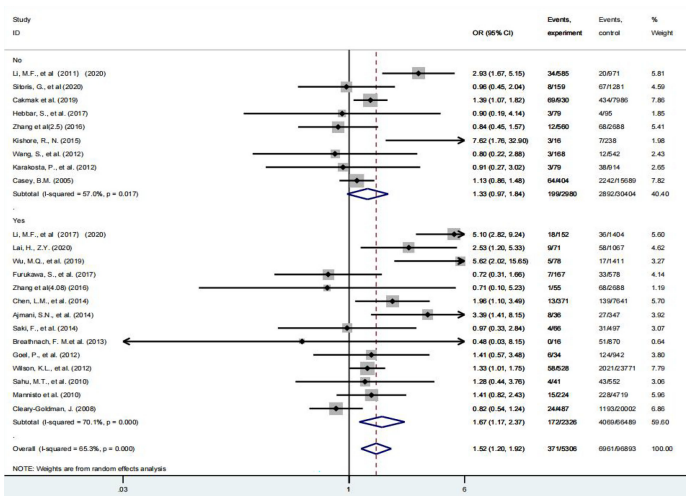

FIGURE 3 | Forest plot of relative risk and 95% CI of pooled studies comparing pregnant women with subclinical hypothyroidism to euthyroid pregnant women for risk of HDP that used a TSH upper limit of 3.0 mIU/L. and (B) that used a TSH upper limit of 4.0 mIU/L.

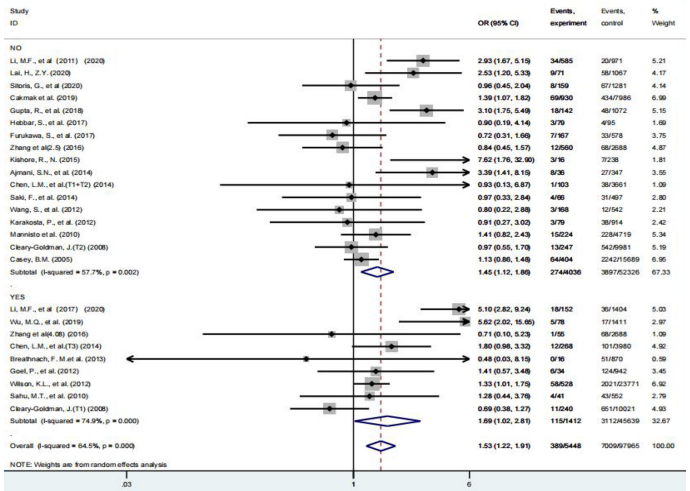

FIGURE 4 | Forest plot of relative risk and 95% CI of pooled studies comparing pregnant women with subclinical hypothyroidism to euthyroid pregnant women for risk of HDP that used a TSH upper limit of 4.0 mIU/L.

turn directly affects the thyroid function of pregnant women and increases the complexity and heterogeneity of thyroid diseases during pregnancy. Generally, the serum HCG level increases and TSH level decreases from 8 to 14 weeks of gestation, TSH decreases to the lowest level from 10 to 12 weeks of gestation, gradually increases in the second trimester, and is even higher than that of the general population in the third trimester (1). Thus, thyroid function parameters are constantly changing in different pregnancy periods, rather than being static. Therefore, it is very necessary to observe the relationship between subclinical hypothyroidism in pregnancy and HDP based on different pregnancy periods. Our study concluded that whether subclinical hypothyroidism was diagnosed in the first or second and third trimester of pregnancy, the risk of HDP increased by more than 1.5 times in the future, but this risk did not decrease after levothyroxine treatment (OR: 1.27 95% CI: 0.85 – 1.88), probably since only five studies have provided data on the development of HDP after the application of levothyroxine for subclinical hypothyroidism. Similarly, Yamamoto's study found that adverse pregnancy outcomes (miscarriage, gestational hypertension, preeclampsia, etc.) were not improved in pregnant women treated with thyroxine (45), so there is currently insufficient evidence to prove that patients can benefit after treatment with thyroxine. Similarly, ATA guidelines also recommend serum TSH testing only for pregnant women with risk factors for hypothyroidism, rather than universal screening (1). Of course, the conclusions of these studies are only based on a small number of original studies, and their real clinical value still needs to be proved by more subsequent clinical studies.

The main limitation of this study is that most of the studies did not describe thyroid autoantibody status, however, thyroid autoantibodies may be associated with a variety of adverse pregnancy outcomes (46), thus leading to an underestimation of the true impact of subclinical hypothyroidism on HDP. It is well-known that iodine intake is the influencing factor of subclinical hypothyroidism, but the selection of evaluation indicators of iodine nutrition status during pregnancy is still a difficult point in current clinical practice, so most studies do not provide specific iodine nutrition status of pregnant women, which may be another limitation of this study. In addition, in the studies conducted after the publication of the new guidelines in 2017, only one study included the diagnostic cut-off value of TSH recommended in the guidelines as the diagnostic criteria so that the results of this analysis were not very significant. In addition, because some studies did not describe whether the included study subjects excluded the intervention of thyroid drugs so that we could not estimate the effect caused by these confounding factors, combined with the existing study results, we do not recommend the treatment of thyroxine for pregnancy

TABLE 2 | Results of subgroup analysis.

Parameter	Category	No.of study	OR (95%CI)	I^2	P
TSH≥3mIU/L	Yes	14	1.67 (1.17-2.37)	70.10%	0.004
	No	9	1.33 (0.97-1.84)	57.00%	0.077
TSH≥4mIU/L	Yes	9	1.69 (1.02-2.81)	74.90%	0.004
	No	17	1.45 (1.12-1.86)	57.70%	0.043
Pregnancy period	first trimester	10	1.79 (1.04-3.07)	77.60%	0.034
	second and third trimester	6	1.70 (1.05-2.75)	48.40%	0.030

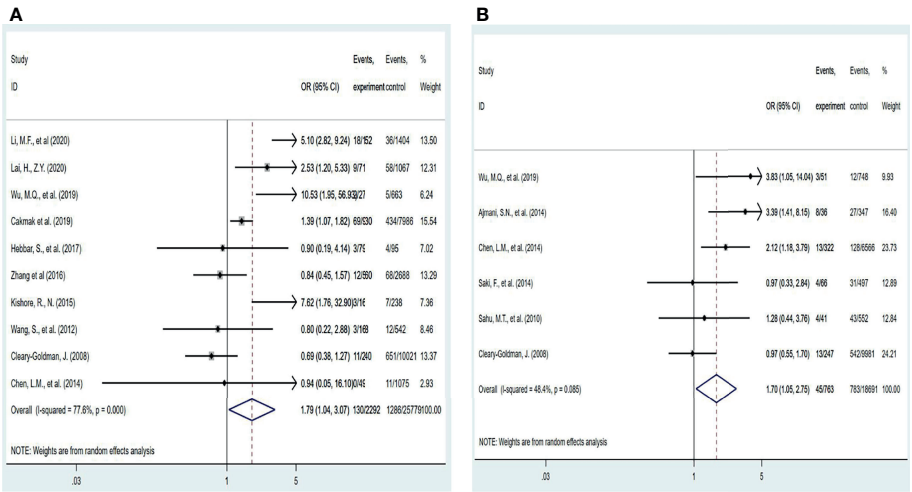

FIGURE 5 | Forest plot of relative risk and 95% CI of pooled studies comparing pregnant women with subclinical hypothyroidism to euthyroid pregnant women for risk of HDP **(A)** gestational age at a screening at the first trimester and **(B)** gestational age at a screening at second and third trimester.

with subclinical hypothyroidism. Although geographic and ethnic diversity in TSH concentrations during pregnancy does exist, guidelines state that the availability of calculated reference ranges for specific pregnancies is limited for most ethnic and populations with adequate iodine intake and no thyroid autoantibodies (1). Therefore, in order to provide guidance to all patients and clinicians, the use of specific reference ranges and cut-off values also has important practical implications, although there may be some bias.

CONCLUSION

The results of this meta-analysis indicate that subclinical hypothyroidism in pregnancy is associated with an increased risk of developing HDP, and this association exists regardless of the gestational period. However, the available evidence cannot support these patients receiving thyroxine intervention can benefit from it, so routine screening is only recommended for pregnant women with risk factors for hypothyroidism. In the future, we hope to carry out more scientific and rigorous clinical studies to clarify the relationship between subclinical hypothyroidism and HDP to improve patient prognosis.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

YH: Protocol development, Data collection or management, Data analysis, Manuscript writing and editing. JW: Manuscript writing and editing. XW: Data collection or management. LO: Data analysis, Manuscript editing. YL: Protocol development, Data analysis, Manuscript editing.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.823710/full#supplementary-material

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Effect of Levothyroxine on Pregnancy Outcomes in Pregnant Women With Hypothyroxinemia: An Interventional Study

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Context: Adverse maternal outcomes and perinatal complications are associated with maternal hypothyroidism. However, the utility of levothyroxine (L-T4) in the treatment of pregnant women with hypothyroxinemia is unclear.

Objective: This study aimed to evaluate the effects of L-T4 on maternal and perinatal outcomes in pregnant women with hypothyroxinemia.

Methods: The nonrandomized interventional study was conducted at Shanghai First Maternity and Infant Hospital, Punan Hospital of Shanghai, and Beicai Community Health Center of Shanghai. The pregnant women with hypothyroxinemia from the first trimester were enrolled and divided into treatment and control groups. 463 taking L-T4 and 501 not administering L-T4 were analyzed in the study. All participants were screened for TPOAB/TGAB antibody status.

Main Outcome: The primary outcome of the study was the hypertensive disorder of pregnancy (HDP), measured as the proportion of HDP. In addition to this primary outcome, some secondary outcomes will be measured: miscarriage, gestational diabetes mellitus, premature rupture of membranes, placental abruption, intrahepatic cholestasis of pregnancy, fetal distress, macrosomia, and neonates admitted to the neonatal intensive care unit (NICU). The effects of L-T4 on the incidence of adverse pregnancy outcomes and perinatal complications were compared.

Results: Multivariate logistic regression analysis showed that L-T4 treatment (adjusted odds ratio = 1.78 [95% CI = 1.00-3.16], $p = 0.04$) significantly reduced the incidence of miscarriage. Otherwise, lower neonates admitted to the NICU were strongly associated with the L-T4 group (adjusted odds ratio = 1.36 [95% CI = 1.01 – 1.83], p = 0.04). There were no significant differences in the incidence rates of other adverse maternal outcomes and perinatal complications between pregnant women with hypothyroxinemia receiving and those not receiving L-T4 treatment.

Conclusion: The incidence of HDP was not significantly reduced using L-T4 in pregnant women with hypothyroxinemia. The results of this study also showed that L-T4 treatment significantly reduced the miscarriages rate and the proportion of newborns admitted to the NICU.

Keywords: levothyroxine, hypothyroxinemia, hypertensive disorder of pregnancy, maternal outcomes, miscarriage

INTRODUCTION

Hypothyroxinemia is defined as a normal maternal thyroid-stimulating hormone (TSH) concentration in conjunction with a low maternal free thyroxine (FT4) concentration. Thyroid hormones are necessary for embryo growth and development (1). Hypertensive disorder of pregnancy (HDP) is a clinically challenging complication of pregnancy, which accounts for 14% of all maternal deaths (2). HDP includes chronic hypertension, pregnancy-induced hypertension, preeclampsia, chronic hypertension with preeclampsia, and eclampsia. Pregnant women with asymptomatic subclinical hypothyroidism are at risk of severe preeclampsia (3). Buimer et al. reported that women with severe HDP may have lower transient FT4 levels, without evidence of a thyroid disorder (4). Pregnant women with preeclampsia have lower FT4 levels in early pregnancy as well as when they develop preeclampsia compared to normotensive pregnant women (5). The results of a study conducted in Chinese pregnant women showed that FT4 levels were lower in preeclamptic and gestational hypertensive women than in normotensive women (6). Our group also found an increased risk of gestational hypertension in pregnant women with isolated maternal hypothyroxinemia (IMH) (the TPOAb-negative type of hypothyroxinemia (7). Furthermore, we have recently shown that hypothyroxinemia was associated with an increased risk of preeclampsia-eclampsia in women with persistent hypothyroxinemia in the first half of pregnancy (8). Therefore, low FT4 in the first trimester may be associated with the development of HDP. However, there are few studies on the effect of L-T4 treatment on the incidence of HDP. To investigate the role of L-T4 in IMH, Gong et al. conducted a prospective study that included 225 cases of IMH in the first trimester, of which 106 received L-T4 treatment and 95 did not receive L-T4 treatment, and there was no statistically significant difference in the incidence of gestational hypertension or preeclampsia between the two groups (9). However, pregnant women in this study were included from the second trimester and the sample size was small. Moreover, this study did not include a comparative study of antibody-positive patients. Therefore, it is necessary to study the therapeutic effect of L-T4 on both antibody-positive and antibody-negative pregnant women with hypothyroxinemia.

Alternatively, hypothyroxinemia is also a risk factor for some other adverse clinical outcomes. hypothyroxinemia in the first trimester is associated with a higher risk of shortening of the head and hip length of the embryos (10), increased spontaneous abortion (11), preterm birth rate (12), and increased incidence of macrosomia (9, 12). Additionally, lower levels of FT4 during pregnancy are risk factors for gestational diabetes mellitus (GDM) (6, 13). Hypothyroxinemia can adversely affect neurodevelopment in the fetus, with the offspring showing an increased risk of autism (14, 15).

Before conducting this interventional study, we first established reference ranges for FT4 and TSH using 193 healthy pregnant women according to the method recommended by the National Academy of Clinical Biochemistry (16). These pregnant women were independent and not included in our subsequent intervention study. We then recruited women with hypothyroxinemia in the first trimester and intervened to assess the impact of L-T4 treatment on adverse maternal outcomes and perinatal complications. Furthermore, for pregnant women with hypothyroxinemia, with or without TPOAb and/or thyroglobulin antibody (TgAb) as adjustment factors to analyze the effect of L-T4 intervention from the first trimester on intrauterine growth and pregnancy outcomes.

METHODS

Study Design and Ethics Approval

This nonrandomized interventional study was approved by the Ethics Committee of the Shanghai First Maternity and Infant Hospital, School of Medicine, Tongji University (Trial registration number: ChiCTR1900025560). Participants were recruited from the clinics of Shanghai First Maternity and Infant Hospital, Punan Hospital of Shanghai, and Beicai Community Health Center of Shanghai. Shanghai is in an iodine-sufficient area, and the Shanghai First Maternity and Infant Hospital is a tertiary academic medical center. Written informed consent was obtained from all the eligible participants.

Diagnosis of Hypothyroxinemia

We established a reference range for the three trimesters according to the National Academy of Clinical Biochemistry (NACB) criteria (16). We measured the levels of TSH and FT4 in 193 pregnant women. The 2.5^{th}, 5^{th}, 10^{th}, 90^{th}, 95^{th}, and 97.5^{th} percentiles of TSH and FT4 in the three trimesters are shown in **Table S1** of **Supplementary Materials**. The diagnostic criteria for hypothyroxinemia were as follows: TSH range, 2.5^{th} – 97.5^{th} percentile; and FT4 levels in the lower 5^{th} percentile of the reference range described above. Detailed method description was provided in the **Supplementary Material**.

Recruitment of Participants

The first participant enrollment started on November 1, 2019, and the final follow-up was completed on October 20, 2021, with follow-up till the postnatal period of all the participants. Routine ultrasound and blood tests for thyroid function, vitamins, liver function, lipid profile, fasting plasma glucose, blood count, and other analyses were performed in all pregnant women at the

study centers. Pregnant women with hypothyroxinemia were eligible for inclusion in the trial if they met the following criteria: (1) aged 19 - 40years; (2) less than 13 + ^{6} weeks of gestation. Exclusion criteria were as follows: (1) multiple pregnancies; (2) conception by assisted reproductive technology; (3) chronic diseases, such as hypertension, diabetes, and systemic lupus erythematosus; (4) history of thyroid diseases or taking drugs affecting thyroid hormones. All participants answered a questionnaire on demographics. All participants underwent ultrasonography at approximately 7 weeks of gestation, and the duration of pregnancy was calculated based on the date of menstruation and confirmed by ultrasonography.

Intervention and Follow-Up

Participants were informed about the study by an investigator. At the time of the initial design of this project, it was indeed designed and registered as a randomized controlled study. However, several problems were encountered in the implementation process: first, we did not finally obtain enough samples due to patient wishes and the COVID-19 pandemic, many pregnant women chose to return to their local hospital but not in Shanghai, in addition, some participants wanted to receive the L-T4 because they were fearful of the adverse effect of hypothyroxinemia on pregnancy and some participants don't bother to attend, so participants were enrolled according to their wishes but not randomized. To reduce the bias, we increased the sample size and controlled the age and gestational age of the subjects.

Participants in the intervention group orally received 25 μg L-T4 once daily, and those in the control group received no treatment. L-T4 was administered immediately after grouping. Participants were seen by the investigators every four weeks. All participants underwent thyroid function tests every 4 weeks until delivery, reporting adverse events and taking L-T4 for the next dose. L-T4 doses were titrated to maintain TSH levels in the 2.5th–97.5th percentile and FT4 levels within the 5th–97.5th percentile in different trimesters. Moreover, if the TSH level was higher than the 97.5th percentile or FT4 was lower than the 5th percentile, the dose of L-T4 was increased; when TSH level was lower than the 2.5th percentile or FT4 was higher than the 97.5th percentile, L-T4 was discontinued. Interviewers performed prenatal visits every 4 weeks to monitor medication adherence. Pregnancy outcome data were extracted from the electronic medical records. If participants in the control group developed subclinical hypothyroidism, hypothyroidism, or hyperthyroidism, an obstetrician managed them with usual care.

Statistical Analysis

Continuous variables are presented as mean (standard deviation [SD]), whereas categorical variables are presented as numbers (percentages). The *t*-test was performed to analyze normally distributed data. The chi-square test and Fisher's exact test were used to analyze categorical variables. The primary outcome was additionally analyzed by binary logistic regression. Independent variables with a p-value of < 0.05 in the univariate analysis were selected for multivariate analysis. Multivariate logistic regression analysis was performed after adjusting for possible confounders to determine significant effects on HDP and calculated as an adjusted odds ratio (95% confidence interval [CI]). The final model retained only significant predictors.

To investigate the effect of L-T4 on secondary outcomes, univariate and multivariate logistic regression analyses were performed to examine the association of independent variables with outcome variables. TPOAB/TGAB positive or not was used as a controlling factor in all the multivariate logistic regression analyses. In addition, age was used as an adjustment factor for miscarriage; age, history of family HBP was used as an adjustment factor for HDP; BMI and history of family HBP were used as an adjustment factor for GDM; GBS positive or not was used as an adjustment factor for premature rupture of membranes (PROM); the uterine scar was used as an adjusted factor for cesarean section.

All statistical analyses were performed using R statistical software v4.0 (package stats). Two-tailed *p*-values < 0.05 were considered statistically significant.

RESULTS

Characteristics of Hypothyroxinemia Participants

A total of 38,215 women were screened, and 964 pregnant women who met the eligibility criteria were included in this study (**Figure 1**). Of these, 463 were assigned to the L-T4 group (intervention group) and 501 to the control group. The gestational weeks of pregnant women in the intervention and control groups were 57.88 days, and 58.78 days (**Table 1**), respectively. The demographic characteristics of the two groups are shown in **Table 1**. There were significant differences in TPOAB/TGAB positive, family history of hypertension, and diastolic pressure at the first prenatal care between the intervention and control groups ($p < 0.05$).

Analysis of Risk Factors of HDP

L-T4 treatment did not reduce the incidence of HDP. Logistic regression was further used to predict factors associated with HDP. Independent variables with $p < 0.05$, in univariate analysis, were selected for multivariate analysis. After controlling for these factors, multivariate logistic regression analysis showed that family history of hypertension (adjusted odds ratio = 2.85 [95% CI = 1.37–6.0], $p = 0.005$) and pre-pregnancy BMI (adjusted odds ratio = 1.23 [95% CI = 1.11–1.37], $p < 0.001$) had significant effects on the incidence of HDP (**Table S2**).

Analysis of Miscarriages

There were 19 cases of miscarriages in the L-T4 group and 36 cases in the control group. There was a significant difference in the number of miscarriages between the two groups (*p*- value = 0.04). After controlling for TPOAB/TGAB positive or not and age, multivariate logistic regression analysis showed that L-T4 treatment (adjusted odds ratio = 1.78 [95% CI = 1.00–3.16], $p = 0.04$) significantly reduced the incidence of miscarriage (**Table 2**).

