Journal Pre-proof

The association between COVID-19 pandemic and maternal isolated hypothyroxinemia in first and second trimesters

Jing Hua, Jiajin Shen, Jiajia Zhang, Yingchun Zhou, Wenchong Du, Gareth J. Williams

PII: S0306-4530(21)00084-6

DOI: https://doi.org/10.1016/j.psyneuen.2021.105210

Reference: PNEC105210

To appear in: *Psychoneuroendocrinology*

Received date: 28 January 2021
Revised date: 10 March 2021
Accepted date: 23 March 2021

Please cite this article as: Jing Hua, Jiajin Shen, Jiajia Zhang, Yingchun Zhou, Wenchong Du and Gareth J. Williams, The association between COVID-19 pandemic and maternal isolated hypothyroxinemia in first and second trimesters, *Psychoneuroendocrinology*, (2021) doi:https://doi.org/10.1016/j.psyneuen.2021.105210

The association between COVID-19 pandemic and maternal isolated hypothyroxinemia in first and second trimesters

Jing Hua [a*#], Jiajin Shen[b#], Jiajia Zhang [a], Yingchun Zhou [b], Wenchong Du[c], Gareth J. Williams [d*]

[a]Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine, 2699, Gaoke Road, Pudong District, Shanghai, China, 201204

[b]KLATASDS-MOE, School of Statistics, East China Normal University, North Zhangshan Road, Shanghai， Pudong District, Shanghai, China, 200062

[c]School of Social Sciences, Nottingham Trent University, 3633, Burton Street, Nottingham, UK, NG1 4BU

[d]Department of psychology, Nottingham Trent University, Burton Street, Nottingham, UK, NG1 4BU

Jing Hua, jinghua@tongji.edu.cn

Jiajin Shen, jiajin_shen@hotmail.com

Jiajia Zhang, zhangjiajia2019@tongji.edu.cn

Yingchun Zhou, yczhou@stat.ecnu.edu.cn

Wenchong Du, vivienne.du@ntu.ac.uk

Gareth J. Williams, gareth.williams@ntu.ac.uk
#Contributed equally

***Corresponding author at:**

Dr. Gareth J. Williams, School of Social Sciences, Nottingham Trent University, Burton Street, Nottingham, UK, NG1 4BU, gareth.williams@ntu.ac.uk and Prof Jing Hua Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine, 2699 Gaoke Road, Shanghai China Jinghua@tongji.edu.cn and

Abstract

Background: The outbreak of COVID-19 epidemic has induced entire cities in China placed under 'mass quarantine'. The majority of pregnant women have to be confined at home may be more vulnerable to stressors. In our study, we aimed to explore the effects of the epidemic on maternal thyroid function, so as to provide evidence for prevention and intervention of sustained maternal and offspring's health impairment produced by thyroid dysfunction.

Methods: The subjects were selected from an ongoing prospective cohort study. we included the pregnant women who receive a thyroid function test during the COVID-19 epidemic and those receiving the test during the corresponding lunar period of 2019. A total of 7148 pregnant women with complete information were included in the final analysis. Multivariate linear and logistic regression models were used for analyzing the association of COVID-19 pandemic with FT4 levels and isolated hypothyroxinemia.

Results: We found a decreased maternal FT4 level during the period of the COVID-19 pandemic in first and second trimesters(β=-0. 131, 95%CI=-0.257,-0.006， *p*=0.040) and in first trimester (β=-0. 0.176, 95%CI=-0.326,-0.026， *p*=0.022) when adjusting for 25 (OH) vitamin D, vitamin B12, folate and ferritin and gestational days, maternal socio-demographic characteristics and health conditions. The status of pandemic increased the risks of isolated hypothyroxinemia in first and second trimesters (OR=1.547, 95%CI= 1.251,1.913, $p<0.001$) and first trimester (OR=1.651, 95%CI=1.289,2.114, $p<0.001$) when adjusting for the covariates. However, these associations disappeared in the women with positive TPOAb ($p>0.05$). Additionally, we found associations between daily reported new case of COVID-19 and maternal FT4 for single-day lag1, lag3 and multi-day lag01 and lag04 when adjusting for the covariates (each $p<0.05$).