Comparison of Incidence in Other Adverse Pregnancy Outcomes

The rates of adverse maternal outcomes and perinatal complications, including GDM, PROM, intrahepatic

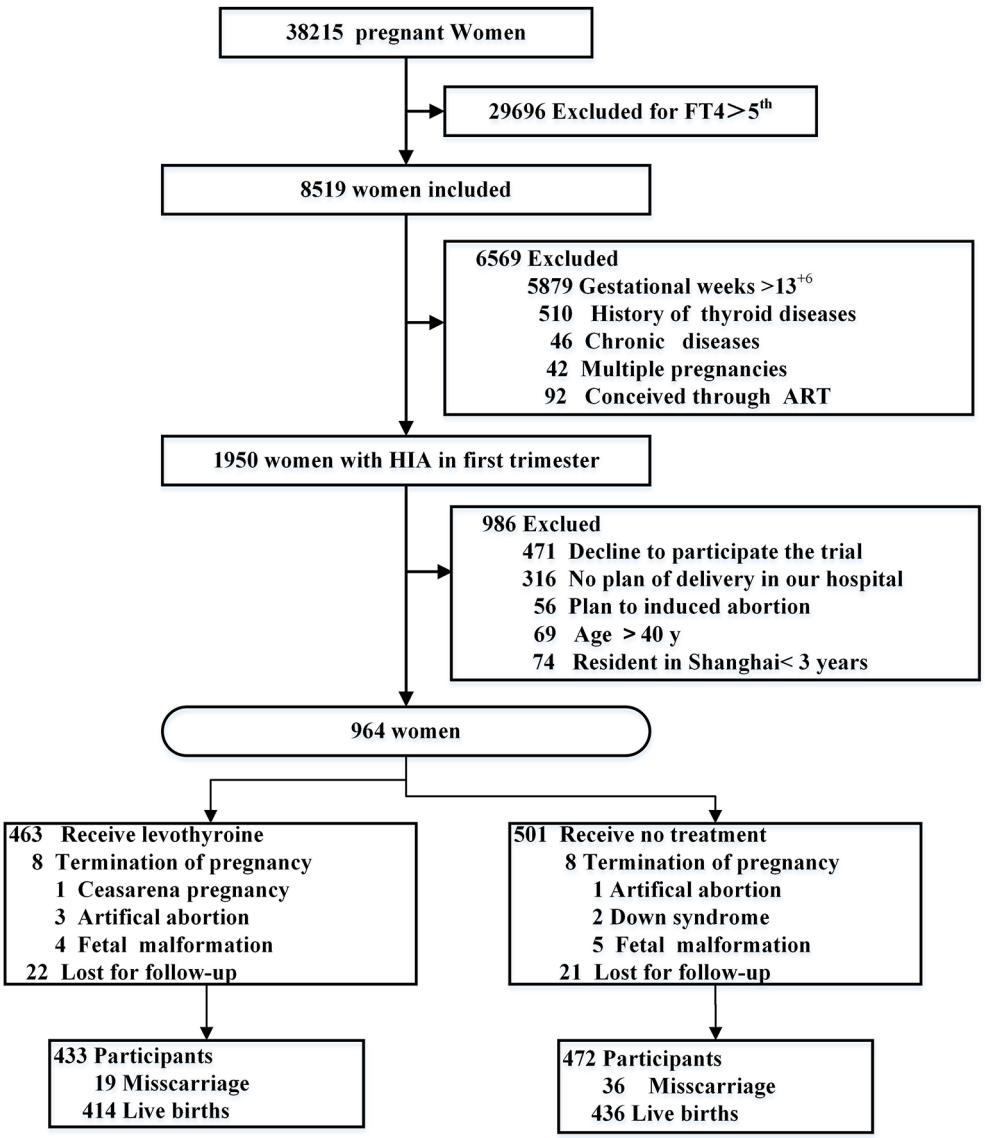

FIGURE 1 | Flowchart of the study population.

cholestasis, placenta praevia, placental abruption, intrauterine growth retardation, premature delivery, cesarean section, breech delivery, group B streptococcus infection, fetal distress, macrosomia, small for gestation age, postpartum hemorrhage, Apgar score at 1 min ≤7, neonates admitted to neonatal intensive care unit (NICU), were analyzed in the intervention and control groups. Since there were significant differences in the levels of autoantibodies between the intervention and control groups, and thus, we performed logistic regression analysis with TPOAB/TGAB positive or not as controlling factors. Controlling for the effect of TPOAB/TGAB positive or not, lower neonates admitted to the NICU were strongly associated with the L-T4 group (adjusted odds ratio = 1.36 [95% CI = 1.01-1.83], p = 0.04). There was no significant difference in the incidence rate of other adverse pregnancy outcomes between the intervention and control groups ($p > 0.05$, **Table 2**).

DISCUSSION

This interventional study showed that controlling for TPOAB/TGAB positivity or not, L-T4 treatment in the first trimester significantly reduced the miscarriage rate of hypothyroxinemia pregnant women and reduced the proportion of newborns admitted to the NICU. There were no significant differences in the incidence of other adverse maternal outcomes and perinatal complications between hypothyroxinemia pregnant women with

TABLE 1 | Demographic characteristics of pregnant women with hypothyroxinemia.

	NoL-T4 N=501	L-T4 N=463	*P* value
Duration of pregnancy at enrollment (day)	57.88 ± 12.20	58.78 ± 10.08	0.22
TPOAB or TGAB	121 (24.2%)	155 (33.5%)	0.01
Age (year)	30.48 ± 3.89	30.31 ± 3.84	0.64
History of term delivery	139 (27.7%)	135 (29.2%)	0.63
History of spontaneous abortion	73 (14.6%)	51 (11.0)	0.10
History of induced abortion	113 (22.6%)	106 (22.9)	0.90
Family history of hypertension	112 (22.4%)	131 (28.3)	0.03
Family history of diabetes	37 (7.4%)	38 (8.2%)	0.63
Systolic pressure at the first prenatal care	105.41 ± 23.02	106 ± 18.25	0.30
Diastolic pressure at the first prenatal care	66.51 ± 15.80	66.77 ± 12.79	0.01
Pre-pregnancy BMI (kg/m^2)	21.44 ± 2.68	21.60 ± 302	0.78
Uterine scar	64 (12.8%)	59 (12.7%)	0.99

501 subjects did not treat with L-T4 and 463 subjects treated with L-T4 are presented in this table. For continuous variables, mean ± standard deviation (SD) are presented; for categorical variables, absolute numbers and percentage of the total are presented. Systolic and diastolic blood pressure at first prenatal care. TPOAB, thyroid peroxidase antibody; TGAB, thyroglobulin antibody.

TABLE 2 | Adverse Pregnancy outcomes among pregnant women with hypothyroxinemia in the levothyroxine (L-T4) treatment group or controls.

	NoL-T4 N=501	L-T4 N=463	Unadjusted			Adjusted model		
	n (%)	n (%)	cOR	95%CI	p value	aOR	95%CI	p value
Miscarriage	36 (7.2)	19 (4.1)	1.81	1.02-3.20	0.04	1.78	1.00-3.16	0.04*
Hypertension disorder of pregnancy	16 (3.2)	24 (5.2)	0.61	0.32-1.15	0.13	0.63	0.32-1.21	0.16
Gestational diabetes mellitus	49 (9.8)	59 (12.7)	0.74	0.50-1.11	0.15	0.76	0.46-1.24	0.27
Premature rupture of membranes	78 (15.6)	82 (17.7)	0.86	0.61-1.20	0.37	0.86	0.61-1.22	0.41
Intrahepatic Cholestasis	6 (1.2)	6 (1.3)	0.92	0.30-2.88	0.89	0.98	0.31-3.09	0.97
Placenta praevia	16 (3.2)	12 (2.6)	1.24	0.58-2.65	0.58	1.20	0.56-2.58	0.64
Placental abruption	3 (0.6)	1 (0.2)	2.78	0.29-26.85	0.38	3.12	0.32-30.43	0.33
Intrauterine growth retardation	6 (1.6)	4 (0.9)	1.39	0.39-4.96	0.61	1.41	0.39-5.05	0.60
Premature delivery	21 (4.2)	20 (4.3)	0.97	0.52-1.81	0.92	0.87	1.06-1.99	0.87
Cesarean section	208 (41.5)	174 (37.6)	0.80	0.61-1.04	0.10	0.75	0.55-1.01	0.06
Breech delivery	17 (3.4)	10 (2.2)	1.59	0.72-3.51	0.25	1.67	0.75-3.69	0.21
Group B streptococcus infection*	22 (4.4)	27 (5.8)	0.74	0.42-1.32	0.31	0.68	0.38-1.22	0.20
Fetal distress*	34 (7.8)	23 (5.6)	1.44	0.83-2.49	0.19	1.40	0.81-2.44	0.23
Macrosomia*	25 (5.7)	33 (8.0)	0.70	0.41-1.20	0.20	0.72	0.42-1.24	0.23
Small for gestation age*	43 (9.9)	34 (8.2)	1.22	0.76-1.96	0.40	1.23	0.77-1.98	0.39
Postpartum hemorrhage*	9 (2.1)	13 (3.1)	0.65	0.28-1.54	0.33	0.71	0.30-1.69	0.43
Apgar score at 1 min ≤ 7*	4 (0.9)	2 (0.5)	1.91	0.35-10.47	0.46	2.39	0.43-13.34	0.32
Neonates admitted to NICU*	148 (33.9)	114 (27.5)	1.35	1.01-1.81	0.04	1.36	1.01-1.83	0.04*
Prematurity[#]	9 (1.8)	14 (3.0)						
Fetal distress[#]	50 (10.0)	21 (4.5)						
Infection suspected or confirmed[#]	75 (15.0)	60 (13.0)						
Other[#]	14 (2.8)	19 (4.1)						

*cOR, crude odds ratio; CI, confidence interval; aOR, adjusted odds ratio; NICU, neonatal intensive care unit. *L-T4 n = 414 NoL-T4 n = 436. TPOAB/TGAB positive or not was used as a controlling factor in all the multivariate logistic regression analyses. In addition, age was used as an adjustment factor for miscarriage; age, history of family HBP was used as an adjustment factor for HDP; BMI and history of family HBP were used as an adjustment factor for GDM; GBS positive or not was used as an adjustment factor for premature rupture of membranes (PROM); the uterine scar was used as an adjusted factor for cesarean section. [#]Reasons for admission to the NICU.*

and without L-T4 treatment. Additionally, as TSH and FT4 levels vary significantly in different populations, an accurate assessment of maternal thyroid function during pregnancy remains difficult; thus, the use of population-based, trimester-specific reference ranges is the best approach to address this problem (17). Therefore, we established a reference for levels of TSH and FT4 in the three trimesters that ensured the reliability of the results of this study.

Gong et al. conducted a prospective study with 225 cases of IMH in the first trimester and found no difference in the occurrence of HDP between women treated with L-T4 (n = 106) and those not treated with L-T4 (n = 95) (9). The sample size in our study was larger, which allowed us to observe differences in spontaneous abortion and NICU in pregnancy outcomes. Moreover, the pregnant women in our study were included from the first trimester (about 58 days on average)

rather than the second trimester. Starting the study in the first trimester was more conducive to our investigation of the effect of L-T4 on spontaneous abortion. Hypothyroidism with clinical symptoms is known to increase the risk of HDP, and several studies have also found low FT4 levels in pregnant women with HDP (3, 4, 6). A previous study by our group found an increased risk of HDP (OR = 2.66; 95% CI: 1.38–5.10) in pregnant women with IMH (7). In this study, we found that L-T4 treatment failed to significantly reduce the incidence of HDP. The possible reason is that L-T4 supplementation alone is not sufficient for improvement, as the causes of HDP development are complex (18).

Normal pregnant women generally have decreased TSH levels and increased FT4 levels due to the effect of human chorionic gonadotropin (hCG) in the first trimester; whereas patients with thyroid disease who are positive for thyroid autoantibodies have mild thyroid dysfunction (19). Thus, levels of FT4 and TSH do not change with hCG in the first trimester (20) and may lead to hypothyroxinemia in these patients with thyroid disease. Hypothyroxinemia in early pregnancy, especially in those with positive thyroid autoantibodies, may persist into the third trimester and adversely affect the mother and child. We also considered the therapeutic effect of LT4 on TPOAb/TgAb-positive and TPOAb/TgAb-negative pregnant women with hypothyroxinemia in the first trimester. We found no significant difference in the incidence of adverse pregnancy outcomes between the intervention and control groups (**Table 2**). A few clinical trials have shown that levothyroxine therapy reduces the incidence of miscarriage and/or preterm birth in TPOAb-positive pregnant women (21, 22). However, subsequent large-scale, multicenter, randomized controlled trials have shown that L-T4 treatment, in comparison to no L-T4 treatment, does not improve maternal and fetal outcomes in pregnant women with TPOAb-positive, subclinical hypothyroidism, or isolated hypothyroidism (23, 24). The findings of the present study are also consistent with the results of two recent systematic reviews of TPOAb-positive women (25, 26). Two randomized controlled trials investigated the effects of screening and treatment of hypothyroxinemia in pregnancy. In a randomized trial (27), antenatal screening and maternal treatment for hypothyroidism did not result in improved cognitive function in children at 3 years of age. Another study (28) that included subclinical hypothyroidism or hypothyroxinemia during pregnancy found no significant differences in pregnancy outcomes or incidence of adverse events. We supplemented these studies in the manuscript and made a discussion. It should be mentioned that the time at a median gestational age of 12.5 weeks was included in the study by John H. Lazaru et al. (27), while 16.7 weeks of gestation in the study by Casey B M et al. was (28). Early thyroid function plays an important role in fetal and pregnancy outcomes. Therefore, it remains unknown whether intervention in the first trimester will have a significant impact on fetal development and pregnancy outcome.

In this study, we found that L-T4 treatment of hypothyroxinemia in early pregnancy can reduce the occurrence of miscarriage. The fetus is completely dependent on maternal thyroid hormone during early pregnancy, a critical period of vulnerability to abortion. Thus, the results of this study suggested that L-T4 supplementation in early pregnancy may be associated with a reduction in the rate of miscarriage. Alternatively, the fetus's critical neurological development occurs in the first trimester, so L-T4 supplementation in early pregnancy may be responsible for reducing neonatal admission to the NICU. Few studies have been conducted on whether L-T4 can reduce spontaneous abortion in the hypothyroxinemia population, mainly due to the late intervention. In a controlled antenatal thyroid screening study, patients were screened at 12 weeks of gestation, and the study subjects were around 8 weeks of gestation, so the outcome of abortion could be observed (29). Therefore, it may be important for the starting time of the intervention for pregnant women with hypothyroxinemia (30). Our findings further support this notion.

This study has some limitations. First, it was conducted in Shanghai, China, and thus, the results must be extrapolated with caution. Second, this study is only an intervention study, and we did not perform neonatal childhood follow-up. Third, the baseline was different between the two groups, although we performed multivariate analysis to control for the effect of confounding factors. The study also had some advantages. First, we established reference levels for TSH and FT4 in the three trimesters and focused on the therapeutic effect of L-T4 on pregnant women with hypothyroxinemia from the first trimester. Second, we considered patients with positive and negative thyroid autoantibody status. Third, the timing of the intervention in this study was in the first trimester (9 weeks), allowing us to better examine the therapeutic effect of L-T4.

In conclusion, this interventional study found no benefit of L-T4 treatment on pregnancy HDP outcomes in pregnant women with hypothyroxinemia in the first trimester. Administration of L-T4 therapy to pregnant women with hypothyroxinemia can significantly reduce the rate of miscarriage and neonatal admission to the NICU. Our results implied that the intervention time of L-T4 may have a significant impact on treatment outcomes, and further multicenter randomized controlled study is needed to investigate the value of L-T4 treatment in the first trimester.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Shanghai First Maternity and Infant Hospital, School of Medicine, Tongji University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

QD and GL proposed and designed the study. YL, SH, and XL collected data. XS performed the statistical analysis work, including the sample size calculation. GL and XS analyzed and interpreted data. GL drafted the manuscript. QD reviewed and edited the manuscript. QD provided administrative support and funding acquisition; All authors read, revised, and approved the final draft.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.874975/full#supplementary-material

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Association of Mild Thyroid Dysfunction and Adverse Prognosis Among Chinese Patients With Acute ST Segment Elevation Myocardial Infarction

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Aims: Thyroid hormones widely affect the cardiovascular system, but the effects of mild thyroid dysfunction on the clinical prognosis of patients with acute ST segment elevation myocardial infarction (STEMI) remains unclear. Our aims were to analyze the relations between mild thyroid dysfunction at admission and clinical outcomes in Chinese patients with STEMI.

Methods: A total of 1,176 STEMI patients with the available data of thyroid function and follow-up were analyzed, including 348 patients with mild thyroid dysfunction [subclinical hypothyroidism (n=81), hyperthyroidism (SHyper) (n=51), and low triiodothyronine syndrome (LT3S) (n=216)] and 828 patients with euthyroid function. During a median 4.4-year follow-up, in-hospital mortality, cardiac and all-cause mortalities were subsequently compared among the four groups.

Results: Compared with the euthyroid group, STEMI patients in the SHyper and LT3S groups faced obviously increased risks of in-hospital death [odds ratio (OR): 5.007, 95% confidence interval (CI): 1.246–20.124, p = 0.023 and OR: 2.491, 95% CI: 1.054–5.887, p = 0.037, respectively) even after adjustment for various confounding factors. During a median 4.4-year follow-up, STEMI patients with LT3S at baseline had higher cardiovascular mortality [hazard ratio (HR): 1.880, 95% CI: 1.178–2.998, p = 0.008] and all-cause mortality HR: 1.647, 95% CI: 1.072–2.531, p = 0.023] than those with euthyroid at baseline, whereas no significantly increased mortality was found for STEMI patients with SCH and SHyper at baseline.

Conclusions: STEMI patients with SHyper at admission had increased risk of in-hospital mortality, and STEMI patients with LT3S at baseline had worse prognosis and higher incidences of in-hospital mortality and cardiovascular and all-cause deaths compared with euthyroid patients.

Keywords: mild thyroid dysfunction, subclinical hypothyroidism, subclinical hyperthyroidism, low T3 syndrome, acute myocardial infarction, ST segment elevation myocardial infarction

INTRODUCTION

Acute myocardial infarction (AMI) is caused by a variety of factors and remains at a high rate of mortality, even though great progresses are made in pharmacotherapy and myocardial reperfusion (1, 2). In the neuroendocrine systems, thyroid hormones play fundamental roles in cardiovascular homeostasis by regulating the heart rate, cardiac contractility, and arterial peripheral resistance. Several observational studies have also shown that mild thyroid dysfunction, including subclinical hypothyroidism (SCH), subclinical hyperthyroidism (SHyper), and low T3 syndrome (LT3S), is quite common in AMI patients (3, 4). Recently, the harmful effects of overt thyroid dysfunctions on the cardiovascular system have been well established in both the general populations and cardiac patients (5, 6). However, conclusions on the associations of mild thyroid dysfunction and adverse outcomes are still controversial and related studies mainly focus on heterogeneous patients with various cardiac diseases. For example, some studies discovered that SCH/SHyper were related with higher risks of coronary heart disease (CHD) and mortality (7, 8), while others found that SCH/SHyper did not cause adverse cardiovascular outcomes (9, 10). In addition, the impacts of mild thyroid dysfunction on the mortality of AMI patients also remain unclear.

Furthermore, the studies regarding the influences of mild thyroid dysfunction on the poor prognosis in Chinese patients suffering from AMI are also extremely limited. One of our aims was to compare and assess the effects of mild thyroid dysfunction on cardiac function and in-hospital mortality in Chinese patients with acute ST segment elevation myocardial infarction (STEMI). Moreover, we also explored and evaluated the impacts of mild thyroid dysfunctional states at baseline on the cardiovascular and all-cause mortality rates during a median follow-up period of 4.4 years.

MATERIALS AND METHODS

Study Population

A total of 1,847 Chinese AMI patients who were admitted to the Department of Cardiology in Shanghai Jiao Tong University Affiliated Sixth People's Hospital during the period from September 2007 to September 2014 were enrolled in the present study. Among them, 671 candidates were successively eliminated due to the following reasons: (1) patients with non-ST-elevation AMI (NSTEMI) (n=95); (2) known or clinically thyroid disorders (n=76); (3) current or previous treatment with thyroid hormone supplementation, antithyroid medications, corticosteroids, dopamine, dobutamine, amiodarone or lithium (n=52); (4) thyroid indicators were obtained after coronary angiography or CTA (n=239); (5) unable to complete coronary examination due to end-stage diseases (n=83);and (6) a lack of clinical data or loss of follow-up (n=126). Ultimately, 1,176 participants took part in this analysis and then they were divided into four groups including euthyroidism, SCH, SHyper, and LT3S according to their thyroid hormone values. During a median 4.4-year follow-up, we subsequently made comparisons on in-hospital mortality, cardiac and all-cause mortalities among the four groups. Our study was approved by the ethics committee of the Shanghai Jiao Tong University Affiliated Sixth People's Hospital, and all participants signed written informed consent forms.

Physical Examination and Laboratory Measurements

The physical and laboratory examinations in this study were collected by well-trained physicians. Briefly, height, weight, blood pressure, and heart rate (HR) were recorded and detailed information on the history of diabetes, hypertension, alcohol use, and smoking habits was collected through a standard interview when the patients entered into the Department of Cardiology. Body mass index (BMI) was obtained as weight divided by the square of height. Thyroid profile including free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH), and other blood indicators such as white blood cell (WBC), hemoglobin, C-reactive protein (CRP), serum creatinine (SCr), serum albumin, total cholesterol (TC), total triglyceride (TTG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting plasma glucose (FPG), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and troponin I (TnI) were obtained from blood samplings after an overnight fast within 24 h after admission and prior to coronary angiography or CTA. The thyroid function profile was gathered using a chemiluminescence technique (Cobas 6000; Roche Diagnostics GmbH, Mannheim, Germany). The estimated glomerular filtration rate (eGFR) was obtained by the simplified MDRD formula: $eGFR = 186.3 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203}$ ($\times$ 0.742 if woman) (11).

Coronary Artery Examination and Follow-Up

All patients underwent coronary angiography or CTA to make a definitive diagnosis, and the culprit vessels were treated by oral medications, percutaneous coronary intervention, or coronary artery bypass graft (1, 12). The echocardiography was performed by experienced ultrasonographers, and left ventricular ejection fraction (LVEF) was recorded *via* an Acuson Sequoia 512 scanner with a probe of 5-13-MHz following a standard protocol. The data regarding Killip class, revascularization (percutaneous coronary intervention or coronary artery bypass graft), medications at discharge, and in-hospital deaths were obtained from their discharge summaries. After the discharge from hospital, a regular clinical follow-up was conducted through telephone or office visits annually.

Diagnostic Criteria and Outcomes

AMI was diagnosed when chest pain for more than 30 min with dynamic 12-lead electrocardiogram (ECG) changes or elevated troponin enzymes and STEMI were defined as AMI accompanied by ST segment elevation in ≥2 contiguous ECG leads according to the ACC/AHA guidelines (1). Severe acute

heart failure was regarded as Killip class > II (13). The reference ranges of thyroid function in our hospital were as follows: FT3 3.1–6.8 pmol/L, FT4 12.0–22.0 pmol/L, and TSH 0.27–4.20 mIU/l, respectively. Euthyroidism was identified as the levels of TSH, FT4, and FT3 within their respective reference ranges. SCH was determined by a TSH level above 4.20 mIU/l with a normal FT4 level. SHyper was regarded as TSH < 0.27 mIU/l with normal FT3 and FT4 levels. LT3S was defined when FT3 < 3.1 pmol/L with normal TSH and FT4 levels.