Conclusions: Mass confinement as a primary community control strategy may have a significant cost to public health resources. Access to health service systems and adequate medical resources should be improved for pregnant women during the COVID-19 pandemic.

Key words: COVID-19 pandemic; maternal isolated hypothyroxinemia; stress-related; pregnant women

1. Introduction

Thyroid function during early pregnancy appears to be linked to risk of fetal loss(Lee et al., 2019), preeclampsia(Su et al., 2019; Wu et al., 2019), low birth weight(Lee et al., 2019), and an offspring's long term emotional and behavioral outcomes(Andersen et al., 2018a; Andersen et al., 2018b; Fetene et al., 2020), due to the fetus depending on maternal thyroid hormones during the critical period of pregnancy(Pakkila et al., 2018). In addition to genetic predisposition, thyroid function is affected by environmental demands such as stress.

Recent evidence has suggested that the hypothalamic–pituitary–thyroid (HPT) axis is responsive to stress(Guo et al., 2015; Helmreich and Tylee, 2011; Zhang et al., 2018), and thyroid dysfunction could be induced(Olivares et al., 2012). Level of serum thyroxine (T4) and triiodothyronine (T3) have been found to be decreased in pregnant and young women(Aliev et al., 1987; Hohtari et al., 1987) in humans after physical or psychological stress. However, the results are inconsistent since the effect of psychological stress on thyroid function are complex and dependent on the kind of stressor, intensity, and duration, as well as an individual’s physiological state(Gianferante et al., 2014; Guo et al., 2015; Helmreich et al., 2005; Kuhlman et al., 2018; Roos et al., 2019).

Since late December of 2019, COVID-19 emerged from Wuhan, and resulted in an outbreak in China that expanded globally(Wu et al., 2020; Zhu et al., 2020). The COVID-19 pandemic has placed entire cities in China under mass confinement (lockdown of cities). The majority of pregnant women have been confined themselves at home during the pandemic, which inevitably causes additional stress(Chua et al., 2020). Women undergoing major physiological changes during pregnancy may be more vulnerable to stressors such as fears of infection, frustration, boredom, inadequate supplies, inadequate information, and financial loss(Brooks et al., 2020).

In this study, we hypothesized that the COVID-19 pandemic could be associated with maternal thyroid function in early pregnancy. The aims of the present study were 1) to compare the level of maternal thyroid function during early pregnancy before and during the COVID-19 pandemic in healthy pregnant women, 2) and to explore the acute effects of daily changes of the pandemic on maternal thyroid function, so as to provide evidence for prevention and intervention in circumstances where sustained maternal and offspring health impairments arise from thyroid dysfunction.

2. Methods

2.1 Study design and subjects

The subjects were selected from an ongoing prospective cohort study, which is to follow up the maternal and offspring's mental health from early pregnancy. The study was conducted at the Shanghai First Maternity and Infant Hospital – which covers about 1/8 of the obstetric services of Shanghai city with 30,000 deliveries per year. During the COVID-19 pandemic, the majority of hospitals closed unscheduled outpatient visits and most scheduled appointments. However, routine maternal health care clinics remained open as usual. Since 21 January 2020, the government of Shanghai has started daily reports regarding the COVID-19 pandemic in Shanghai. Therefore, we included pregnant women who received a thyroid function test during the COVID-19 pandemic from 21 January to 24 March of 2020. The pregnant women who receiving the test during the corresponding period of 2019 according to Chinese lunar calendar were included in the control population. A total of 7148 pregnant women with complete information were included in the final analysis (Figure 1). Additionally, because the COVID-19 infection is also related with thyroid disease(Chen et al., 2021), the pregnant women infected with COVID-19 were included from our study. All pregnant women infected with COVID-19 in Shanghai will be confined and received the treatment in a designated hospital (Shanghai Public Health Clinical Center) according to government's regulation. The Human Ethics Committee of Shanghai First Maternity and Infant Hospital approved the study (KS20172), and all participants provided written informed consent prior to enrollment.

2.2 Definition of variables

We used daily outbreak situation reports communicated by provincial health authorities, covered by state television and media, and posted on DXY.cn(Huang et al., 2020; Wang et al., 2020). Shanghai confirmed its first case of the novel coronavirus-related pneumonia in the evening of 20, January 2020 and reported the first case on 21 January. It is until 24 March of 2020 when the last local case of COVID-19 was reported during the first half year of 2020. Therefore, we included pregnant women who receive a thyroid function test during the COVID-19 pandemic (from 21 January to 24 March of 2020) and those receiving the test during the corresponding period of 2019 (from 1 February to 5 April of 2019) according to the traditional Chinese lunar calendar. We considered using the corresponding period (lunar calendar) as controls because the Spring Festival within this period has important effects on the psychological status and other activities in the Chinese population(Chen et al., 2020; Zhong et al., 2020).

A maternal blood sample was collected at the first antenatal visit (in the first or second trimester). The thyroid function indexes including TSH, FT4, TPOAb were measured using fluorescence and chemiluminescence immunoassays with ADVIA Centaur instruments and kits (Siemens, Munich, Germany). Isolated hypothyroxinemia is defined by a lower FT4 level (≤5th percentile) of study population in conjunction with a normal maternal TSH concentration (2.5th-97.5th) using trimester-specific reference in our institution according to the 2017 Guidelines of the American Thyroid Association(Alexander et al., 2017). For the first trimester, the reference intervals were 0.028-3.761mIU/L for TSH and <14.860 pmol/L for FT4. For the second trimester, they were 0.030-4.353 mIU/L for TSH and <13.764 pmol/L for FT4. TPOAb were categorized as negative (≤ 60 IU/mL) or positive (> 60 IU/mL) according to the Chinese Society of Endocrinology. Detailed information on thyroid function tests was described in our previously published article(Ying et al., 2016). Circulating 25(OH) vitamin D is the principal biomarker of vitamin D status in humans which is related with outdoor activity. We quantified 25(OH) vitamin D concentrations in maternal plasma. Fasting venous blood was collected at the first antenatal visit. Plasma levels of 25(OH) vitamin D were determined by chemiluminescence method using Abbott's chemiluminescence immunoassay analyzer (ARCHITECT i2000 SR). Vitamin B12, folate and ferritin levels were measured in blood plasma using chemiluminescent microparticle immunoassay (CMIA) technology, which is detected on the Beckman DxI800 automatic immunoassay analyzer.

We chose socio-demographic information collected from our ongoing cohort which was likely to moderate the association between the status of the COVID-19 pandemic and thyroid function. We divided maternal age at enrollment into three age bands of '<20', '⩾20 and <35' and '⩾35'. Pre-pregnancy BMI was calculated according to mother's height and pre-pregnancy weight. We categorized maternal BMI into '<18.5 kg/m^2 (underweight) ', '≥18.5 and <25kg/m^2(normal weight) ' and '⩾25 kg/m^2 (overweight or obesity) ' according to the WHO BMI classification(Consultation, 2004).

2.3 Statistical analysis

Multivariate linear regression models were used for analyzing the association of COVID-19 pandemic with FT4 levels during the first and second trimester. The multivariate logistic regression models were built for odds ratio (OR) between pandemic status and isolated hypothyroxinemia. For each regression model, we adjusted for covariates including the nutrients relating with daily activity and diets such as 25 (OH) vitamin D, vitamin B_{12}, folate and ferritin, and maternal age at enrollment, occupation, marital status, pre-pregnancy BMI, parity, and the day in gestation when the thyroid functions were measured. Additionally, a stratified analysis was performed to analyze the above associations according to the TPOAb status.