Accidental death was excluded, and all deaths were caused by any natural factor. Cardiovascular death was defined as the mortality attributable to myocardial infarction, cardiogenic shock, significant arrhythmia, progressive heart failure, or pulmonary embolism without a precipitating factor. Sudden unexpected death outside the hospital was regarded as a cardiac death, and no autopsy was performed. In-hospital deaths were not included into all-cause mortality and cardiovascular death. All events were identified and sorted by two cardiologists. We calculated the survival times from the date of the STEMI to the date of death.

Statistical Analyses

Data were analyzed by SPSS 19.0 software. Firstly, normality was checked for continuous variables by Q-Q plots. Normally distributed variables were expressed as mean ± standard deviation and were compared using one-way ANOVA with LSD, whereas unevenly distributed variables were represented as median with interquartile range (IQR) and were compared by the Kruskal–Wallis test. Secondly, categorical variables were expressed as absolute numbers (percentages) and were compared by the $\chi 2$ test. Thirdly, three binary logistic regression models were used to assess the association of mild thyroid dysfunction and in-hospital mortality: a non-adjusted model; an age- and sex-adjusted model; and a multivariable model that included all variables with p-value < 0.05 from the univariate analyses through the forward stepwise procedure. The results were expressed as odds ratios (ORs) with associated 95% confidence intervals (CIs). Fourthly, the univariate, age-, and sex-adjusted and multivariate Cox regression analyses were performed to analyze the effects of mild thyroid dysfunction states on cardiovascular and all-cause mortality. All baseline variables with p-value <0.05 in univariate analyses were entered into the multivariate Cox regression analysis and analyzed by forward stepwise regression. Results were reported as hazard ratios (HRs) with associated 95% CIs. The cumulative survival rates were described by Kaplan–Meier curves and were compared between groups by the log rank test based on the euthyroid group as the reference group. P < 0.05 was considered as statistically significant.

RESULTS

Baseline Characteristics of Studied Subjects

Of the 1,176 participants analyzed, 828 patients (70.4%) were euthyroid, 81 patients (6.9%) had SCH, 51 patients (4.3%) had SHyper, and 216 patients (18.4%) had LT3S. The baseline demographic and clinical characteristics of these four groups are displayed in **Table 1**. Individuals in the SCH and LT3S groups tended to be older and women and had lower LDL-C, hemoglobin and eGFR and less smoking and revascularization, as well as higher SCr and CRP compared with the euthyroid and SHyper groups. In addition, the prevalence of diabetes mellitus and hypertension, BMI, SBP, DBP, HR, FT3, TSH, FPG, serum albumin, WBC, and discharge medical therapy (angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, diuretics) were also significantly different among the four groups (all p < 0.05).

Comparison of Myocardial Injury and Cardiac Dysfunction Among the Four Groups at Baseline

A comparison of myocardial injury and cardiac dysfunction among the four groups is shown in **Figure 1**. Compared with the subjects in the euthyroid group, the value of TnI for STEMI patients in the SHyper and LT3S groups was significantly higher (11.50 [IQR 6.73-19.68] ug/L and 15.43 [IQR 7.28-34.30] ug/L versus 7.04 [IQR 2.93-16.89] ug/L, respectively) (**Figure 1A**). The LVEF for STEMI patients in the SCH, SHyper, and LT3S groups was remarkably lower than that in the euthyroid group (54 [IQR 48-59] %, 54 [IQR 49-58] %, and 50 [IQR 42-59] % vs. 57 [IQR 50-61] %, respectively) (**Figure 1B**). The percentage of Killip class > II for STEMI patients in the SCH and LT3S groups was also obviously higher than that in the euthyroid group (35.8% and 25% vs. 17.1%) (**Figure 1D**). In addition, only participants in the LT3S group had obviously higher levels of NT-proBNP (1091 [IQR 400-2,600]ng/L vs. 483.25 [IQR 169.9-1,371]ng/L, respectively) compared with those in euthyroid group (**Figure 1C**).

Comparison of Mortality Rate Among the Four Groups

The comparison of mortality rate among the four groups is displayed in **Figure 2**. Compared with the subjects in the euthyroid group, the STEMI patients in SCH, SHyper, and LT3S groups successively had significantly higher in-hospital mortality rate (7.4%, 9.8%, and 14.4% vs. 3%, respectively) (**Figure 2A**). During a median follow-up period of 4.4 (IQR2-6.1) years, 186 deaths occurred and 114 of them were caused by cardiovascular events. Compared to the euthyroid group, STEMI patients in the LT3S group at baseline had remarkably higher cardiovascular and all-cause mortality rates (18.9% vs. 8.8%, and 28.6% vs. 14.3%, respectively), whereas those STEMI patients in the SCH and SHyper groups at baseline did not exhibit significant discrepancies on the long-term mortality rate (**Figures 2B, C**).

Association of Mild Thyroid Dysfunction and Short- and Long-Term Mortality Risks

Table 2 presents the comparison of in-hospital mortality among mild thyroid dysfunction *via* binary logistic regression analyses. The SCH group exhibited a remarkably higher risk of in-hospital death than the euthyroid group in the non-adjusted model, but the significant association disappeared after adding other

TABLE 1 | Baseline characteristics of study population by mild thyroid dysfunctional states.

Variables	Euthyroid (n=828)	SCH group (n=81)	SHyper group (n=51)	LT3S group(n=216)	p-value
[a]Age (years)	70 (57-78)	76 (69-82)	63 (54-73)	76 (66-82)	<0.001
Male (n,%)	573 (69.2%)	42 (51.9%)	44 (86.3%)	130 (60.2%)	<0.001
Diabetes mellitus (n,%)	244 (29.5%)	27 (33.3%)	4 (7.8%)	83 (38.4%)	<0.001
Hypertension (n,%)	533 (64.4%)	53 (65.4%)	18 (35.3%)	141 (65.3%)	<0.001
Prior PCI or CABG (n,%)	24 (2.9%)	1 (1.2%)	2 (3.9%)	5 (2.3%)	0.756
Smoking (n,%)	505 (61%)	35 (43.2%)	39 (76.5%)	120 (55.6%)	0.001
Alcohol (n,%)	48 (5.8%)	3 (3.7%)	3 (5.9%)	8 (3.7%)	0.571
BMI (kg/m^2)	24.10 ± 2.19	23.52 ± 2.60	23.93 ± 1.49	23.41 ± 2.54	<0.001
Vital signs and laboratory tests at admission					
SBP (mmHg)	130 ± 22	130 ± 23	119 ± 19	125 ± 25	0.002
DBP (mmHg)	75 ± 13	73 ± 13	72 ± 13	71 ± 14	0.005
[a]HR (beats/min)	75 (60-82)	82 (65-89)	83 (62-92)	80 (61-89)	<0.001
[a]FT3 (pmol/L)	3.92 (3.60-4.37)	3.80 (3.35-4.18)	3.80 (3.50-4.10)	2.70 (2.36-2.90)	<0.001
FT4 (pmol/L)	16.07 ± 2.27	16.05 ± 2.40	15.78 ± 2.30	15.81 ± 2.36	0.429
[a]TSH (mIU/L)	1.32 (0.78-2.04)	5.53 (4.66-6.89)	0.21 (0.15-0.23)	1.11 (0.61-1.82)	<0.001
[a]FPG (mmol/L)	5.99 (5.28-7.48)	6.35 (5.39-7.84)	6.54 (5.71-7.78)	6.69 (5.60-8.76)	0.001
TC (mmol/L)	4.55 ± 1.15	4.26 ± 1.10	4.64 ± 1.27	4.43 ± 1.19	0.111
TTG (mmol/L)	1.51 ± 0.89	1.55 ± 0.83	1.42 ± 0.53	1.34 ± 0.99	0.095
HDL-C (mmol/L)	1.13 ± 0.24	1.05 ± 0.30	1.10 ± 0.32	1.08 ± 0.28	0.861
LDL-C (mmol/L)	2.96 ± 1.03	2.67 ± 0.96	3.13 ± 1.11	2.78 ± 1.00	0.011
[a]SCr (μmol/L)	83 (69-101)	99 (75-130)	83 (72-93)	98 (75-136)	<0.001
eGFR ($ml/min/1.73\ m^2$)	76.78 ± 33.79	60.93 ± 29.12	82.97 ± 32.72	61.31 ± 30.97	<0.001
Serum albumin (g/L)	41 ± 6	40 ± 5	40 ± 4	38 ± 6	<0.001
[a]WBC ($\times 10^9$/L)	7.8 (6.1-10.2)	7.2 (5.6-9.1)	8.4 (6.5-11.9)	9.4 (6.8-12.5)	<0.001
[a]Hemoglobin (g/L)	139 (126-143)	123 (115-138)	141 (136-143)	126 (114-133)	<0.001
[a]CRP (mg/L)	3.4 (1.8-7.2)	4.9 (2.6-12.4)	3.4 (2.8-20.7)	11.6 (5.8-29.7)	<0.001
Revascularization (n,%)	587 (70.9%)	43 (53.1%)	42 (82.4%)	119 (55.1%)	<0.001
Discharge medical therapy					
Aspirin (n,%)	801 (99.9%)	75 (100%)	46 (100%)	185 (100%)	0.858
Clopidogrel/Ticagrelor (n,%)	796 (99.1%)	75 (100%)	46 (100%)	185 (100%)	0.443
Statin (n,%)	799 (99.5%)	75 (100%)	46 (100%)	185 (100%)	0.675
β-receptor blocker (n,%)	471 (58.7%)	54 (72%)	27 (58.7%)	110 (59.5%)	0.173
ACEI/ARB (n,%)	413 (51.4%)	31 (41.3%)	30 (65.2%)	104 (56.2%)	0.034
Diuretic (n,%)	564 (70.2%)	45 (60%)	38 (82.6%)	147 (79.5%)	0.002

PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; FPG, fasting plasma glucose; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TTG, total Triglyceride; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; WBC, white blood cell; CRP, C-reactive protein; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Continuous variables were expressed as mean ± standard deviation or median with interquartile range, while categorical variables were expressed as percentages.

[a]Non-normal distribution of continuous variables.

confounders. Additionally, given the euthyroid group as a reference, the SHyper group and LT3S group showed an obviously increased risk for in-hospital death (OR: 5.007, 95% CI: 1.246–20.124, p = 0.023 and OR: 2.491, 95%CI: 1.054 to 5.887, p = 0.037, respectively) even after adjusting for various confounding factors.

Table 3 shows the comparison of long-term cardiovascular and all-cause mortality among mild thyroid dysfunction at baseline by Cox proportional hazards analyses. After adjusting for covariates, a significantly increased risk of cardiac and all-cause mortalities was found in the LT3S group at baseline but not in the SCH or SHyper group at baseline. Accordingly, the risk of cardiovascular mortality in the LT3S state at baseline remained 1.880 folds (95%CI: 1.178–2.998; p = 0.008) and the risk of all-cause mortality in the LT3S state at baseline was still 1.647 folds (95%CI: 1.072–2.531; p = 0.023) using the euthyroid state at baseline as the reference, whereas STEMI patients in SCH and SHyper groups at baseline were not associated with increased cardiac and all-cause mortalities. The Kaplan–Meier analysis also demonstrated that the cardiovascular death-free survival and overall survival of STEMI patients in the LT3S group at baseline were obviously shorter than those in the euthyroid group at baseline (**Figure 3**).

DISCUSSION

In this prospective, single-center observational study, the impacts of mild thyroid dysfunction on in-hospital mortality, long-term cardiovascular and all-cause mortality were assessed in Chinese STEMI patients. Our results demonstrated that the STEMI patients with SHyper and LT3S faced a remarkably increased risk of in-hospital mortality in relation to euthyroid patients. During a long (median 4.4-year) follow-up, we found that LT3S at baseline was still associated with worse cardiovascular and all-cause mortality while SCH or SHyper at baseline did not affect the long-term prognosis of STEMI patients.

For AMI patients with SCH, the research on the associations of SCH and worse clinical outcomes was quite limited, although

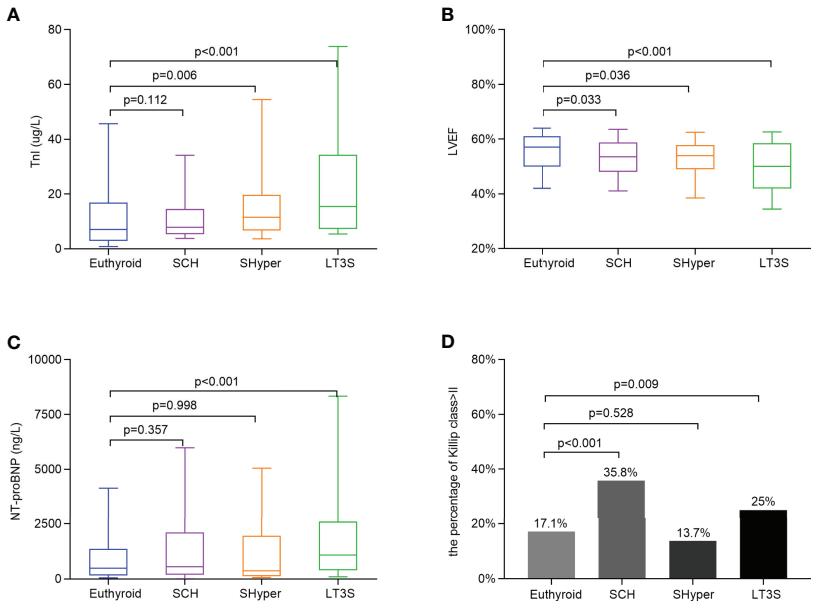

FIGURE 1 | Comparison of myocardial injury and cardiac dysfunction by mild thyroid dysfunction status at baseline. **(A)** Comparison of the TnI levels among the four groups. **(B)** Comparison of the LVEF among the four groups. **(C)** Comparison of NT-proBNP levels among the four groups. **(D)** Comparison of the percentage of Killip class > II among the four groups. Data are shown as the median with 10th and 90th percentiles.

several observational studies suggested that elevated TSH beyond the normal range was a reliable marker for adverse outcome in AMI patients. For example, Zhu et al. (14) reported that increased TSH above the reference range was related to worse long-term prognosis and TSH > 3.5 mIU/L worked as an independent predictor for worse 2.5-year mortality in STEMI patients. Soeiro et al. (15) also found that acute coronary syndrome (ACS) patients with TSH > 4 mIU/L at admission had lower LVEF and faced more major adverse cardiac events but not mortality than those patients with TSH ≤ 4 mIU/L during hospitalization. However, both two studies above did not consider T3 and T4 when grouping and the elevated TSH group would have been divided into SCH and overt hypothyroidism subgroups if considered. Whether SCH and overt hypothyroidism alone are a risk factor for worse clinical outcomes in AMI patients arouses more interest, and it is also worth exploring. Recently, Seo et al. (16) showed that among AMI patients, the all-cause mortality was significantly higher in the elevated TSH group than that in the normal TSH group; whereas in the subgroup analysis, the SCH group was only remarkably correlated with all-cause mortality in model 1, but no significant differences were found in other 5 models after adding other confounding factors compared with the euthyroid group. The results of another prospective cohort study also displayed that there was no association between SCH and all-cause and cardiac mortality in Chinese patients with ACS undergoing percutaneous coronary intervention (PCI) after adjustment for confounders; however, ACS included AMI and unstable angina (17). Aligned with them, our present study found that SCH patients with STEMI exhibited significantly

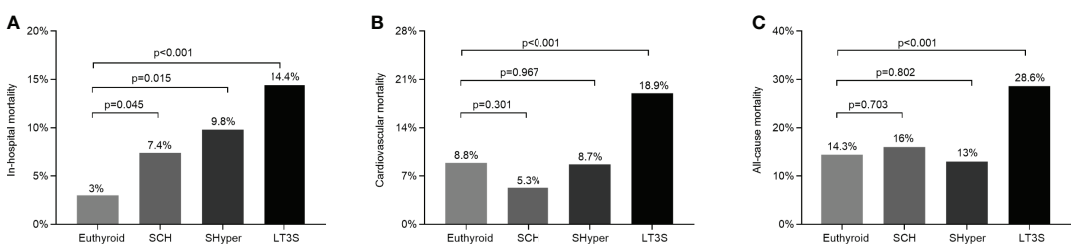

FIGURE 2 | Comparison of in-hospital, cardiovascular, and all-cause mortality by mild thyroid dysfunction status. **(A)** Comparison of in-hospital mortality among the four groups. **(B)** Comparison of cardiovascular mortality among the four groups. **(C)** Comparisons of all-cause mortality among the four groups. Cardiovascular and overall mortality did not include in-hospital mortality.

TABLE 2 | Comparison of in-hospital mortality among mild thyroid dysfunction status.

	Mortality	Univariate model			Age- and sex-adjusted model			Multivariate model*		
	n (%)	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value
Euthyroid	25 (3%)		**1 [reference]**			**1 [reference]**			**1 [reference]**	
SCH	6 (7.4%)	2.570	1.022-6.460	0.045	1.978	0.772-5.072	0.155	2.086	0.540-8.057	0.286
SHyper	5 (9.8%)	3.491	1.278-9.539	0.015	3.928	1.407-10.969	0.009	5.007	1.246-20.124	0.023
LT3S	31(14.4%)	5.382	3.104-9.334	<0.001	4.083	2.309-7.221	<0.001	2.491	1.054-5.887	0.037

**Variables with p < 0.05 in univariate analysis [age, SBP, WBC, hemoglobin, serum albumin, FPG, eGFR, LVEF, NT-proBNP, and revascularization (PCI, CABG)] were included in the multivariate model.*

NT-proBNP, N-terminal pro-B-type natriuretic peptide; LVEF, left ventricular ejection fraction.

decreased LVEF rather than any mortality in comparison with the euthyroid patients in other models after adding other confounders, although SCH had an obviously higher risk of in-hospital death in univariate analysis. The present findings regarding LVEF were also confirmed by Pingitore and colleagues on the animal models of AMI (18), which showed the administration of thyroid hormone-enhanced myocardial remodeling and improved left ventricular function.

Different from us, a retrospective observational study by Izkhakov et al. (19) in STEMI patients undergoing PCI showed that SCH patients suffered from a higher incidence of poor in-hospital outcomes and short- and long-term mortality than euthyroid patients. The different basic characteristics of patients may help to explain the discrepancy between us, that is, the SCH patients in the study of Izkhakov et al. (19) were more likely to be men and smokers, while the SCH patients in our study were inclined to be women and non-smokers. Up to now, only a few studies assessed the specific association between SCH and mortality in patients with ischemic heart diseases and concluded contradictory results. The study of Izkhakov et al. (19) and two recent studies by Zhang et al. (20) and Lee et al. (21) reported that patients who were treated with PCI faced a higher risk of cardiovascular or all-cause mortality, while our present study and a large cohort study of older patients who were treated with PCI (22) showed that no associations were found between SCH and all-cause and cardiac deaths. The systematic review and meta-analysis of prospective cohort studies may help to explain the above difference, which showed that SCH had a stronger association with cardiovascular and all-cause mortality in individuals < 65 years than people ≥ 65 years (23). Additionally, the mean age in the studies of Izkhakov et al. (19), Zhang et al. (20), and Lee et al. (21) was successively 62, 64.6, and 66.2 years while the mean age in our present study and the cohort study of older patients (22) was 76 and 70.4 years, respectively. However, given the current few studies, the results on the prognostic significance of SCH in AMI patients need to be detailed interpretations and further verifications in the future studies.

With respect to the relations of SHyper with cardiovascular and total mortality, many studies have been made but with conflicting conclusions. For example, seven meta-analyses were found to discuss this issue so far. The third of them demonstrated that patients with SHyper faced a rising risk of total mortality and CHD mortality, particularly for those with suppressed TSH levels < 0.10 mIU/L (7, 8, 24), while other four studies did not (9, 10, 25, 26). Nevertheless, there is a lack of specific data on AMI as most of the above studies were mainly made in general population. Molinaro et al. (27) firstly found that SHyper was associated with an increased risk of cardiac and overall mortality in 1,026 patients with acute cardiac diseases during a 30-month follow-up, whereas only 285 of them were caused by AMI.

TABLE 3 | Comparison of cardiovascular and all-cause mortality among mild thyroid dysfunction status.

	Mortality	Univariate model			Age- and sex-adjusted model			Multivariate model		
	n (%)	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value
Cardiovascular mortality										
Euthyroid	71 (8.8%)		**1 [reference]**			**1 [reference]**			**1 [reference][a]**	
SCH	4 (5.3%)	0.723	0.264-1.981	0.528	0.564	0.205-1.551	0.267	0.277	0.067-1.150	0.077
SHyper	4 (8.7%)	0.897	0.327-2.459	0.833	1.286	0.467-3.539	0.626	0.871	0.270-2.808	0.817
LT3S	35 (18.9%)	2.688	1.791-4.035	<0.001	2.118	1.395-3.217	<0.001	1.880	1.178-2.998	0.008
All-cause mortality										
Euthyroid	115 (14.3%)		**1 [reference]**			**1 [reference]**			**1 [reference][b]**	
SCH	12 (16%)	1.344	0.741-2.438	0.330	1.049	0.576-1.909	0.876	0.485	0.176-1.336	0.162
SHyper	6 (13%)	0.842	0.370-1.914	0.681	1.146	0.503-2.613	0.745	0.973	0.388-2.438	0.954
LT3S	53 (28.6%)	2.519	1.817-3.491	<0.001	2.006	1.437-2.800	<0.001	1.647	1.072-2.531	0.023

[a]*Variables with p < 0.05 in univariate analysis [age, smoking, WBC, Hb, TC, TG, LDL-c, eGFR, CRP, LVEF, Killip class, and revascularization (PCI, CABG)] were entered into the multivariate model for cardiovascular mortality.*

[b]*Variables with p < 0.05 in univariate analysis [age, sex, smoking, diabetes, TnTI, WBC, Hb, Alb, TC, TG, LDL-c, eGFR, CRP, NT-proBNP, LVEF, Killip class, and revascularization (PCI, CABG)] were included in the multivariate model for all-cause mortality.*

TnI, troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LVEF, left ventricular ejection fraction.