To further confirm whether the serum FT4 variation was induced by stress, we explored the effects of daily reported new cases on maternal FT4 and isolated hypothyroxinemia. We firstly analyze the linear or non-linear relationship of daily reported new cases with FT4 and risk of isolated hypothyroxinemia at lag1 using a generalized additive mixed model (GAMM) with the thin plate regression splines. The result showed that there was linear relationship of daily reported new cases with FT4 and risk of isolated hypothyroxinemia (Appendix A). Therefore, the mixed effect model and multilevel logistic regression models were used to calculate the effect estimates of daily reported new case on FT4 and isolated hypothyroxinemia respectively based on their linear relationship, and when considering the random effects (correlation of samples under pandemic status of the same day). We further fitted the model with different lag structures, including both single-day lag (from lag0 to lag4) and multi-day lag (lag01 and lag04). In single-day lag models, a lag of Day 0 (lag0) corresponds to the current-day change, and a lag of Day 1 (lag1) refers to the previous-day change; in multi-day lag models, lag 01 and lag 04 corresponds to 2-day and 5-day moving average of reported case of the current and previous 4 days. All analyses were performed in R 3.6.1 using the GLMMTMB and GAMM4 packages. A $p<0.05$ was considered statistically significant.

3. Results

Of 7148 participants included in final analysis, the means of FT4 and TSH were 17.791 pmol/L and 1.485 mIU/L, with standard deviations (SD) of 2.657 and 2.088 respectively. According to the laboratory reference ranges and diagnostic standards, 854 (11.9%) subjects were identified as TPOAb positive, and 6294 subjects were negative (88.5%). A total of 398 (5.6%) subjects were identified as maternal isolated hypothyroxinemia. The thyroid function by status of COVID-19 pandemic and gestational age was presented in table 2.

We found a decreased maternal FT4 level during the period of COVID-19 pandemic when adjusting for 25 (OH) vitamin D, vitamin B12, folate and ferritin and gestational days, maternal socio-demographic characteristics and health conditions in first and second trimesters(β=-0. 131, 95%CI=-0.257,-0.006， *p*=0.040) and in first trimester (β=-0. 0.176, 95%CI=-0.326,-0.026， *p*=0.022). The stratified analysis showed that the statistically significant association remained in subjects with negative TPOAb when adjusting for covariates in first and second trimesters (β=-0.147, 95%CI=-0.280, -0.015, p=0.030), first trimester (β=-0.176, 95%CI=-0.336, -0.016, p=0.031) and second trimester (β=-0.269, 95%CI=-0.501, -0.037, p=0.023). However, the association disappeared in women with positive TPOAb (each p>0.05).

The status of the COVID-19 pandemic increased the risks of isolated hypothyroxinemia when adjusting for 25 (OH) Vitamin D, vitamin B12, folate and ferritin and gestational days, maternal socio-demographic characteristics and health conditions in first and second trimesters (OR=1.547, 95%CI= 1.251,1.913, p<0.001) and first trimester (OR=1.651, 95%CI=1.289,2.114, p<0.001). Stratified analysis showed that the adjusted risks remained statistically significant in subjects with negative TPOAb in the first and second trimesters (OR=1.702, 95%CI=1.352, 2.144, p<0.001), and in first trimester (OR=1.756, 95%CI=1.343,2.297, p<0.001) and second trimester (OR=1.940, 95%CI=1.189,3.190, p=0.008). However, the risk disappeared in women with positive TPOAb (p>0.05).

To further confirm whether the serum FT4 variation was induced by stress-related pandemic, we explored the association between daily reported cases of COVID-19 and maternal FT4. We found that the increased reported case was associated with the a deceased

FT4 level when adjusting for 25 (OH) vitamin D, vitamin B12, folate and ferritin and gestational days, maternal socio-demographic characteristics and health conditions, and the acute effect estimates varied by lag structure. Statistically significant associations between daily new report case of COVID-19 and maternal FT4 were observed for single-day lag1, lag 3 and multi-day lag 01, lag 04 (Figure 2). We did not find any associations of daily reported new case with the isolated hypothyroxinemia by lag structure (Figure 3).