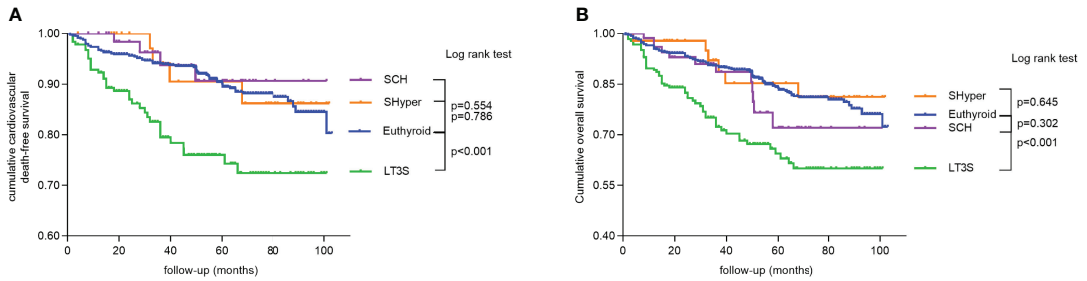

FIGURE 3 | Kaplan–Meier curves for long-term survival to demonstrate the association of mild thyroid dysfunction status with mortality. **(A)** Cumulative cardiovascular death-free survival among the four groups. **(B)** Cumulative overall survival among the four groups.

In contrast, in a recent retrospective study with a median 2.5-year follow-up, no relation was observed between the decreased TSH and poor clinical outcomes in the population of STEMI; however, studied subjects were not further stratified by FT3 or FT4 in this study (14). The ThyrAMI-1 study also showed that AMI patients in the SHyper group did not alter all-cause mortality relative to those in the euthyroid group (28). Consistent with the above studies on AMI, our current study demonstrated that the SHyper group did not correlate with the risks of cardiovascular deaths and all-cause deaths compared with the euthyroid group during a median 4.4-year follow-up in patients with STEMI; however, we also found that the SHyper group had a significantly higher in-hospital mortality than the euthyroid group. Our findings suggested that SHyper patients at the early stage of AMI may tend to face the risk of short-term worse clinical implications, which should be given additional management strategy. Further, a large scale of prospective cohorts is needed to verify these findings.

Recently, a systematic review and meta-analysis discovered that the prevalence of LT3S in heart failure (24.5%), myocardial infarction (18.9%), and acute coronary syndrome (17.1%) is quite high (29). Similar to this, the rate of LT3S in our present study was 18.4% among Chinese STEMI patients. In our study, we found that STEMI patients with LT3S had more serious myocardial injury that was diagnosed by higher TnI and more severe cardiac dysfunction that was assessed by lower LVEF and higher NT-proBNP compared with the euthyroid patients, which was in line with previous studies (30, 31) and suggested that LT3S was correlated with the severity of AMI. In addition, accumulating evidence has supported the hypothesis of the role for LT3S in the prognosis of AMI patients. For example, clinical studies in some developed countries have reported that the prognosis of AMI patients with LT3S was significantly worse than those AMI patients with euthyroid functions, independent of other risk factors (32, 33). Nevertheless, thyroid dysfunction and the occurrences of heart diseases changed with ethnicities (34, 35), and the rates of reperfusion therapy in China were lower than those in western countries (36, 37). Therefore, it is extremely important to clarify the relations between LT3S and the prognosis of Chinese AMI patients as limited studies were made in Chinese AMI patients by far. Su et al. (38) explored that patients with LT3S faced a remarkably higher in-hospital cardiovascular death rate than those without LT3S; however, long-term outcomes were not conducted in their studies. Zhang et al. (31) and Song et al. (39) discovered that independent associations existed between low fT3 levels and 30-day and 1-year all-cause deaths in Chinese AMI patients; however, the TSH and FT4 were not considered when grouping and the periods of follow-up seemed to be relatively short. In line with them, our present study further displayed that STEMI patients in the LT3S group had a remarkably higher in-hospital mortality rate and obviously higher incidences of cardiovascular and all-cause deaths during a relatively long (4.4-year) follow-up compared with the euthyroid group, which was verified by the multivariate Cox proportional hazard regression analyses. The above conclusions and our results indicated that LT3S may be a reliable marker of adverse clinical results for AMI patients and may increase the predictive power of current risk core models in the future clinical practice.

Several limitations should be mentioned. Firstly, the objects who took part in our study were STEMI and from a single center of Chinese Han population, which may confine the generalizability of our results to patients with NSTEMI and other ethnic groups. Secondly, a thyroid function test was performed only before coronary angiography or CTA without tracking follow-up, but all samples were collected in the morning to avoid a circadian variation of thyroid hormones (40). Thirdly, given the primary purpose of our study and limited number of patients with mild thyroid dysfunction in our study, we think that our results would have been more valuable if the studied objects in our study were further stratified by age or revascularization. Therefore, more multicenter studies may need to validate our findings and further evaluate whether an altered thyroid function or treatment of thyroid dysfunction could help to improve the clinical outcomes.

CONCLUSIONS

Our results suggested that SHyper may be a risk factor for in-hospital deaths in STEMI patients. Furthermore, LT3S may be considered as a prognostic indicator for poor short- and long-term mortality. The current findings indicate that a routine testing of thyroid function prior to coronary angiography or CTA should be

recommended and is highly valued to help identify and administer AMI patients at high risk of adverse events and deaths. Further studies are needed to evaluate the additional role of mild thyroid dysfunction in a prognostic algorithm of AMI severity and whether thyroid replacement therapy lowers mortality in AMI patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Shanghai Jiao Tong University Affiliated Sixth People's Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Q-MF and J-BL designed the study, revised and reviewed the manuscript. M-FL, Z-TW and SL collected clinical data and follow-up. M-FL and Z-TW worked together, performed statistical analysis and wrote the manuscript. All authors edited the manuscript and approved the final manuscript.

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SYSTEMATIC REVIEW
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The Effect of Subclinical Hypothyroidism on Coagulation and fibrinolysis: A Systematic Review and Meta-Analysis

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Background: Despite patients with thyroid dysfunction show obvious abnormal hemostatic indicators in the peripheral blood, the current research on whether and how subclinical hypothyroidism (SCH) influence hemostatic function (the coagulation and fibrinolytic system) still remains controversial.

Objective: We conducted this study to evaluate how SCH influence on the coagulation and fibrinolytic system in human body.

Methods: Prior to March 2022, Web of Science, Embase, PubMed, WanFang, CNKI data and reference lists were searched to identify eligible researches. Two of us independently extracted the data and evaluated study quality. The effect size is represented by standard mean difference (SMD). Both fixed and random-effects models were used where appropriate. Review Manager 5.3 and STATA 16.0 were used to analyze the eligible data.

Results: 1325 patients from twelve observational studies were involved in our research. Our study revealed that SCH changed the heamostatic balance towards hypercoagulable and hypofibrinolytic conditions accompanied by an increase in tissue fibrinogen, plasminogen activator and plasminogen activator inhibitor-1. By contrast, there was no statistically difference in acivated partial thromboplastin time (APTT) and D-Dimer in SCH group compared with that in control subjects.

Conclusions: Our study confirmed that SCH is related with a prothrombotic state, as reflected by changes in both coagulation and fibrinolysis. It is highly recommended for screening cardiovascular risk factors in combination with an adequate evaluation of SCH state.

Systematic Review Registration: [https://www.crd.york.ac.uk/prospero/#recordDetails] PROSPERO [CRD42021275313]

Keywords: coagulation, fibrinolysis, subclinical hypothyroidism, cardiovascular disease, meta-analysis

INTRODUCTION

Subclinical hypothyroidism (SCH) is a condition associated with an elevated thyroid stimulating hormone (TSH) level with normal levels of free thyroid hormone (1). Since advances have been made recently on assays for TSH measurement with better sensitivity and specificity, SCH is becoming more prevalent, resulting in increased attention (2). Despite the fact that most patients with SCH don't present with classical symptoms and signs of hypothyroidism due to the abnormal thyroid hormone level, the increase in atherosclerosis and cardiovascular disease in SCH patients is similar to that in patients with clinical hypothyroidism (3, 4).

Thromboembolism and cardiovascular disease are linked to various abnormalities of the haemostatic indicators related to coagulation and the fibrinolytic system. However, the published data about the heamostatic abnormalities among SCH patients remain controversial. Accumulating evidence has shown that levels of factor VII (FVII):C, the ratio FVII:C/FVII : Ag, fibrinogen (5) and plasminogen activator inhibitor-1 (PAI-1) (6, 7) are elevated, while von-Willebrand factor (vWF), antithrombin III (AT III) concentration and factor VIII (FVIII) activities (8) are decreased in patients diagnosed with SCH. However, conflicting outcomes exist in other researches (9, 10).

In this study, we aimed to analyze systematically the impact of SCH on the coagulation-fibrinolytic system in the human body, develop well-founded hypotheses, and provide recommendations for future research.

MATERIALS AND METHODS

The meta-analyses of observational researches face special challenges due to inherent biases and design differences from different studies. Hence, we conducted and detailed the analysis in accordance with the guidelines of the Meta-analysis of Observational Studies in Epidemiology Group (11).

Search Strategy

A publication search was performed for studies in the Web of Science, PubMed, Embase, CNKI and WanFang data up to March 2022 by two independent investigators. Search strategies consisted of the following: the Medical Subject Headings terms "Hypothyroidism" or "Thyroid Disease" or "Thyrotropin"; and the text word terms "subclinical hypothyroidism" or "subclinical thyroid dysfunction" or "thyroid-stimulating hormone"; and the text word terms "haemostasis" or "blood coagulation/clotting" or "blood coagulation/clotting tests" or "blood coagulation/clotting factors" or "blood coagulation/clotting disorders". In order to avoid omitting any relevant research, we also scanned the references of the retrieved articles for more studies. Language was not restricted in the document retrieval. Unpublished researches were not included within this study. The titles and abstracts of all retrieved articles were scanned. After that, we read the full text of studies which were possibly related for further appropriateness assessments to accomplish the article. Within the meta-analysis, all researches were firstly published in the primary literature with no reproduction in other articles. The whole researches that met the inclusion criteria were retrieved for additional assessment and information extraction.

Inclusion Criteria

Principle consideration basis was that the research needed to assess the impact of SCH on the coagulation-fibrinolytic system in human. Take it one step further, a review need to meet the accompanying terms: 1) reported SCH whose TSH was high while free thyroxin within normal range; 2) reported the coagulation-fibrinolytic framework information (including tissue plasminogen activator (t-PA), plasminogen activator inhibitor type 1(PAI-1), fibrinogen, activated partial thromboplastin time (APTT) and D-Dimer) for SCH patients and that was contrasted with data of the control whose thyroid function was normal; and 3) the 95% CIs were given or we could compute the 95% CI with given data.

Exclusion Criteria

The following sorts of studies were excluded: 1) Patients who were taking drugs or received treatment which could influence TSH and free thyroxin levels; 2) Participants suffered from clinical hypothyroidism or hyperthyroidism; 3) Case series, Case reports, editorials, reviews, *in vitro*, and non-human researches; 4) Because tumor may influence TSH and free thyroxin levels, researches on tumor patients were likewise removed; 5) the same study published before; 6) researches without sufficient to figure out the statistic or value.

Study Selection and Data Extraction

Headlines and summary of these original studies were scanned to see whether the inclusion criteria were met by two researchers separately. When we could not remove a study just from headlines and summary, we needed to review this article thoroughly. Choices with respect to incorporation were made independently, outcomes were contrasted, and discussion was made for dispute resolution if there was any difference. If different publications came from the same research, we chose the recent article. When there was a need, information from other prior articles was used to replenish it. These data below was

collected from every article: features of the research (writer, publication year, region, research design, exclusion criteria, TSH assay), particulars of member features (number of patients enrolled, mean age, sex and TSH level), coagulation and fibrinolysis indexes of the SCH groups and the control [fibrinogen, tissue plasminogen Activator (t-PA), PAI-1, D-Dimer and activated partial thromboplastin time (APTT)].

Quality Assessment

The Newcastle-Ottawa Quality Assessment Scale (NOS) for evaluating quality of observational researches was utilized as a direct to evaluate research quality of cross-sectional and intervention researches (12, 13). Three categories were hence recognized: high quality (low risk of bias), medium quality (moderate risk of bias), or low quality (high risk of bias). Quality of the included researches was evaluated by two independent analysts and any contrasts were settled by agreement or the supposition of the third analyst, when necessary.

Statistical Analysis

We drew the effect sizes that compared the experimental and non-exposure situations from each study. And then, for all eligible studies, the weighted mean difference (WMD) or Standard mean difference (SMD) and 95% CIs in coagulation and fibrinolysis indexes were calculated. Both fixed- and random-effects models were used where appropriate (14) in the meta-analysis. We examined the heterogeneity across studies through Q test and I^2 statistics. If $P< 0.1$ or $I^2 \geq 50\%$, when heterogeneity was thought to be obvious across these study outcomes, we chose the random-effect modeling the combinational analysis. If not, the fixed-effect model was used. We assessed the stability and reliability of our study through sensitivity analysis. The possible publication bias was evaluated through Egger's and Begg's test (15, 16). We performed the analysis by Review Manager 5.3 software (Cochrane Collaboration, http://www.cochrane.org) and STATA 16.0 software (Stata: Software for Statistics and Data Science | Stata https://www.stata.com/).

RESULTS

Study Selection

Figure 1 shows a flow diagram from which we can understand the search tactics and study selection process. The initial search tactics identified 1238 articles. Two records were involved when search of reference lists and review articles were performed further. In view of the headlines and abstract, we involved 70 potentially relevant publications in all. Of these, 58 failed to match the inclusion criteria (7 case reports,16 review articles,7 duplicate data,19 articles with insufficient data,3 studies not define TSH cut-off and 6 studies on cancer patients) and a total of 12 studies (5, 6, 8–10, 17–23) with 1325 patients were involved in the final analysis (**Figure 1**).

Study and Patient Characteristics

Table 1 presents the features of the individuals in the SCH and control groups and the main characteristics of these studies, including region, study design, quality, exclusion criteria, outcome parameters, TSH assay and matched or adjusted factors. Among the final 12 articles, 4 were (19, 20, 22, 23) were reported in Chinese, 8 were in English (5, 6, 8–10, 17, 18, 21). Of these, ten were case–control studies and two prospective cohort studies. Of these involved researches, four medium quality studies were confirmed. The rest of researches were confirmed to be of inferior quality. **Table 1** summed up the features of these involved researches. Moreover, **Table 2** summed up information of age, sex, the sample size and numerical value of TSH, and **Table 3** displayed the coagulation and fibrinolytic parameters.

Quantitative Synthesis

Tissue Plasminogen Activator (tPA)

Here, we included 8 studies (5, 6, 8, 9, 18, 19, 21, 23) (388 SCHs) for the impact of SCH on tPA. Taking the heterogeneity (heterozygosity test, $Chi^2 = 33.24$, $P < 0.0001$, $I^2 = 79\%$) into account, 1 study was removed at a time to identify the heterogeneous source. When the research by Y. H. Chen et al. (2009) (19) was detached, the heterogeneity decreased significantly (the I^2 reduced from 79% to 44%, P increased from <0.0001 to 0.10). After a careful reading, age difference may be one of the sources of heterogeneity, but may not the only one. Therefore, SMD values was merged by means of the fixed-effect model and the pooled SMD was 0.20 (95%CI, 0.05 to 0.35; $P = 0.01$; **Figure 2**), which means that SCH patients showed higher level of tPA compared with control subjects.

Plasminogen Activator Inhibitor Type 1 (PAI-1)

A total of 8 studies were included (5, 6, 8, 9, 18, 19, 21, 23) (388 SCHs) for the effect of SCH on PAI-1. There was significant statistical heterogeneity in these studies ($P<0.00001$, $I^2 = 88\%$). Therefore, a random-effect model was used to pool SMD. A significant increase was represented when estimated together in PAI-1 among subjects in SCH group compared with the control (SMD,0.61, 95% CI 0.17 to 1.06; $P = 0.007$, **Figure 3**).

Fibrinogen

The effect of SCH on fibrinogen was favorable in 6 studies (5, 8, 9, 20, 22, 23). Overall, the alter within the SMD for fibrinogen was 0.35 (95% CI, 0.20 to 0.50, $P<0.00001$; **Figure 4**). Heterogeneity analysis shows a moderate heterogeneity (heterozygosity test, $Chi^2 = 8.65$, $P=0.12$, $I^2 = 42\%$). It indicated that there was significantly higher in fibrinogen in SCH group, compared with euthyroid subjects. Further analysis based on whether TSH higher than 10uIU/mL or not (20, 23) showed higher fibrinogen levels in patients with TSH >10uIU/mL compared to those with TSH ≤ 10uIU/mL (WMD,0.43; 95% CI, 0.24 to 0.62; $P<0.0001$,$I^2 = 0\%$). Due to the limited numbers

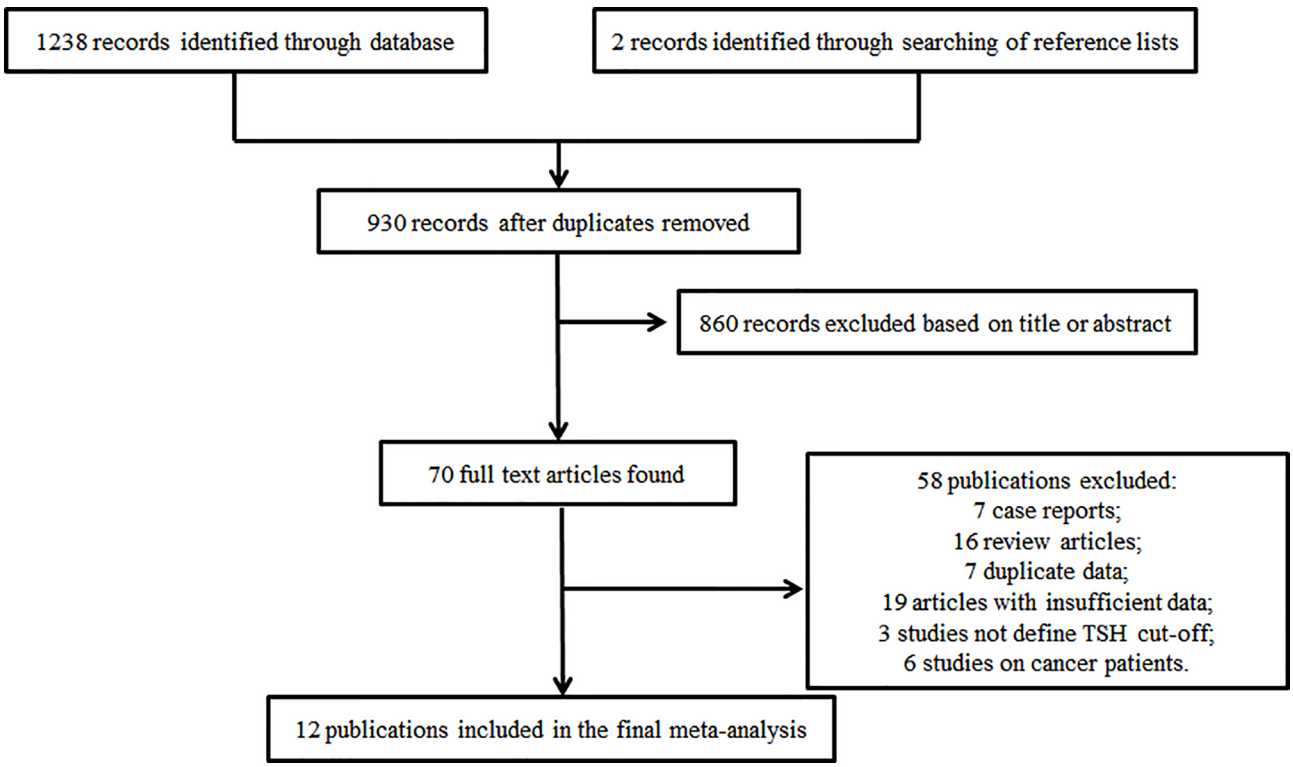

FIGURE 1 | Study selection process.

TABLE 1 | Characteristics of included studies.

First author and year of publication	Region	Study design	Quality	Exclusion criteria	Outcome parameters	TSH assay	Matched or adjusted factors
B. Müller (5)	Switzerland	Case-control study	Medium	1) male, 2) nonthyroid illnesses, 3) on medication affecting thyroid function	APTT, fibrinogen, tPA,PAI-1	By an immunoradiometric assay (h-TSH, RIA gnost, Behring).	Age and gender
Z. Cantürk (8)	Turkey	Case-control study	Low	1) received LT4 replacement therapy, 2) had previous history of external radiation, radioiodine treatment, and/or drug therapy that would cause SH, 3) with severe obesity, alcohol consumers, patients receiving drugs such as diuretics and b-blockers, 4) with diabetes mellitus, impaired glucose tolerance, coronary hearth disease, familial or secondary dyslipidemia, and hepatic, renal, or other systemic diseases	APTT, tPA, PAI-1, D-dimer, fibrinogen	By chemiluminescence immunoassay method with Immulite 2000 (DPC, Los Angeles, CA) kits	Age
M.A. Ozcan (6)	Turkey	Case-control study	Low	1) had atrial fibrillation, collagen disease, diabetes mellitus, liver or renal diseases, 2) taking any drugs effecting the levels of serum thyroid hormones	t-PA,PAI-1	By non-isotopic automated immunochemiluminometric system (ACS:180, Chiron Daignostics, UK).	Age and gender
S. Guldiken (17)	Turkey	Case-control study	Low	1) received thyroid hormone replacement therapy, 2) overt obesity (≥30kg/m^2), 3) smoking, 4) alcohol consumption, 5) diabetes mellitus, 6) cardiac,renal,and other systemic diseases, 7) on drugs affecting haemostasis and thyroid function	D-dimer	By immunometric assay method(DPC, Immulite 2000, Los Angeles, CA)	Age and BMI
S. Gullu (10)	Turkey	Prospective cohort study	Medium	1) past or current serious medical diseases including diabetes mellitus and coronary heart disease, 2) using any medication, including aspirin or diuretics, that might affect	APTT	By commercially available automated chemiluminescence system	Age,BMI, gender, smoking

(Continued)

TABLE 1 | Continued

First author and year of publication	Region	Study design	Quality	Exclusion criteria	Outcome parameters	TSH assay	Matched or adjusted factors
				the study parameters, 3) had symptoms and signs of clinical bleeding, 4) current smokers		kits (ACS: 180, Chiron Diagnostics, East Walpole, MA, USA)	status and blood pressure
R. Jorde (18)	Norway	Case-control study	Medium	1) a history of coronary infarction, angina pectoris or stroke in the questionnaire, 2) using thyroid medication	tPA,PAI-1	_	Age,BMI, gender, and smoking status
C. Erem (9)	Turkey	Case-control study	Low	taking drugs or had diseases (e.g.diabetes mellitus, overt obesity, coronary heart disease, collagen disease, liver cirrhosis, atrial fibrillation or renal disease) known to affect blood coagulation or fibrinolysis	APTT, D-dimer, fibrinogen, t-PA, PAI-1	By automated chemiluminescence (Bayer Corporation, Tarrytown, NY, USA)	Age and gender
Y.H. Chen (19)	China	Case-control study	Low	1) Taking estrogen, glucocorticoids, iodine, lipid-lowering drugs or β- Receptor blockers, 2) with diabetes, nephrotic syndrome, liver disease, chronic pancreatitis or familial hyperlipidemia	D-dimer,t-PA,PAI-1	ECLIA by Beckman Coulter Chemiluminescence immunoassay analyzer and kit	Age, BMI and gender
S.C. Zhong (20)	China	Case-control study	Low	TSH greater than 20 uIU/mL	APTT, fibrinogen	By automated Electrochemiluminescence immunoassay (COBAS, E411,Roche,Switzerland)	Age and gender
R. Lupoli (21)	Italy	Prospective cohort study	Medium	1) known inherited alterations in primary and/or secondary hemostasis, 2) treatment with anticoagulant or antiplatelet drugs, 3) personal and/or family history of arterial or venous thrombosis, 4) other conditions known to impact on hemostatic variables levels (liver disease, active inflammatory processes, pregnancy, malignancy, hematologic diseases, puerperium, oral contraceptive (OC) intake and hormone replacement therapy), 5) history of chronic infectious disease (including hepatitis B and C), 6) unstable medical conditions	PAI-1, t-PA, D-Dimer	By chemiluminiscent enzyme immunoassay (Elecsys E170, Roche Diagnostics, Mannheim)	Age, gender
Y.X. Ren (22)	China	Case-control study	Low	1) Hyperthyroidism and hypothyroidism, 2) Other heart diseases other than coronary heart disease, 3) Adrenal insufficiency, 4) Malignant tumor, acute cerebrovascular disease or hereditary hyperlipidemia, 5) In recent 3 months, taking drugs that affect thyroid function (such as amiodarone, thyroxine preparation, dopamine and hormone, etc.)	fibrinogen	By automated electrochemiluminescence immunoassay (COBAS8000,Roche, Switzerland)	Age, gender
F. Gao (23)	China	Case-control study	Medium	1) Age< 18 years old, 2) Taking drugs that affect thyroid function and hypolipidemic drugs, 3) with coronary heart disease, diabetes,hypertension, hyperlipidemia, chronic liver disease, chronic kidney disease, acute and chronic inflammation or connective tissue disease, 4) Postpartum or pregnancy	D-dimer, APTT, fibrinogen, t-PA, PAI-1	By automated electrochemiluminescence immunoassay (COBAS e601,Roche,Switzerland)	Age,blood pressure and BMI

APTT, activated partial thromboplastin time; t-PA, tissuetype-plasminogen activator; PAI-1, plasminogen activator inhibitor type 1; BMI, body mass index.

of article, no heterogeneity was found (heterozygosity test, Chi^2 = 0.65, P=0.42, I^2 = 0%).

Activated Partial Thromboplastin Time (APTT)

Six studies (5, 8–10, 20, 23) compared APTT levels between SCH patients with controls. Due to the large heterogeneity was found (heterozygosity test, Chi^2 = 41.05, P<0.0001, I^2 = 88%), random-effect model was used to pooled the data. In our analysis, it was of no statistically difference in APTT (WMD,0.65;95% CI, −1.22 to 2.51; P<0.00001; **Figure 5**). Further analysis based on difference TSH level (20, 23) did not found the effect of TSH level difference on APTT level (WMD, 2.25; 95%CI, -6.86 to 11.36; P=0.63). Also, a large heterogeneity was found (heterozygosity test, Chi^2 = 28.44, P<0.0001, I^2 = 96%), ***D-Dimer.*** Here, the association between D-Dimer and SCH was analyzed in 6 independent studies (8, 9, 17, 19, 21, 23) (268 SCHs). No statistically difference was found in D-Dimer between SCH group and normal thyroid function group (SMD, 0.28;95% CI, −0.28 to 0.83; P = 0.33) from analysis and the heterogeneity among trials was obvious (heterozygosity test, Chi^2 = 41.14, P<0.00001, I^2 = 88%; **Figure 6**).

TABLE 2 | Patient characteristics by risk factors and outcomes by trials for SCH.

First author and year of publication	TSH cutoff value	T4 measured?	Age (year)		Gender (female %)		TSH		Sample size	
			SCH	EU	SCH	EU	SCH	EU	SCH	EU
B. Müller (5)	≥6 mIU/l	Yes	59.0 ± 13.0	49.0 ± 13.0	100	100	16.0 ± 16.9	2.0 ± 1.0	42	66
Z. Cantürk (8)	–	Yes	42.2 ± 11.6	44.3 ± 6.7	100	100	8.69 ± 5.40	1.47 ± 1.04	35	30
M.A. Ozcan (6)	>5 uIU/ml	Yes	39.3 ± 13.9	46.4 ± 5.7	20.0	31.3	13.74 ± 4.85	2.09 ± 1.69	10	16
S. Guldiken (17)	>4 uIU/ml	Yes	31.0 ± 7.6	31.2 ± 6.4	100	100	7.3 ± 2.1	1.4 ± 0.8	15	15
S. Gullu (10)	>5mIU/l	Yes	47.6 (21-68)	49.2 (25-61)	100	100	7.1 (5.2-10)	1.3 (0.6-1.9)	15	15
R. Jorde (18)	>3.5 mIU/l	Yes	62.2 ± 11.8	60.8 ± 12.6	51.8	53.9	5.28 ± 1.42	1.54 ± 0.63	83	141
C. Erem (9)	>5 mIU/l	Yes	41.0 ± 13.5	41.7 ± 12.8	76.7	80	10.3 ± 5.03	1.69 ± 1.06	30	20
Y.H. Chen (19)	> 4.8 mIU/l	Yes	67.9 ± 4.8	67.8 ± 4.2	100	100	9.38 ± 2.55	–	52	50
S.C. Zhong (20)	>4.3 uIU/ml	Yes	55 (35-75)	55 (36-73)	51.7	53.3	–	–	60	30
R. Lupoli (21)	>4.5 uIU/ml	Yes	41.4 ± 13.0	42.2 ± 11.9	80.5	80.5	7.3 ± 4.8	2.1 ± 0.9	41	41
Y.X. Ren (22)	–	Yes	64.21 ± 10.38	60.92 ± 10.3	48.5	23.1	–	–	101	268
F. Gao (23)	>4.2 uIU/ml	Yes	55.7 ± 7.78	52.11 ± 8.73	100	100	7.22 ± 3.75	1.65 ± 0.71	95	54

TABLE 3 | Coagulation and fibrinolytic changes in the two groups of each study.

First author and year of publication	APTT		D-Dimer		Fibrinogen		t-PA		PAI-1	
	SCH	EU	SCH	EU	SCH	EU	SCH	EU	SCH	EU
B. Müller (5)	26 ± 3	27 ± 3	—	—	2.5 ± 0.5	2.4 ± 0.4	6 ± 4	6 ± 4	56 ± 35	52 ± 38
Z. Cantürk (8)	29.6 ± 3.4	28.3 ± 1.8	0.52 ± 0.75	0.39 ± 0.27	329.0 ± 51.2	314.5 ± 27.1	3.60 ± 1.70	4.05 ± 1.76	19.78 ± 6.20	10.18 ± 3.61
M.A. Ozcan (6)	—	—	—	—	—	—	6.05 ± 2.61	6.27 ± 2.21	51.11 ± 20.97	46.03 ± 27.24
S. Guldiken (17)	—	—	0.29 ± 0.22	0.18 ± 0.11	—	—	—	—	—	—
S. Gullu (10)	26.9 ± 8.5	25.7 ± 7.6	—	—	—	—	—	—	—	—
R. Jorde (18)	—	—	—	—	—	—	11.1 ± 4.3	10.5 ± 5.1	15.3 ± 10.3	14.4 ± 13.1
C. Erem (9)	31.5 ± 3.1	30.0 ± 2.4	0.41 ± 0.3	0.24 ± 0.15	291.9 ± 50.5	309.6 ± 69.8	11.0 ± 8.5	8.6 ± 2.5	26.4 ± 10.2	27.1 ± 8.1
Y.H. Chen (19)	—	—	0.29 ± 0.16	0.15 ± 0.08	—	—	0.27 ± 0.16	0.42 ± 0.19	0.78 ± 0.33	0.40 ± 0.19
S.C. Zhong (20)	34.38 ± 6.56	30.41 ± 2.77	—	—	2.83 ± 0.60	2.64 ± 0.35	—	—	—	—
R. Lupoli (21)	—	—	220.3 ± 67.1	252.1 ± 72.4	—	—	5.56 ± 2.22	4.75 ± 1.61	33.6 ± 13.9	22.5 ± 5.74
Y.X. Ren (22)	—	—	—	—	3.93 ± 0.91	3.61 ± 0.89	—	—	—	—
F. Gao (23)	23.88 ± 4.46	26.19 ± 2.97	0.62 ± 0.28	0.73 ± 0.29	3.11 ± 0.69	2.67 ± 0.59	6.60 ± 2.10	5.43 ± 1.99	28.74 ± 7.35	25.77 ± 8.17

APTT, activated partial thromboplastin time; t-PA, tissue type-plasminogen activator; PAI-1, plasminogen activator inhibitor 1; —, undescribed.

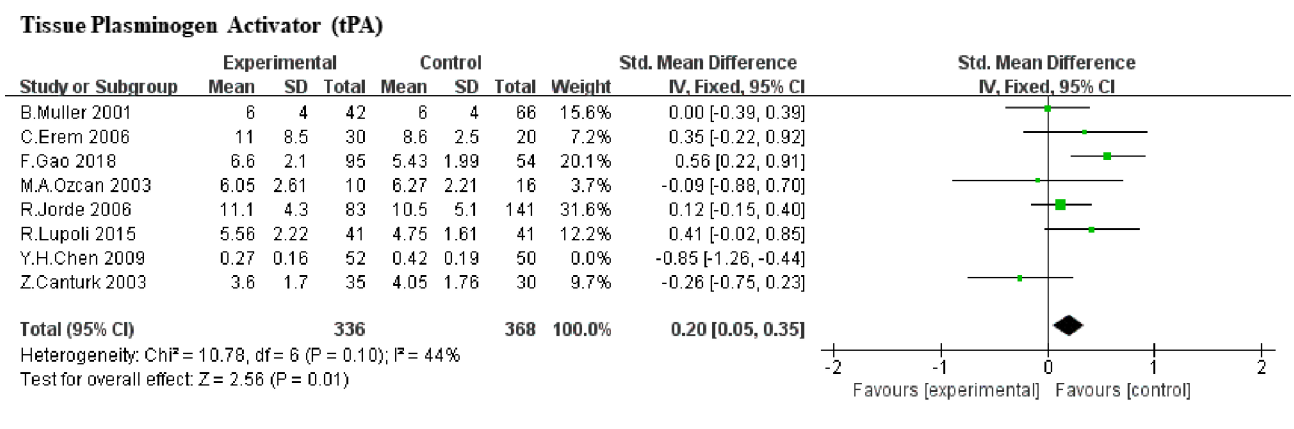

FIGURE 2 | Comparison of tPA in subclinical hypothyroidism and euthyroidism.

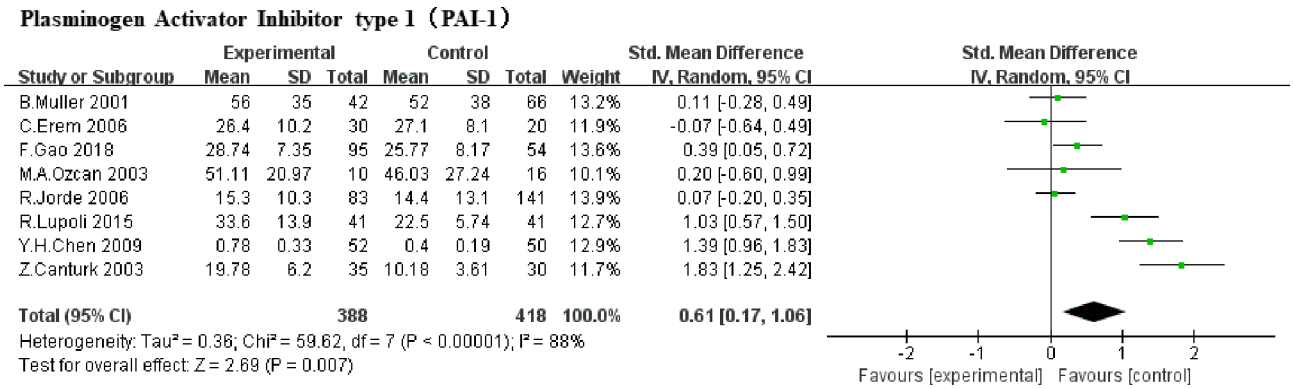

FIGURE 3 | Comparison of PAI-1 in subclinical hypothyroidism and euthyroidism.

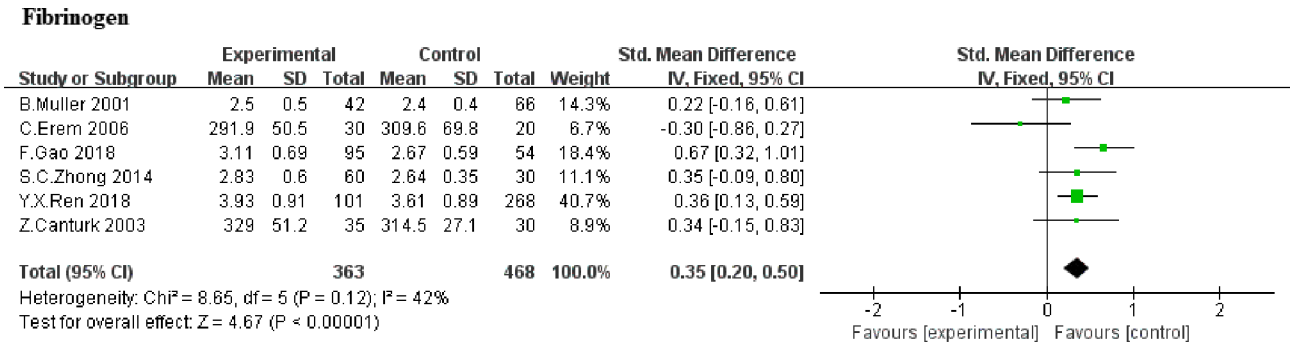

FIGURE 4 | Comparison of Fibrinogen in subclinical hypothyroidism and euthyroidism.

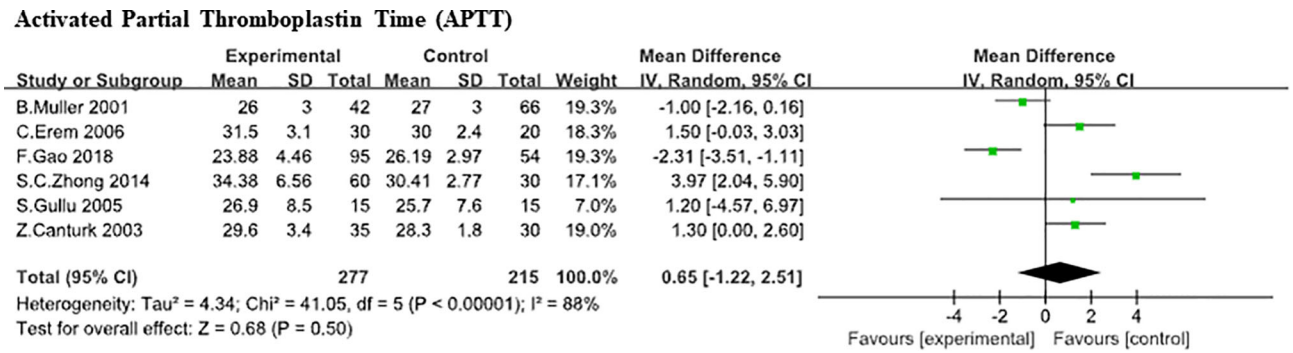

FIGURE 5 | Comparison of APTT in subclinical hypothyroidism and euthyroidism.

Sensitivity and Subgroup Analysis

We made further efforts to conduct a subgroup and sensitivity analysis on account of study heterogeneity. Subgroup analyses were conducted by ethnicity, age, gender, TSH cut-off value and study design. However, the results of PAI-1 in SCH patients were not affected. A sensitivity analysis was performed to assess the influence of each research on the final results. There was no any single study that had an impact on the total pooled effect,

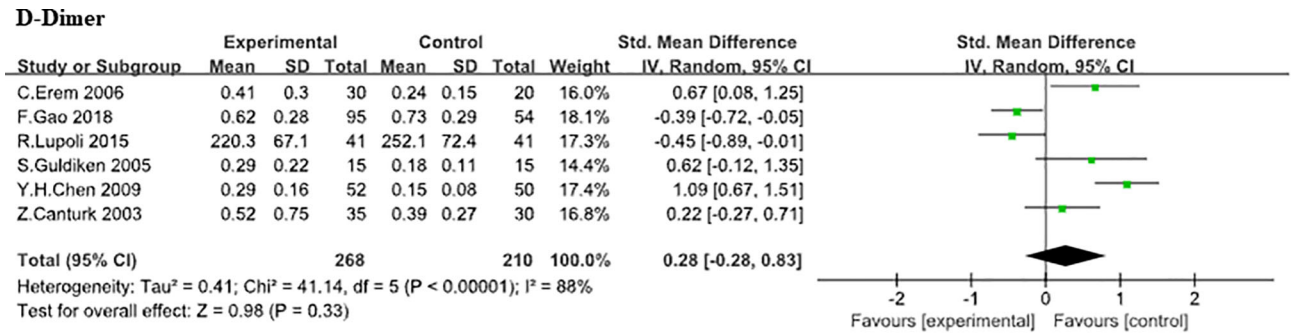

FIGURE 6 | Comparison of D-Dimer in subclinical hypothyroidism and euthyroidism.

sensitivity analysis, which indicated that none of the studies interfered with OR or 95% CI (**Figure 7**).

Publication Bias Evaluation

Publication bias was examined using funnel plot. There was no notable publication bias among articles included in our meta-analysis (**Figure 8**). Furthermore, no significant bias were found both by Egger's and Begg's test (both $P>0.1$).

DISCUSSION

Subclinical hypothyroidism (SCH) is defined when serum TSH is above the reference range but circulating thyroid hormones are still normal. In Iniodine-sufficient populations, SCH affects up to 16% of the population (24). Notably, researches have indicated that the risk of atherosclerosis and myocardial infarction increased independently in patients with SCH (4). However, it is still controversial that whether SCH influences coagulation and fibrinolysis in the human body. To reply this question, we did this systematic review and discovered that people suffered from SCH had hemostasis and fibrinolysis changes, consistently reflecting a prothrombotic condition.

Our study revealed that patients diagnosed with SCH displayed a prothrombotic tendency. It was showed that both t-PA and PAI-1 were above the normal range in these people, compared with the control, which indicated a hypercoagulable condition with a decline in fibrinolysis because of the pattern of alterations (21, 25). Especially, the equilibriums of t-PA and PAI-1 determine the total fibrinolytic potential of human blood, which has been extensively regarded as a predictive factor of venous as well as arterial thrombosis (26). In addition, increased

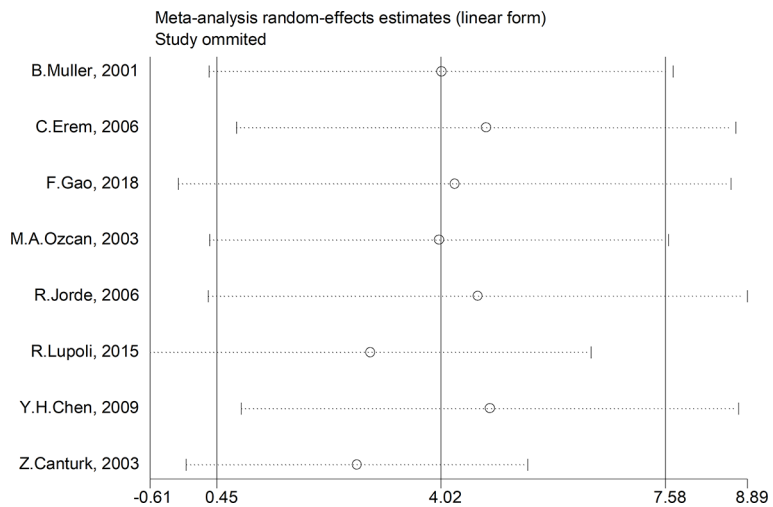

FIGURE 7 | Sensitivity analysis to assess the impact of every study on the overall conclusions.

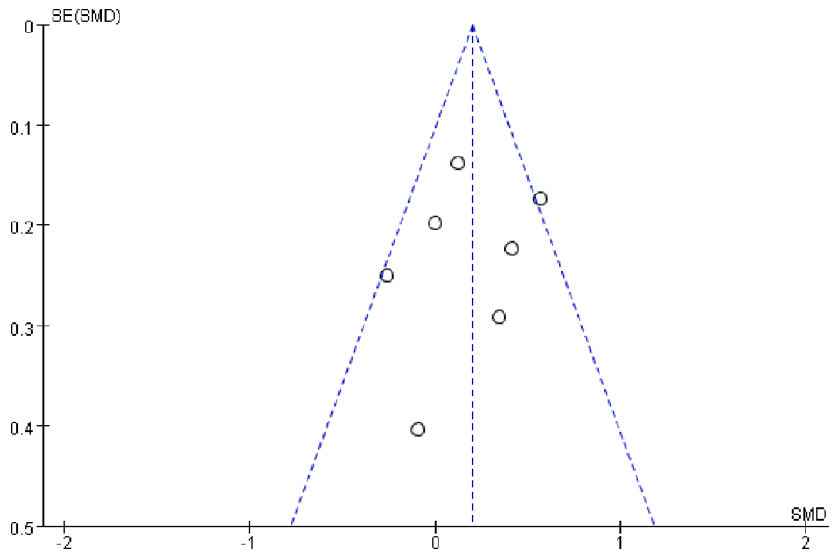

FIGURE 8 | Funnel plot of publication bias-qualitative evaluation of publication bias, performed by Review Manager 5.3.

t-PA levels could give expression to a compensatory reaction to a hypofibrinolysis as a result of an increased inhibitory effect of PAI-1 (26). Moreover, elevated PAI-1 concentrations may increase the tendency to myocardial infarction (MI), which suggests clinical significance of high PAI-1 levels (21, 27).

We analyzed the changes in various other hemostatic parameters and evaluate fibrinolytic balance in the current study. Especially, the increment of fibrinogen in SCH patients comparing to normal populations, which reflected both the human inflammatory state and the tendency of thrombosis and haemorrhage, contributes to atherosclerosis as well as thrombotic complications (28, 29). Data from clinical and epidemiological studies suggested that higher serum fibrinogen level could predict the risk of both primary cardiovascular events and secondary events (29–32).

Existing literatures that show an impaired fibrinolysis and a hypercoagulable in SCH patients agree to our observations (8, 17, 21, 33). This condition may be the precipitating factors of cardiovascular disease, as a mechanism how mild thyroid failure is associated with cardiovascular disease. Just as Chadarevian et al. observed (7), there was an overall decrease of fibrinolytic activity, manifested as lower D-Dimer levels, increased α2-antiplasmin reaction and increased numerical value of tPA and PAI-1, in SCH groups whose TSH level lies in 10 and 50 mIU/l. Meanwhile, Muller et al. (5) reported that subjects with SCH had a significant elevation in factor VII reaction. In a group of individuals with SCH, Canturk et al. (8) suggested elevated fibrinogen, factor VII and PAI-1 levels along with decreased AT III concentrations. It came to light that the condition resulted in more severe atherosclerosis. Furthermore, Lupoli et al. (21) have seen recovery improvements in these parameters after LT4 replacement therapy, such as a significant reduction in PAI-1 and tPA. It was concluded that SCH was a state of hypercoagulable and hypofibrinolytic and this can be reverted by L-T4 treatment. Above all, we propose the following recommendations: for patients with SCH, active LT4 treatment is recommended to reduce the incidence of thrombotic events, especially for patients with a personal history of coronary heart disease, cerebrovascular disease or early family history.

As with any study, there are some limitations in our research. Firstly, by the inclusion of no randomized clinical studies, trials with only data from observational researches, and studies mainly discussed the connection between SCH and the coagulation or fibrinolysis, it is necessary to cautiously interpret the results of our analysis (34). Secondly, the inconsistency of the standard TSH cut-off value and the definition of SCH in the final included studies may add the clinical heterogeneity in our study. Finally, factors including study samples, participants' characteristics, the method used to test the coagulation and fibrinolysis indexes, and various confounding factors included for the adjustment, may all also added the clinical heterogeneity to our analysis.

In summary, we suggest that SCH is related to a prothrombotic state in our study, which may be caused by alterations in coagulation and fibrinolysis. Therefore, it is important to screen SCH dysfunction for detecting the earliest signs of cardiovascular disease. However, larger and high-quality studies are necessary to evaluate our observations. If future studies clearly revealed the casual association of prothrombotic state with SCH leading to an elevated risk of cardiovascular disease, effective treatments, such as replacement therapy with Levothyroxine (LT4), to revert the abnormalities should be recommended routinely.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

All the authors contributed to the work. WZ and QF defined the research theme. QX and YW designed the methods, analyzed the data, interpreted the results and wrote the manuscript. XS and YZ prepared tables and figures. All authors have read and agreed to the published version of the manuscript.

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Association of Maternal Mild Hypothyroidism With Offspring Neurodevelopment in TPOAb-Negative Women: A Prospective Cohort Study

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Objectives: Adequate maternal thyroid hormone availability is crucial for fetal neurodevelopment, but the role of maternal mild hypothyroidism is not clear. We aim to investigate the association of maternal mild hypothyroidism with neurodevelopment in infants at 1 year of age among TPOAb-negative women.

Methods: The present study was conducted within the Jiangsu Birth Cohort. A total of 793 mother–infant pairs were eligible for the present study. Maternal thyroid function was assessed by measuring serum thyroid-stimulating hormone, free thyroxine, and thyroid peroxidase antibodies. Neurodevelopment of infants was assessed by using the Bayley Scales of Infant and Toddler Development third edition screening test (Bayley-III screening test).

Results: In the multivariate adjusted linear regression analyses, infants of women with subclinical hypothyroidism and isolated hypothyroxinemia were associated with decreased receptive communication scores (β = –0.68, p = 0.034) and decreased gross motor scores (β = –0.83, p = 0.008), respectively. Moreover, infants of women with high-normal TSH concentrations (3.0–4.0 mIU/L) and low FT4 concentrations were significantly associated with lower gross motor scores (β = –1.19, p = 0.032), while no differences were observed in infants when the mothers had a high-normal TSH concentration and normal FT4 levels.

Conclusions: Maternal subclinical hypothyroidism is associated with decreased receptive communication scores in infants at 1 year of age. In addition, maternal TSH concentration greater than 4.0 mIU/L and maternal isolated hypothyroxinemia are associated with impaired gross motor ability of infants, especially in infants of women with high-normal TSH concentrations (3.0–4.0 mIU/L).

Keywords: thyroid hypofunction, pregnancy, neurodevelopment, infancy, cohort study

INTRODUCTION

Maternal mild hypothyroidism is a common endocrine condition and occurs in 5%–18% of all pregnancies, depending on the definition used and population studied (1–3). Thyroid hormone is essential for optimum neurodevelopment of the fetus, acting on various stages of fetal neurological development, including neuronal migration, synaptogenesis, glial cell proliferation, and glial cell myelination (4, 5). Because the fetal thyroid gland is not functional until mid-gestation, the fetus predominantly depends on the supply of maternal thyroid hormone during that period (6). Therefore, maternal mild hypothyroidism may impair the neurodevelopment in offspring.

Results from animal studies have shown that shortage of thyroid hormone is associated with impaired brain development (7). Data from a large case–control study have demonstrated reduced scores on tests of intelligence, attention, and visual-motor performance at 8 years of age among children of mothers with untreated overt hypothyroidism (OH) during pregnancy compared to euthyroid controls (8, 9). Evidence from observational studies has demonstrated that maternal isolated hypothyroxinemia (IH) is predominantly associated with various types of neurodevelopmental disorders in children (10–12). However, the detrimental effects of maternal subclinical hypothyroidism (SCH) on fetal neurodevelopment remain less well established. Some studies have demonstrated that the offspring of women with SCH have decreased intelligence and motor ability or increased risk for delay in neurodevelopment (13–15), whereas others have shown conflicting results (10, 16, 17). This variation may be attributed to the different criteria for elevated thyroid-stimulating hormone (TSH) used in different studies (18).

Previous international guidelines have recommended using fixed upper limits of 2.5 mIU/L for the first trimester and 3.0 mIU/L for the second and third trimesters (1–3). Because studies have demonstrated that using these fixed upper limits in the 2011 guidelines results in overdiagnosis of SCH (19–22), the upper limit of TSH at 4.0 mIU/L for each trimester of pregnancy was advocated by the American Thyroid Association (ATA) 2017 guidelines (18). Moreover, only a few studies have investigated infant neurodevelopment among women with TSH concentrations between 3.0 and 4.0 mIU/L. Thus, the present study aimed to examine the association of maternal mild hypothyroidism with infant neurodevelopment, especially in women with high-normal TSH concentrations (3.0–4.0 mIU/L).

METHODS

Study Design and Participants

This cohort study was embedded in the Jiangsu Birth Cohort (JBC), a population-based prospective and longitudinal study recruiting women who planned to receive assisted reproductive technology (ART) and who are at their first trimester of spontaneous pregnancy (SP) at clinics in Jiangsu, China (23). When infants reached 1 year of age, they were invited to hospitals for systematic medical examination. The present study included the mother–infant pairs if the maternal TSH, free thyroxine (FT4), and thyroid peroxidase antibody (TPOAb) had been measured during pregnancy. Only mother–infant pairs with infants who had neurodevelopment data at the age of 1 year were included. We excluded pairs if the mother had a pre-existing thyroid disorder, if the mother had treatment for a thyroid disorder or the maternal TPOAb was positive, and we further exclude pairs if the mother had elevated concentrations of FT4 or suppressed TSH. The detailed cohort design and data collection have been previously published (23). This study was approved by the institutional review board of Nanjing Medical University, China NJMUIRB (2017) 002. Written informed consent was obtained from all the participants or the infants' parents or guardians.

The participants were divided into four groups according to maternal thyroid hormone levels as follows: euthyroidism (ET, normal concentration of TSH and FT4), overt hypothyroidism (OH, elevated concentration of TSH with low concentration of FT4), subclinical hypothyroidism (SCH, elevated concentration of TSH with normal concentration of FT4), and isolated hypothyroxinemia (IH, normal concentration of TSH and low concentration of FT4).

Maternal Thyroid Parameters

Measures of thyroid functions including TSH, FT4, and TPOAb, were evaluated by electro-chemiluminescent microparticle immunoassays kits using the Architect system (Roche GmbH, Mannheim, Germany) in the Department of Clinical Laboratory in the Nanjing Maternity and Child Health Care Hospital. The intra-assay coefficients of variations were as follows: TSH < 5.3% and FT4 < 5.3%. The normal range for TSH was 0.2–4.0 mIU/L according to the ATA 2017 guidelines (18). The specific reference intervals (95% CI: 10.55–17.21 pmol/L) of FT4 for the study population were obtained according to the National Institute of Clinical Biochemistry (NACB) (24). TPOAb was considered positive at concentrations greater than 34 IU/ml.

Assessment of Neurodevelopment

When infants reached approximately 1 year of age, their neurodevelopment was assessed with the Bayley Scales of Infant and Toddler Development third edition screening test (Bayley-III screening test) by standardized trained pediatricians or occupational therapists in the presence of a primary caregiver (25). This test uses a subset of items from the full-length Bayley-III Scales, which has been widely validated and extensively used to compare developmental outcomes across individuals worldwide (25). Following standard procedures, we administered the following five subscales of the Bayley-III screen test: cognition, receptive language, expressive language, fine motor, and gross motor. Each subscale consisted of a series of developmental play tasks, and the subscale-specific raw scores of completed items were then recorded.

In the present study, a series of approaches was adopted to ensure the validity and reliability of the infant neurodevelopmental evaluation. The evaluation environment was quiet and non-interfering. One developmental neuropsychologist was appointed to provide professional training of the standardized administration before the investigation. Additionally, with the informed consent of guardians, the entire assessments of all examiners were filmed, and some of the videos were randomly selected for secondary evaluation monthly. The pediatricians and occupational therapists who performed the tests were unaware of any other test outcomes, including maternal thyroid hormone levels during pregnancy.

Covariates

Detailed information was obtained through questionnaires administered by trained interviews and comprised information on maternal and infant demographics, pregnancy-related information, and medical history. The covariates were chosen based on what was available within the data and following the literature review (18, 23). Potential confounding variables accounted for in the study were childbearing age (years) (26), maternal pre-pregnancy BMI (kg/m^2) (27), parity (nulliparous/multiparous) (28), maternal education (<12/≥12 years) (29), mode of conception(spontaneous/ART) (30), diseases during pregnancy (diabetes/non-diabetes, and hypertension/non-hypertension) (31, 32), gestational age (33), and infant sex (male/female) (34).

Statistical Analyses

Continuous variables with a normal distribution were expressed as mean (standard deviation, SD) and compared using Student´s *t*-test. Non-normally distributed variables were expressed as median (interquartile range, IQR) and compared using the Wilcoxon rank test. Categorical variables were expressed as percentage (%) and compared by the chi-squared test. Non-response analyses were performed to compare with the characteristics of the mother–infant pairs grouped by neurodevelopment assessment data availability according to different thyroid function groups.

Multivariate linear regression models were constructed to estimate the associations of maternal SCH, IH, and OH with offspring neurodevelopment. We developed a directed acyclic graph (DAG; **Figure S1**) to document our assumptions about the association between the covariates, exposure, and outcome, and specifically to hypothesize which variables were confounders (preceding both exposure and outcome). The casual directed acyclic graphs (DAGs) is a useful tool for researchers to understand the potential interplay among variables and to deduce which variables require control to minimize bias and which variables could introduce bias if controlled in the analysis (35). This DAG informed our staged modeling approach: model 1 was crude (unadjusted) and model 2 was adjusted for confounders (childbearing age, pre-pregnancy BMI, parity, maternal education level, mode of conception, and sex of infants). Gestational age at birth and diseases during pregnancy were considered potential intermediates and not included in the main model.

Considering that the ATA 2011 guidelines define the upper limit for TSH at 3.0 mIU/L during mid-trimester (2), we further investigated the association of maternal mild hypothyroidism and infant neurodevelopment by different maternal TSH levels (0.2–3.0 vs. 3.0–4.0 mIU/L). The participants were divided into the following groups (**Figure 1**): Group ET^a-ET^b (0.2–3.0 mIU/L TSH and normal FT4), Group SCH^a-ET^b (3.0–4.0 mIU/L TSH and normal FT4), Group SCH^a-SCH^b (TSH > 4.0 mIU/L and normal FT4), Group IH^a-IH^b (0.2–3.0 mIU/L TSH and FT4 < 10.55 pmol/L), Group OH^a-IH^b (TSH 3.0–4.0 mIU/L and FT4 < 10.55 pmol/L), and Group OH^a-OH^b (TSH > 4.0 mIU/L and FT4 < 10.55 pmol/L)

We conducted two sensitivity analyses. First, we repeated our main analysis restricting to infants born at full term (37 weeks or greater), to examine whether adjusting for gestational age in our main models may have inadvertently introduced bias through unmeasured confounding between gestational age and infant neurodevelopment. Second, we repeated our main analysis in women without diseases during pregnancy, to examine whether associations differed.

Information on missing data is outlined in **Table 1**, and missing data on covariates were coded as a missing indicator for categorical variables and with median values for continuous variables in multivariable linear regression models. Two-sided $p < 0.05$ was considered statistically significant. All statistical analyses were conducted in R statistical software version 4.10.

RESULTS

From December 2018 to September 2020, a total of 1,693 singleton infants born in Nanjing Maternal and Child Health Hospital had reached 1 year old. Data on TSH, FT4 and TPOAb were obtained for 1,533 mothers. In total, 178 mother–infant pairs were excluded because they met exclusion criteria, and 562 mother–infant pairs were excluded because the infants did not have neurodevelopment assessment at the age of 1 year. Thus, the final study population was composed of 793 mother–infant pairs. Of these 793 mother–infant pairs, 4.92% of the women

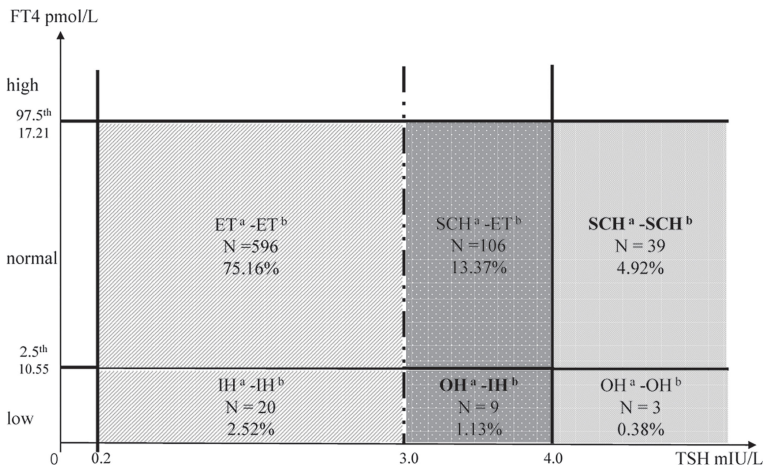

FIGURE 1 | Thyroid function grouped on different TSH thresholds. ET, euthyroidism; SCH, subclinical hypothyroidism; OH, overt hypothyroidism; IH, isolated hypothyroxinemia. [a]TSH thresholds at 3.0 mIU/L (2011 ATA guidelines). [b]TSH thresholds at 4.0 mIU/L (2017 ATA guidelines).

were identified as SCH, 3.65% of the women were identified as IH, and only 0.38% of the women were identified as OH according to the 2017 ATA guidelines; 2.52% (20/793) of the women who had elevated concentrations of FT4 or suppressed TSH were excluded (**Figure 2**). The remaining 773 pairs had 1.0%, 1.3%, 1.3%, and 2.2% missing values of pre-pregnancy BMI, drinking during pregnancy, maternal education, and duration of breastfeeding.

TABLE 1 | Characteristics of mother–infant pairs.

Characteristics	ET (*n* = 702)	SCH (*n* = 39)	IH (*n* = 29)	OH (*n* = 3)
TSH (mIU/L)	2.01 (1.43–2.60)	4.72 (4.26–5.45)**	2.07 (1.47–3.31)	5.48 (4.86–5.77)**
FT4 (pmol/L)	13.34 (12.30–14.40)	12.42 (11.81–13.94)*	10.15 (9.68–10.35)**	9.58 (9.54–10.01)**
Gestational age at blood sampling (weeks)	23.87 (0.67)	23.85 (0.50)	24.04 (0.56)	23.76 (0.59)
Childbearing age (years)	30.64 (3.89)	29.83 (4.49)	33.14 (4.00)**	31.40 (2.11)
Pre-pregnancy BMI (kg/m^2), *n* (%)	21.63 (2.92)	20.79 (2.63)	22.94 (2.91)*	22.30 (3.55)
<18.5	76 (10.8)	7 (17.9)	1 (3.4)	0 (0.0)
18.5–23.9	487 (69.4)	24 (61.5)	17 (58.6)	2 (66.7)
24–27.9	110 (15.7)	6 (15.4)	10 (34.5)	1 (33.3)
≥28	23 (3.3)	0 (0.0)	1 (3.4)	0 (0.0)
Missing	6 (0.8)	2 (5.1)	0 (0.0)	0 (0.0)
Spontaneous conception, *n* (%)	559 (79.6)	30 (76.9)	17 (58.6)*	1 (33.3)
Primiparous, *n* (%)	546 (77.8)	30 (76.9)	21 (79.3)	3 (100.0)
Smoking during pregnancy, *n* (%)	0 (0.0)	0 (0.0)	1 (3.4)*	0 (0.0)
Drinking during pregnancy, *n* (%)				
Yes	4 (0.6)	2 (5.1)*	0 (0.0)	0 (0.0)
Missing	10 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Maternal education (years), *n* (%)				
>12	614 (87.5)	30 (76.9)	20 (69.0)*	3 (100.0)
Missing	9 (1.3)	0 (0.0)	1 (3.4)	0 (0.0)
Diseases during pregnancy[a]				
Diabetes, *n* (%)	191 (27.2)	6 (15.4)	13 (44.8)	3 (100.0)*
Hypertension, *n* (%)	41 (5.8)	1 (2.6)	4 (13.8)	0 (0.0)
Vaginal delivery, *n* (%)	384 (54.7)	23 (59.0)	9 (31)*	1 (33.3)
Infant sex (female), *n* (%)	340 (48.4)	23 (59.0)	13 (44.8)	1 (33.3)
Birthweight (g)	3,411 (456)	3,407 (343)	3,365 (421)	4,107 (189)*
Gestational age (weeks)	39.46 (1.34)	39.72 (1.13)	39.26 (1.20)	39.48 (0.21)
Prematurity, *n* (%)	27 (3.8)	1 (2.6)	1 (3.4)	0 (0.0)
Duration of breastfeeding (months), *n* (%)				
>6	423 (60.3)	18 (46.2)	19 (65.5)	3 (100.0)
Missing	17 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
Age at Bayley-III screening test (days)	365.62 (6.56)	366.38 (6.67)	365.90 (6.99)	361.33 (0.58)

*TSH, thyroid stimulation hormone; FT4, free thyroxine; ET, euthyroidism; SCH, subclinical hypothyroidism; OH, overt hypothyroidism; IH, isolated hypothyroxinemia; BMI, body mass index. Continuous variables are expressed as mean (SD) or median (IQR), whereas categorical variables are expressed as percentages. *p-value <0.05; **p-value <0.01. [a]Diabetes includes chronic and gestational diabetes mellitus; hypertension includes chronic and pregnancy-induced hypertension.*

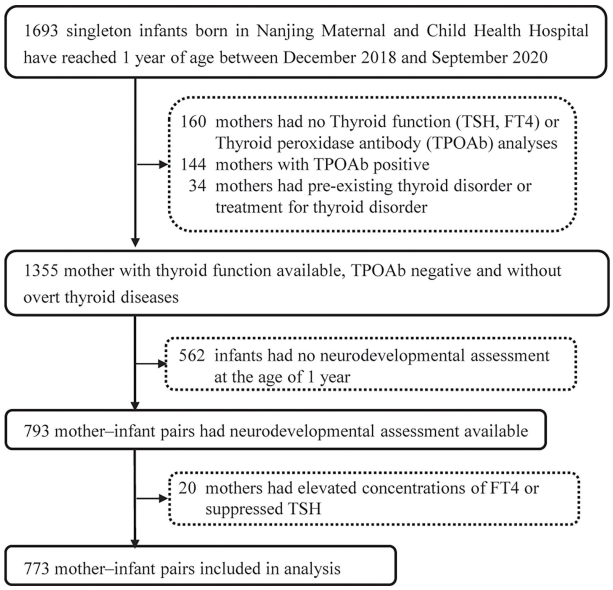

FIGURE 2 | Flowchart of participants through the study. TSH, thyroid-stimulating hormone; FT4, free thyroxine.

Compared to euthyroid women (ET group), the SCH group was more likely to have consumed alcohol during pregnancy, and the IH group was more likely to have higher childbearing age, higher pre-pregnancy BMI, and lower educational levels (**Table 1**). Comparisons of the characteristics of the mother–infant pairs grouped by neurodevelopment assessment data availability according to different groups showed no differences between participants and non-participants. However, the ET group of mother–infant pairs with available neurodevelopment data had higher mean pre-pregnancy BMI, and the SCH group of mother–infant pairs had lower FT4 concentration (**Table S1**)

Multivariate linear regression models showed that maternal SCH during pregnancy was associated with decreased receptive communication scores at 1 year of age ($\beta = -0.68$, $p = 0.034$). Infants exposed to maternal IH had decreased gross motor scores ($\beta = -0.83$, $p = 0.008$), while no significant difference was observed in infants of mothers with OH, which may be attributed to the small sample size (**Table 2**). When the 2011 ATA guidelines were used, similar results were obtained, and the infants exposed to maternal OH had lower gross motor scores ($\beta = -1.11$, $p = 0.021$) (**Table S2**). The stratified analysis results revealed that there was no statistically significant association of Group SCH^a-ET^b (TSH 3.0–4.0 mIU/L and normal FT4) with infant neurodevelopment compared to Group ET^a-ET^b (TSH 0.2–3.0 mIU/L and normal FT4), but Group SCH^a-SCH^b (TSH >4.0 mIU/L and normal FT4) showed decreased receptive communication scores ($\beta = -0.73$, $p = 0.025$). Group IH^a-IH^b (TSH 0.2–3.0 mIU/L and FT4 < 10.55 pmol/L) was associated with lower gross motor scores, but there was no significance after adjustment for potential confounders. However, Group OH^a-IH^b (TSH 3.0–4.0 mIU/L and FT4 < 10.55 pmol/L) had lower gross motor scores ($\beta = -1.19$, $p = 0.032$) (**Table 3**). In the sensitivity analyses, we repeated our main analysis restricting to infants born at full term (37 weeks or greater) or in women without diseases during pregnancy, and the results were not significantly altered (**Tables S3, S4**).

DISCUSSION

In this population-based prospective cohort study, we observed impaired neurodevelopment in infants prenatally exposed to maternal mild hypothyroidism. Interestingly, associations differed in magnitude by subtype of maternal mild hypothyroidism and domains of infant neurodevelopment. Infants of women with maternal SCH were associated with decreased receptive communication scores only with maternal TSH levels greater than 4.0 mIU/L. For gross motor ability, maternal IH was predominant, and the effect was mainly attributed to mothers with high-normal TSH levels (3.0–4.0 mIU/L). To the best of our knowledge, this is the first study to evaluate the association of maternal mild hypothyroidism with offspring neurodevelopment as stratified by maternal TSH concentration.

Our findings in this prospective cohort study agreed with previous results (13, 14). A retrospective study from China has demonstrated that the offspring of women with SCH (TSH > 4.21 mIU/L) tend to have lower mental development index (MDI) and psychomotor development index (PDI) scores (14). Similarly, a meta-analysis of 39 original articles, including 909,176 individuals, has shown that maternal SCH has distinctly higher risk of intellectual disability in offspring (36).

TABLE 2 | Association of maternal hypothyroidism with infant Bayley-III scores by the 2017 ATA guidelines.

Scores	*N*	Mean (SD)	Model 1		Model 2	
			β (95% CI)	*p*	β (95% CI)	*p*
Cognition						
ET	702	15.78 (2.09)	Ref		Ref	
SCH	39	15.74 (1.29)	–0.04 (–0.70, 0.62)	0.912	–0.09 (–0.75, 0.57)	0.788
IH	29	15.03 (1.97)	–0.75 (–1.51, 0.01)	0.055	–0.65 (–1.43, 0.12)	0.096
OH	3	16.33 (0.58)	0.55 (–1.77, 2.87)	0.641	0.51 (–1.82, 2.83)	0.670
Receptive communication						
ET	702	11.34 (2.01)	Ref		Ref	
SCH	39	10.74 (1.09)	–0.60 (–1.23, 0.03)	0.063	–0.68 (–1.31, –0.05)	0.034*
IH	29	10.83 (1.49)	–0.51 (–1.24, 0.21)	0.165	–0.35 (–1.09, 0.38)	0.347
OH	3	9.67 (1.53)	–1.68 (–3.89, 0.54)	0.139	–1.60 (–3.81, 0.62)	0.157
Expressive communication						
ET	702	12.09 (2.13)	Ref		Ref	
SCH	39	12.21 (1.98)	0.12 (–0.57, 0.80)	0.737	0.11 (–0.57, 0.80)	0.746
IH	29	11.97 (1.95)	–0.12 (–0.91, 0.66)	0.760	0.02 (–0.77, 0.82)	0.955
OH	3	12.33 (2.08)	0.25 (–2.16, 2.65)	0.842	0.41 (–1.99, 2.81)	0.739
Fine motor						
ET	702	13.11 (1.54)	Ref		Ref	
SCH	39	13.31 (1.56)	0.20 (–0.30, 0.69)	0.440	0.13 (–0.37, 0.62)	0.615
IH	29	12.86 (1.60)	–0.25 (–0.82, 0.33)	0.395	–0.09 (–0.67, 0.49)	0.760
OH	3	13.00 (1.00)	–0.11 (–1.86, 1.64)	0.901	0.01 (–1.74, 1.75)	0.993
Gross motor						
ET	702	14.56 (1.62)	Ref		Ref	
SCH	39	14.62 (1.68)	0.05 (–0.47, 0.58)	0.844	0.01 (–0.52, 0.53)	0.977
IH	29	13.25 (1.62)	–0.91 (–1.51, –0.30)	0.003**	–0.83 (–1.44, –0.22)	0.008**
OH	3	13.67 (2.89)	–0.90 (–2.74, 0.95)	0.341	–0.86 (–2.71, 0.98)	0.359

*Model 1: crude. Model 2: adjusted for childbearing age, pre-pregnancy BMI, parity, mode of conception, maternal education, and sex of infants. CI, confidence interval; ET, euthyroidism; SCH, subclinical hypothyroidism; OH, overt hypothyroidism; IH, isolated hypothyroxinemia. *p-value <0.05; **p-value <0.01.*

In contrast, a retrospective study of the Danish National Birth Cohort has indicated no adverse association between SCH (TSH beyond 2.5 mIU/L), and offspring verbal IQ was found (10, 16). These findings indicate that the different TSH cutoff values may be important confounders in various studies, thereby underlining the importance of performing in-depth analyses of observed associations.

Our study identified a significant association between maternal SCH (TSH > 4.0 mIU/L) and decreased receptive communication score in infants, while no significance was observed when maternal TSH levels were greater than 3.0 mIU/L but within the normal range (TSH < 4.0 mIU/L). These findings confirmed that the use of 4.0 mIU/L as the cutoff for TSH avoids the potential risk of overdiagnosis in women with SCH, thereby strengthening the association between SCH during pregnancy and adverse neurodevelopment, mainly when the TSH level is greater than 4.0 mIU/L. In summary, our results further validated and enhanced the current body of evidence suggesting that SCH diagnosed by the ATA 2017 standards is appropriate for screening high-risk women.

We also observed that maternal IH was associated with lower gross motor score in infants. Because maternal OH increases the risk of motor neurodevelopmental delay (37), most studies have shown that IH during early pregnancy is associated with an increased risk of a delay in infant motor development (10, 38). Furthermore, findings from animal studies support the observed associations. Animal studies have demonstrated that the primary brain region affected by decreased availability of maternal FT4 includes the cerebellum, which plays a critical role in motor coordination and motor activity (39). However, the present study is the first to elucidate the association of high-normal TSH levels with offspring neurodevelopment. In the present study, maternal IH with TSH levels between 3.0 and 4.0 mIU/L resulted in significantly decreased gross motor scores in infants compared to infants of mothers with TSH levels lower than 3.0 mIU/L (1.19 vs. 0.70).

Clinical guidelines clearly indicate that OH in pregnant women should be treated (18). Although the above studies have reported adverse outcomes in children born to mothers with IH, no interventional data have yet been published demonstrating the beneficial effects of levothyroxine (LT4) therapy (17, 40). Additionally, a recent guideline from the American College of Obstetrics and Gynecology (ACOG) provides a more conservative approach, essentially advocating treatment only for OH (41). In the present study, among 29 women identified as IH, 9 of them were originally diagnosed as OH according to the ATA 2011 guidelines, indicating that they were previously advised to be treated but later were not. Therefore, these women deserve more attention considering the worse effects on neurodevelopment compared to those with TSH levels below 3.0 mIU/L. Additionally, the lack of treatment effects in large randomized clinical trials (RCTs) should be reviewed. Current RCTs lack stratification of TSH concentration, which may indicate that the treatment effect on the low-risk group (e.g., TSH < 2.5 or 3.0 mIU/L) is diluted, leading to the conclusion of no benefit of treatment. Therefore,

TABLE 3 | Multivariable regression analysis to demonstrate the association of maternal TSH with infant Bayley-III scores.

Scores	*N*	Mean (SD)	Model 1		Model 2	
			β (95% CI)	*p*	β (95% CI)	*p*
Cognition						
ET[a]-ET[b]	596	15.77 (2.10)	Ref		Ref	
SCH[a]-ET[b]	106	15.82 (2.02)	0.05 (–0.38, 0.47)	0.827	0.06 (–0.36, 0.48)	0.786
SCH[a]-SCH[b]	39	15.74 (1.29)	–0.03 (–0.69, 0.63)	0.930	–0.08 (–0.75, 0.58)	0.810
IH[a]-IH[b]	20	15.30 (1.66)	–0.47 (–1.39, 0.44)	0.309	–0.35 (–1.27, 0.57)	0.456
OH[a]-IH[b]	9	14.44 (2.55)	–1.33 (–2.68, 0.02)	0.054	–1.32 (–2.69, 0.05)	0.060
OH[a]-OH[b]	3	16.33 (0.58)	0.56 (–1.76, 2.88)	0.637	0.51 (–1.82, 2.84)	0.668
Receptive communication						
ET[a]-ET[b]	596	11.39 (1.98)	Ref		Ref	
SCH[a]-ET[b]	106	11.09 (2.14)	–0.29 (–0.70, 0.11)	0.157	–0.29 (–0.70, 0.11)	0.154
SCH[a]-SCH[b]	39	10.74 (1.09)	–0.64 (–1.28, –0.01)	0.047*	–0.73 (–1.36, –0.09)	0.025*
IH[a]-IH[b]	20	10.85 (1.57)	–0.54 (–1.41, 0.33)	0.228	–0.43 (–1.31, 0.44)	0.335
OH[a]-IH[b]	9	10.78 (1.39)	–0.61 (–1.89, 0.68)	0.354	–0.32 (–1.62, 0.98)	0.631
OH[a]-OH[b]	3	9.67 (1.53)	–1.72 (–3.94, 0.50)	0.129	–1.64 (–3.86, 0.57)	0.147
Expressive communication						
ET[a]-ET[b]	596	12.09 (2.14)	Ref		Ref	
SCH[a]-ET[b]	106	12.07 (2.10)	–0.03 (–0.46, 0.41)	0.906	–0.03 (–0.47, 0.40)	0.883
SCH[a]-SCH[b]	39	12.21 (1.98)	0.11 (–0.57, 0.80)	0.747	0.11 (–0.58, 0.80)	0.757
IH[a]-IH[b]	20	12.30 (1.78)	0.21 (–0.74, 1.15)	0.666	0.35 (–0.60, 1.29)	0.476
OH[a]-IH[b]	9	11.22 (2.22)	–0.87 (–2.26, 0.52)	0.222	–0.73 (–2.14, 0.69)	0.314
OH[a]-OH[b]	3	12.33 (2.08)	0.24 (–2.16, 2.64)	0.844	0.4 (–2.01, 2.80)	0.746
Fine motor						
ET[a]-ET[b]	596	13.09 (1.53)	Ref		Ref	
SCH[a]-ET[b]	106	13.25 (1.62)	0.16 (–0.16, 0.48)	0.332	0.16 (–0.15, 0.48)	0.315
SCH[a]-SCH[b]	39	13.31 (1.56)	0.22 (–0.28, 0.72)	0.388	0.15 (–0.35, 0.65)	0.549
IH[a]-IH[b]	20	13.15 (1.79)	0.06 (–0.63, 0.75)	0.858	0.23 (–0.46, 0.92)	0.509
OH[a]-IH[b]	9	12.22 (0.83)	–0.87 (–1.88, 0.15)	0.096	–0.74 (–1.77, 0.28)	0.156
OH[a]-OH[b]	3	13.00 (1.00)	–0.09 (–1.84, 1.66)	0.922	0.03 (–1.72, 1.77)	0.977
Gross motor						
ET[a]-ET[b]	596	14.58 (1.58)	Ref		Ref	
SCH[a]-ET[b]	106	14.45 (1.85)	–0.13 (–0.47, 0.21)	0.450	–0.12 (–0.46, 0.21)	0.467
SCH[a]-SCH[b]	39	14.62 (1.68)	0.03 (–0.49, 0.56)	0.902	–0.01 (–0.54, 0.52)	0.969
IH[a]-IH[b]	20	13.80 (1.47)	–0.78 (–1.51, –0.06)	0.035*	–0.70 (–1.43, 0.03)	0.061
OH[a]-IH[b]	9	13.33 (1.32)	–1.25 (–2.32, –0.18)	0.022*	–1.19 (–2.28, –0.10)	0.032 *
OH[a]-OH[b]	3	13.67 (2.89)	–0.92 (–2.76, 0.93)	0.331	–0.89 (–2.73, 0.96)	0.348

*Model 1: crude. Model 2: adjusted for childbearing age, pre-pregnancy BMI, parity, mode of conception, maternal education, and sex of infants. CI, confidence interval; ET, euthyroidism; SCH, subclinical hypothyroidism; OH, overt hypothyroidism; IH, isolated hypothyroxinemia. [a] TSH thresholds at 3.0 mIU/L (2011 ATA guidelines). [b] TSH thresholds at 4.0 mIU/L (2017 ATA guidelines). *p-value <0.05.*

further studies should be conducted to identify the optimal treatment threshold of TSH where the benefits of LT4 administration outweigh the risks.

The strengths of the present study included its population-based prospective design, the long follow-up period, and our findings were obtained from TPOAb-negative pregnant women. We observed that maternal SCH was associated with detrimental neurodevelopment of infants, even in women with negative tests for TPOAb, which provided robust evidence to support LT4 treatment of pregnant women with TSH levels ranging from 4.0 to 10.0 mIU/L independent of their thyroid autoantibody status (42). Although the Bayley-III screening test is a validated instrument, it is not a diagnostic tool, and relying on one informant for assessment of neurodevelopment is a major limitation. We did not collect data for thyroid hormone parameters of the offspring after birth, but studies have shown that maternal thyroid function with child neurodevelopment is not mediated or modified by differences in postnatal child thyroid function (43). In addition, the present study was conducted in a single center and had a small sample size. Therefore, our conclusion needs to be further confirmed by multicenter studies with large sample sizes.

CONCLUSIONS

In summary, the present study demonstrated that maternal SCH is associated with decreased receptive communication scores in infants at 1 year of age. In addition, maternal TSH concentrations greater than 4.0 mIU/L and maternal IH are associated with impaired gross motor ability, especially in women with high-normal TSH concentrations (3.0–4.0 mIU/L). In addition, these findings suggest that clinicians should actively determine the primary cause of the decline in FT4 concentration for pregnant women in the higher end of the normal range (3.0–4.0 mIU/L) of TSH and low concentrations of FT4. Further studies are required to identify specific subgroups of women who may benefit from LT4 treatment.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This study was approved by the institutional review board of Nanjing Medical University, China NJMUIRB (2017) 002. Written informed consent was obtained from all the participants or the infants' parents or guardians.

AUTHOR CONTRIBUTIONS

QW, YJ, and HL drafted the manuscript, analyzed the data, and interpreted the data. QW, TJ, and GZ designed the study, supervised the study, and critically revised the manuscript. All authors contributed to data collection, critically reviewed the article, and approved the final version to be published.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.884851/full#supplementary-material

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Association Between Thyroid Dysfunction and Incidence of Atrial Fibrillation in Patients With Hypertrophic Obstructive Cardiomyopathy

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Objective: To explore the correlation between the incidence of atrial fibrillation (AF) and thyroid dysfunction in patients with hypertrophic obstructive cardiomyopathy (HOCM).

Methods: Thyroid function testing in 755 consecutive patients with HOCM were examined at the National Center for Cardiovascular Diseases (China) from October 2009 to December 2013. Patients were divided into four groups according to the TSH levels: TSH<0.55 mIU/L (n=37)、0.55~2.49 mIU/L (n=490)、2.50~9.9 mIU/L (n=211) and >10.00mIU/L(n=17).

Results: A total of 107 patients were diagnosed with AF (14%).(1) Compared to HOCM patients without AF,HOCM patients with AF have older age (P<0.001), higher NT-proBNP (P=0.002), higher Cr (P=0.005), larger left atrial diameter(P=0.001), lower FT3 (P=0.046), higher FT4 (P=0.004).(2) In the four groups according to the TSH levels: TSH<0.55 mIU/L, 0.55~2.49mIU/L, 2.50~9.9mIU/L and ≥10.00mIU/L, the incidence of AF was 27.02%(10/37),10.20%(50/490), 19.43%(41/211), and 35.29%(6/17), respectively. Both high and low TSH levels were associated with an increased incidence of AF. After adjusting for the common risk factor (age, NT-proBNP, and so on), stepwise multiple logistic regression analysis revealed that TSH levels were significantly related to AF incidence.Compared to patients with TSH 0.55~2.49 mIU/L, the adjusted odds ratio of AF for TSH<0.55, 2.50~9.99, ≥10.00 mIU/L were 1.481 (95% CI 0.485~4.518,P=0.490), 1.977 (95%CI 1.115~3.506, p=0.02), 4.301 (95%CI 1.059~17.476, P=0.041), respectively.

Conclusion: Our results suggested that thyroid dysfunction was associated with an increased risk of AF in patients with HOCM.

Keywords: thyroid dysfunction, hypertrophic obstructive cardiomyopathy, atrial fibrillation,TSH, risk factors

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INTRODUCTION

More and more studies have shown that thyroid dysfunction is a significant risk factor for the progression of cardiovascular disease (1, 2). Our previous research and other clinical evidence suggest (3, 4), The level of thyroid hormone is related to the deterioration of cardiac function and the occurrence of arrhythmia. Hypertrophic cardiomyopathy (HCM) is a kind of cardiomyopathy characterized by asymmetric myocardial hypertrophy, which usually occurs at the base of the interventricular septum and the lateral wall of the left ventricle (5). HCM has a variety of clinical manifestations, can occur in all age groups and has a familial genetic tendency, which is a common cause of sudden cardiac death. Heart failure and electrophysiological disorders may occur in the later stage of the disease (6–8). Atrial fibrillation is the most common persistent arrhythmia in patients with HCM. It has been found that 2% to 3.8% of HCM patients are newly diagnosed with atrial fibrillation each year, which increases the risk of heart failure, stroke/embolism, and death, especially in patients with hypertrophic obstructive cardiomyopathy with left ventricular outflow tract obstruction (9). Left ventricular filling in patients with HCM mainly depends on atrial contraction. Atrial fibrillation will shorten the left ventricular filling time and damage the left ventricular diastolic function, resulting in frequent hospitalization and declining quality of life. Atrial fibrillation is one of the risk factors for the poor prognosis of HCM. Therefore, the clinical management of hypertrophic cardiomyopathy complicated with atrial fibrillation is a very important topic (10).

However, only a few clinical studies have shown that thyroid dysfunction is related to left ventricular diastolic dysfunction in patients with HCM (11). There is no study on the role of thyroid function in predicting atrial fibrillation in patients with HCM. This study was based on 756 patients with hypertrophic obstructive cardiomyopathy to investigate the relationship between thyroid function and atrial fibrillation in patients with hypertrophic obstructive cardiomyopathy.

METHODS

Ethics Statement

The study followed the ethical guidelines of the declaration of Helsinki and China's regulations and policies on good clinical practice. The Ethics Committee approved it of the Fuwai Hospital. Before the study, we got written informed consent from all participants.

Study Patients

All patients in this study were evaluated at the Fuwai Hospital (National Center of Cardiovascular Diseases, China). Between October 1, 2009, and December 31, 2013, a total of 824 patients (age≥16 years) were diagnosed with HOCM. Among those participants, 755 subjects, with complete information on thyroid function, clinical information, and medical history, in the absence of any other cardiac or systemic disease capable of producing the magnitude of hypertrophy evident, such as uncontrolled hypertension (home blood pressure monitoring ≥140/90 mmHg), congenital heart disease, cardiac valve disease, and amyloidosis, were selected. The diagnosis of HOCM was based on (12, 13): (1) Echocardiography showed asymmetric interventricular septal thickening > 13 mm, and interventricular septal (IVS)/left posterior ventricular wall (LVPW) > 1.3 or left ventricular apical or free wall localized thickening > 15 mm. (2) tissue Doppler echocardiography, and MRI showed hypertrophy of apical and near apical IVS, dense myocardium or disordered interstitial arrangement. (3) echocardiography showed that the pressure difference of the left ventricular outflow tract was ≥ 30mmHg.

This study passed the review of the Medical Ethics Committee of Fuwai Hospital of the Chinese Academy of Medical Sciences, and all the subjects signed informed consent forms.

Collect Clinical Data

The demographic data (age, sex, weight, height), lifestyle (smoking history, drinking history), basic heart disease history, concomitant diseases (hypertension, diabetes, stroke, ventricular arrhythmia), (NYHA) cardiac function classification of New York Cardiology Association, electrocardiogram (admission ECG, postoperative ECG) and echocardiography were collected through the electronic medical record system of Fuwai Hospital. Thyroid hormone determination equipment adopts ADVIA immune detection system produced by Siemens. The levels of serum thyrotropin (TSH), free triiodothyronine (FT3), free thyroid hormone (FT4), total triiodothyronine (TT3), and total thyroid hormone (TT4) were detected by the Immunochemical luminescence method. The kit used was a Siemens kit. The normal reference values of thyroid hormones are as follows: TSH:0.55~4.78mIU/L, FT3:2.76~6.30 pmol/L.FT4:1.23~2.90pmoL/L,TT3:1.00~2.94nmol/L.TT4:55.34~160.86nmol/L.All subjects received a full set of laboratory tests simultaneously, including blood lipids, liver and kidney function, blood glucose, NT-proBNP, and so on.

Definition of Thyroid Function and Diagnosis of Atrial Fibrillation

TSH, FT3, FT4, TT3, and TT4 are all defined as normal thyroid function in the normal reference range. Hypothyroidism (hypothyroidism) is elevated TSH levels, with FT3, FT4, TT3, and TT4 levels within or below the normal reference range. In contrast, hyperthyroidism (hyperthyroidism) decreases TSH levels, with FT3, FT4, TT3, and TT4 levels in or above the normal reference range. In addition to the routine grouping methods (clinical and subclinical hyperthyroidism, clinical and subclinical hypothyroidism, and normal thyroid function), some researchers carry out grouping analysis according to TSH level, based on these previous literature reports and expert consensus (14). In this study, TSH, the most sensitive indicator of thyroid function, was divided into three groups: TSH < 0.55, 0.55 ± 2.49, 2.50 ± 9.99, and > 10.00mIU/L. The diagnosis of paroxysmal atrial fibrillation and persistent atrial fibrillation was based on the 2010 European ESC guidelines for diagnosing and treating atrial fibrillation (15).

Data Analysis

Statistical analysis was assessed with SPSS 21.0 statistical package for Windows. All continuous variables are presented as means ± SD, and analysis of variance was used to compare means across multiple groups. The relationships between parametric variables were assessed by multiple linear regression analysis. Initial differences in baseline characteristics between achieved treatment groups were sought in a bivariable investigation using $\chi 2$ tests, Fisher exact tests, and Student t-tests. Univariate and multivariate logistic regression analysis was used to explore the relationship between thyroid function and atrial fibrillation in patients with hypertrophic cardiomyopathy.

RESULTS

Study Population and Baseline Clinical Characteristics

Seven hundred fifty-six people were included in this study, including 456 males and 300 females. **Table 1** summarizes all the selected subjects' general clinical data, thyroid hormone levels, and echocardiography. The patients were divided into two groups according to whether they had atrial fibrillation or not: hypertrophic obstructive cardiomyopathy with atrial fibrillation (n=107) and hypertrophic obstructive cardiomyopathy without atrial fibrillation (n = 649). The incidence of atrial fibrillation in this study population was 14%. Patients with hypertrophic obstructive cardiomyopathy with atrial fibrillation were older than patients with simple hypertrophic obstructive cardiomyopathy ($p<0.001$). The levels of serum creatinine, NT-proBNP, and FT4 were higher ($p<0.05$), but the level of FT3 was lower ($p=0.046$) (**Table 1**).

Baseline Data and Indicators of Patients Grouped by Different TSH Levels

According to the plasma TSH level, the patients were divided into four groups: TSH < 0.55,0.55 ~ 2.49,2.50 ~ 9.99and ≥ 10.00 mIU/L groups. There were significant differences in sex, smoking history, TC, LDL-C, TSH, FT3, FF4, left ventricular end-diastolic

TABLE 1 | Clinical baseline characteristics of patients with hypertrophic obstructive cardiomyopathy with or without atrial fibrillation.

	Hypertrophic obstructive cardiomyopathy with atrial fibrillation (n= 107)	Hypertrophic obstructive cardiomyopathy without atrial fibrillation (n=648)	P-value
Age (years)	56.99±11.73	50.18±12.81	<0.001
Female (n, %)	43 (40.19)	257 (39.60)	0.908
BMI (kg/m2)	26.00±5.10	25.73±5.94	0.688
Hypertension disease (n, %)	41 (38.32)	221 (34.05)	0.403
Diabetes history (n, %)	6 (5.61)	42 (6.47)	0.729
History of hyperlipidemia (n, %)	32 (29.90)	191 (29.43)	0.935
A clear family history of HCM (n, %)	9 (8.41)	40 (6.16)	0.396
Drinking history (n, %)	33 (30.84)	186 (28.66)	0.680
Smoking history (n, %)	48 (44.86)	294 (45.30)	0.879
Systolic blood pressure (mmHg)	122.10±18.00	120.98±5.94	0.563
Diastolic pressure (mmHg)	74.59±11.47	73.90±11.43	0.560
Heart rate (b.p.m.)	71.50±13.13	71.69±27.59	0.944
LDL-C (mmol/L,x±s)	2.48±0.89	2.35±0.93	0.186
HDL-C (mmol/L,x±s)	0.96±0.30	0.97±0.33	0.809
Triglyceride (mmol/L,x±s)	1.59±0.88	1.68±0.98	0.354
Total cholesterol (mmol/L,x±s)	4.12±1.11	4.02±1.11	0.428
NT-proBNP (fmol/mL)	2476.08±1808.93	1814.85±1712.95	0.002
Serum creatinine (μmol/L)	82.77±23.73	76.56±20.05	0.005
TSH (mIU/L)	3.02±3.82	2.45±4.10	0.180
FT4 (ng/dL)	1.26±0.26	1.18±0.23	0.002
FT3 (pg/mL)	2.88±0.59	2.99±0.54	0.046
TT4 (ng/mL)	8.00±1.93	7.81±1.79	0.322
TT3 (ug/dL)	1.02±0.33	1.08±0.29	0.092
Echocardiography			
RV end-diastolic diameter (mm)	21.74±5.77	20.28±4.38	0.003
LA diameter (mm)	44.82±8.04	39.25±13.28	0.001
Interventricular septal thickness (mm)	19.79±4.52	20.27±5.68	0.415
LV end-diastolic diameter (mm)	42.65±6.21	42.49±6.02	0.801
LV posterior wall thickness (mm)	11.86±2.77	11.94±2.90	0.780
LV ejection fraction (%)	67.07±8.52	68.14±8.91	0.248
LV outflow tract gradient, at rest (mmHg)	63.42±32.70	74.56±33.42	0.002

The data in the table is expressed in the form of "mean ±SD" or "n (%)". BMI, body mass index; NT-proBNP, amino terminal pro-brain natriuretic peptide; TSH, thyrotropin; FT3, free triiodothyronine; FT4, free thyroxine; TT3, serum total triiodothyronine; TT4, serum total thyroxine.

diameter, LVEF, and the incidence of atrial fibrillation among different TSH levels groups. The incidence of atrial fibrillation in the TSH (0.55~2.49mlU/L) group was the lowest (10.20%), while TSH(> 10.00 mIU/L) group was the highest (35.29%). In TSH (< 0.55 mlU/L) group and TSH(2.50 ~ 9.99 mIU/L) group, the incidence of atrial fibrillation was 27.02% and 19.43%, respectively. There was a significant difference between those four groups (P < 0.001). In addition, compared with the TSH (0.55 ~ 2.49 mIU/L) group (normal control group), the average level of total cholesterol and LDL-C in the abnormal TSH group was higher (p<0.05), but there was no significant difference in NT-proBNP, creatine kinase isoenzyme (CK-MB), uric acid, LAEDD and LVEDD (P > 0.05) (**Table 2**).

Univariate Logistic Regression Analysis of Thyroid Hormone Level and Atrial Fibrillation in Patients With Hypertrophic Obstructive Cardiomyopathy

Age: (OR: 1.045, 95%CI: 1.027~1.063,p<0.001), NT-proBNP(Per 100 fmol/mL):(OR: 1.017,95%CI:1.006~1.029,p=0.003),serum-creatinine:(OR:1.013, 95%CI:1.004~1.022,p=0.006),FT3: (OR:0.616,95%CI:0.392~0.968,p=0.035),FT4:(OR: 3.336, 95% CI:1.483~7.503,p=0.004) (**Table 3**).

Multivariate Logistic Regression Analysis of TSH Level and the Risk of Atrial Fibrillation

After adjusting for the common risk factor (age, NT-proBNP, serum creatinine, FT3, and FT4), stepwise multiple logistic regression analysis revealed that TSH levels were significantly related to AF incidence.Compared to patients with TSH (0.55 ~ 2.49 mIU/L) group, the adjusted odds ratio of AF for TSH(<0.55) group, TSH (2.50~9.99) group, TSH (≥10.00 mIU/L) group were 1.481 (95% CI 0.485~4.518,P=0.490), 1.977 (95%CI 1.115~3.506, p=0.02), 4.301 (95%CI 1.059~17.476, P=0.041), respectively (**Figure 1**).

DISCUSSION

This study explored the relationship between thyroid function and atrial fibrillation in patients with hypertrophic obstructive cardiomyopathy. In this study, the incidence of hypertrophic

TABLE 2 | General clinical data of patients with different TSH levels.

	TSH level (mIU/L)				P-value
	<0.55 (n=37)	0.55~2.49 (n=490)	2.50~9.99 (n=211)	≥10.00 (n=17)	
Age (years)	53.79±15.78	50.95±12.26	50.86±13.82	53.31±10.26	0.522
Female (n, %)	20 (54.05)[a]	162 (33.06)	100 (47.39)[a]	7 (41.18)	<0.001
BMI (kg/m2)	25.15±4.44	26.16±6.68	24.94±3.64[a]	26.38±3.19	0.099
Hypertension disease (n, %)	14 (37.84)	173 (35.31)	70 (33.18)	4 (23.53)	0.699
Diabetes history (n, %)	1 (2.70)	32 (6.53)	13 (6.16)	2 (11.76)	0.637
History of hyperlipidemia (n, %)	9 (24.32)	142 (28.98)	68 (32.23)	4 (23.53)	0.672
A clear family history of HCM (n, %)	2 (5.40)	32 (6.53)	13 (6.16)	2 (11.76)	0.836
Drinking history (n, %)	11 (29.73)	150 (30.61)	55 (26.07)	3 (17.65)	0.450
Smoking history (n, %)	18 (48.65)	249 (50.82)	68 (13.88)[a]	7 (41.18)	<0.001
Systolic blood pressure (mmHg)	122.03±19.83	121.43±18.38	120.70±18.51	117.24±17.94	0.803
Diastolic pressure (mmHg)	72.58±10.36	74.17±11.37	73.70±11.65	75.29±13.40	0.797
Heart rate (b.p.m.)	71.97±13.47	72.24±31.11	69.92±10.06	75.65±22.61	0.667
LDL-C (mmol/L,x±s)	2.09±0.76	2.38±0.92	2.33±0.92	3.10±1.20	0.002
HDL-C (mmol/L,x±s)	0.93±0.32	0.97±0.35	0.97±0.29	1.09±0.33	0.415
Triglyceride (mmol/L,x±s)	1.83±1.41	1.66±0.95	1.66±0.95	1.65±0.43	0.792
Total cholesterol (mmol/L,x±s)	3.80±0.86	4.04±1.10	3.99±1.11	4.84±1.38[a]	0.012
NT-proBNP (fmol/mL)	2265.36±1910.45	1802.25±1625.36	2008.33±1841.96	2326.71±2364.00	0.264
Serum creatinine (μmol/L)	78.34±28.65	77.47±18.88	75.92±20.54	83.18±19.56	0.466
TSH (mIU/L)	0.29±0.19[a]	1.45±0.51	3.73±1.15[a]	23.56±14.68[a]	<0.001
FT4 (ng/dL)	1.38±0.58[a]	1.20±0.18	1.16±0.20[a]	0.96±0.26[a]	<0.001
FT3 (pg/mL)	3.25±1.77[a]	3.00±0.38	2.91±0.40[a]	2.61±0.45[a]	<0.001
TT4 (ng/mL)	8.22±2.91	7.93±1.71	7.70±1.54	6.32±2.95[a]	0.001
TT3 (ug/dL)	1.12±0.68	1.07±0.26	1.05±0.26	1.05±0.28	0.566
Echocardiography					
RV end-diastolic diameter (mm)	21.00±4.83	20.61±4.74	20.07±4.42	20.94±3.42	0.457
LA diameter (mm) (mm)	38.69±9.07	39.79±6.66	40.67±21.63	41.76±5.79	0.706
Interventricular septal thickness (mm)	20.54±7.36	20.17±5.29	20.16±5.76	20.88±5.76	0.934
LV end-diastolic diameter (mm)	45.32±7.20	42.87±5.92	41.13±5.55[a]	41.88±7.01[a]	<0.001
LV posterior wall thickness (mm)	11.60±2.88	11.96±2.83	11.93±2.91	11.58±3.63	0.864
LV ejection fraction (%)	62.99±14.24[a]	68.36±8.54	67.97±7.93	70.69±5.28	0.002
LV outflow tract gradient, at rest (mmHg)	71.37±42.35	72.886±33.62	73.94±32.22	71.70±27.65	0.968
AF (n, %)	10 (27.02%)[a]	50 (10.20%)	41 (19.43%)[a]	6 (35.29%)[a]	<0.001

[a]*is compared with TSH 0.55~2.49mlU/L group (normal control group).*

TABLE 3 | Univariate logistic regression analysis of atrial fibrillation in patients with HOCM.

	OR	95%CI	P-value
Female	1.025	0.675-1.555	0.908
Age (years)	1.045	1.027-1.063	<0.001
NT-proBNP (per 100 fmol/mL)	1.017	1.006-1.029	0.003
Serum creatinine (μmol/L)	1.013	1.004-1.022	0.006
FT3 (pg/mL)	0.616	0.392-0.968	0.035
FT4 (ng/dL)	3.336	1.483-7.503	0.004

obstructive cardiomyopathy complicated with atrial fibrillation was about 14%, which was significantly higher than that of 2% - 4% in the general population (16), but lower than the previous hypertrophic cardiomyopathy in which the incidence rate of atrial fibrillation is 18-32% (17). Previous studies have shown that the prevalence and incidence rate of atrial fibrillation are different in different regions. The incidence rate of atrial fibrillation in the Asian population is lower than that in North America or Europe (18). This difference may be related to the underestimation of the prevalence of atrial fibrillation in the Asia Pacific region. At the same time, it also suggests that we should pay attention to the screening of atrial fibrillation in patients with hypertrophic cardiomyopathy.

This study found that the increase or decrease of TSH as a sensitive indicator of thyroid function can increase the occurrence of atrial fibrillation. In patients with hypertrophic obstructive cardiomyopathy complicated with abnormal TSH, the high incidence of atrial fibrillation may be due to the local or systemic effect of inflammatory mediators. At the same time, in univariate logistic regression analysis, it was found that the increase in age, the rise of NT-proBNP level, the rise in serum creatinine level, and the abnormality of FT3 and FT4 were significantly related to AF incidence. After adjusting for age, NT-proBNP, serum creatinine, FT3, FT4, and other risk factors, multivariate logistic regression analysis showed that the increase of TSH was an independent risk factor for atrial fibrillation in patients with hypertrophic obstructive cardiomyopathy and had predictive value for the prognosis of hypertrophic obstructive cardiomyopathy. This study further supports the hypothesis of thyroid hormone levels on hypertrophic cardiomyopathy.

In this study,the incidence of atrial fibrillation in TSH (0.55~2.49mlU/L) group was the lowest (10.20%), while TSH(> 10.00 mIU/L) group was the highest (35.29%). In TSH (< 0.55 mlU/L) group and TSH(2.50 ~ 9.99 mIU/L) group, the incidence of atrial fibrillation was 27.02% and 19.43%, respectively. It seemed that the incidence of atrial fibrillation in patients with hypothyroidism was higher than in patients with hyperthyroidism. The trend of my research results is similar to some previous studies. In a cohort study of 18021 patients with atrial fibrillation, 89% had normal thyroid function, 9% had hypothyroidism, and 2% had hyperthyroidism, suggesting that many patients with hypothyroidism also develop atrial fibrillation (19). Patients with hypothyroidism have abnormally high TSH levels and often insufficient T4 levels. Hypothyroidism also increases the risk of atrial fibrillation. With the deepening of research, researchers also realized that both hyperthyroidism and hypothyroidism will increase the risk of atrial fibrillation. This evidence involves thyroid hormone-induced changes in autoantibodies, inflammation, and ion channels. However, the mechanism of atrial fibrillation in patients with hyperthyroidism or hypothyroidism is very different. The arrhythmia of hyperthyroidism may be mainly due to the up-regulation of hyperdynamic circulation, cardiac structural and functional proteins, ion channels, and gap junction proteins (20–22). Hypothyroidism is associated with a variety of cardiovascular risk factors, such as metabolic syndrome, obesity, hypertensive heart disease, diabetes, and oxidative stress, which in turn can lead to

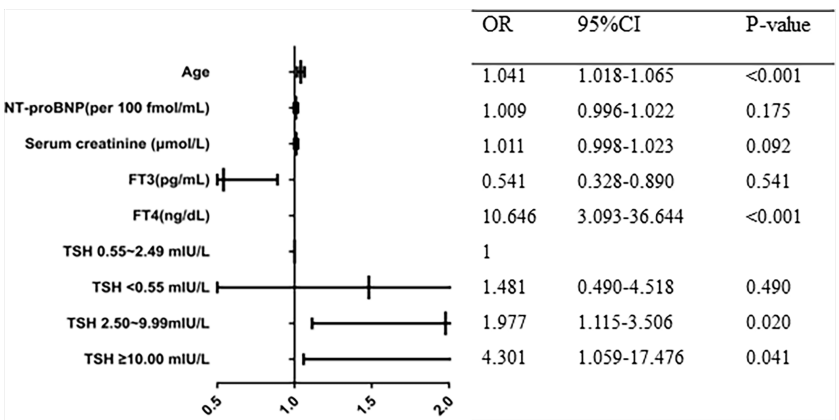

FIGURE 1 | Multivariate logistic regression analysis of atrial fibrillation in patients with HOCM.

atrial fibrillation (23–25). Hypothyroidism can reduce heart rate, prolong the atrial effective refractory period, increase atrial collagen in hypothyroid animals, and promote myocardial fibrosis. This leads to conduction heterogeneity and QT dispersion, which increases the risk of atrial fibrillation (26).

Some studies of non hypertrophic cardiomyopathy found that there is a certain relationship between TSH and the prevalence of atrial fibrillation. A previous study showed that (27), an apparent linear relationship between levels of thyroid dysfunction and atrial fibrillation risk—that is, a low atrial fibrillation risk in hypothyroid patients, a high risk in hyperthyroidism, and a TSH level-dependent (a dose-response relation) increased risk of atrial fibrillation in all levels of hyperthyroid disease, even in high normal euthyroid subjects. Notably, in subjects with reduced serum TSH levels but normal free thyroid hormone levels the risk of developing atrial fibrillation was increased by approximately 10% in individuals with high normal thyroid function and increased about 40% in those with subclinical hyperthyroidism with suppressed TSH levels. Another study shows that (28), the risk of AF increased with low normal TSH levels and slightly decreased with higher TSH levels (but remaining close to a hazard ratio [HR] of 1.0) compared to the reference level of 3.5mIU/l.

Previous studies have confirmed that different types of hypothyroidism, including subclinical hypothyroidism, low T3 syndrome, and clinical hypothyroidism, can affect the long-term prognosis of cardiovascular disease (29, 30). Animal experiments have confirmed that thyroid hormone has many effects on the cardiovascular system (31). Thyroid hormone can directly affect the metabolism and functional protein expression of cardiomyocytes and the remodeling of myocardial interstitium and microcirculation and electrophysiological disorders (32). In the state of hyperthyroidism, myocardial hypertrophy and a decrease of collagen fibers in the myocardial interstitium can be observed, which is related to the increase of matrix metalloproteinase-1 by thyroid hormone (33). Under the condition of hypothyroidism, collagen accumulation occurred in myocardial tissue. Thyroid hormone must affect the role of myocardial matrix collagen (34). In animal experiments, hypothyroidism has been shown to contribute to myocardial fibrosis and cause electrophysiological disorders (35). In 1992, Yao J et al. first reported that thyroid hormone could induce cardiac hypertrophy. This pathological change was characterized by reduced biosynthesis at type I collagen's mRNA and protein levels (32). *In vitro* experiments conducted by Chen WJ et, al. showed that hypothyroidism could lead to an increase in the concentration of mRNA expressing pro-α1 (I) collagen, and this response can be inhibited by thyroid hormone receptors (TR-β1) (34). The conclusion of our study is consistent with that of the above basic research. It is well known that T3 is important for cardiac remodeling. In our study, for patients with obstructive hypertrophic cardiomyopathy complicated with atrial fibrillation, the FT4 value is high, but the FT3 value is low, and the possible mechanisms are diverse. Previous studies have shown that there may be obstacles in the process of T4 to T3 in the state of heart failure (36), We speculate that a similar mechanism may exist in patients with hypertrophic cardiomyopathy complicated with atrial fibrillation.

In this study, elevated TSH was an independent risk factor for atrial fibrillation in patients with HOCM. Therefore, the level of thyroid function should be regarded as an essential factor in evaluating the prognosis of HOCM. In addition, animal studies have shown that thyroid hormone replacement therapy can inhibit or even reverse cardiac cardiomyocyte fibrosis, which provides a further reference for the Future Treatment of hypertrophic cardiomyopathy, prevention of atrial fibrillation, and improvement of its prognosis (37, 38).

This study is a cross-sectional study; the sample size is limited, and there are some limitations. A large cohort study needs to verify further the correlation between thyroid hormone levels and survival and myocardial injury in patients with hypertrophic cardiomyopathy. However, this study found that abnormal TSH can predict the risk of atrial fibrillation in patients with hypertrophic obstructive cardiomyopathy, which can provide a reference for clinicians in the prognosis and treatment of patients with hypertrophic cardiomyopathy.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Ethics Committee approved it of the Fuwai Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Study concept and design: Y-DT, W-YW, XM, X-LW. Acquisition, analysis, or interpretation of data: Y-DT, XM, W-YW, KZ, JG, J-LZ, Z-YZ. Drafting of the manuscript: XM, X-LW, W-YW, KZ, CS, Y-DT, Z-YZ. Critical revision of the manuscript for important intellectual content: all authors. English language editing: KZ. Statistical analysis: XM, W-YW, X-LW, Y-PL, J-JW. Obtained funding: Y-DT. Study supervision: Y-DT.

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