4. Discussion

The results of this study confirm and expand our limited knowledge about the impact of the COVID-19 pandemic on health outcomes. We observed a lower maternal FT4 level and a higher risk of isolated hypothyroxinemia during the pandemic when adjusting for the nutrients which are related with diets and outdoor activity. There was a relationship with more reported new cases of COVID-19 following lower maternal FT4 level. To the best of our knowledge, there has been little research examining the influence of COVID-19 pandemic on thyroid function. The thyroid dysfunction during pregnancy, as a result of the COVID-19 pandemic, could suggest a long-term risk to maternal and offspring health.

Our results showed a decreasing level of maternal FT4 and a higher risk of isolated hypothyroxinemia during COVID-19 pandemic even adjusting for the serum nutrients such as vitamin B_{12}, folate, 25 (OH) vitamin D and ferritin, and other maternal socio-demographic and health characteristics. The outbreak of the COVID-19 pandemic has seen entire cities in China effectively placed under a mass confinement. The implementation of unprecedented strict quarantine in China has kept a large number of people in isolation and affected many aspects of people's lives. The previous study has reported that the serum 25 (OH) vitamin D was related with outdoor activity (Musa et al., 2018). Although we did not found significant difference of vitamin-D levels between the pregnant women before and under COVID-19 pandemic in our study, we still considered it as one of the adjusting variables when exploring the association between COVID-19 pandemic and thyroid function for its possible confounding effect. Additionally, the deficiency of iron, vitamin B12, and folate has been implicated as an etiologic factor in maternal isolated hypothyroxinemia which mostly intake through diet could have been affected during the COVID pandemic(Avnon et al., 2020; Collins and Pawlak, 2016; Singh et al., 2017). However, in our study, these serum nutrients did not mediate and moderate the effects of COVID pandemic on FT4 and isolated hypothyroxinemia.

It has been reported that COVID-19 pandemic has triggered a wide variety of psychological problems(Brooks et al., 2020). Therefore, we inferred that the stress induced by the COVID-19 pandemic might influence the maternal FT4 level and isolated hypothyroxinemia. There was a nationwide survey in China showed higher scores of psychological distress, and females are much more vulnerable to stress than their male counterparts(Qiu). More than two months of confinement at home during the pandemic could induce a mild stress in pregnant women, and which may alter the rhythmicity of the HPT axis, dropping levels of T3 and T4 according to a previous study in rats(Guo et al., 2015). Serum T4 levels progressively dropped following capture and confinement of naturally fasting penguins(Groscolas and Leloup, 1989). Repeated exposure to mild-electric foot-shock causes a decrease in peripheral thyroid hormone levels in an animal trial(Helmreich et al., 2005). In human beings, it has been reported that stress leads to a drop in serum thyroid hormones in pregnant women(Aliev et al., 1987). Recent researches supported that patients with hyperthyroidism report a history of more stressful life events than their normal counterparts (Khan et al., 2020; Lang et al., 2020; Winsa et al., 1991).

Additionally, we found an association between daily reported new cases of COVID-19 and maternal FT4 measured on following 1(lag1) and 3 days(lag3), as well as the cumulative effects (lag01 and lag04). It further confirmed that the drop in FT4 during COVID-19 pandemic might be stress-induced. A study has found that T3 tends to diminish two hours after a stressor such as acute electric shocks(Helmreich et al., 2005). An increase in T3 and T4 were observed within two minutes of acute immobilization, with a following decrease two hours later(Langer et al., 1983). Unfortunately, we did observe higher risk of isolated hypothyroxinemia in response to daily reported cases. Evidence from previous research has observed hypothyroidism after more than one week of social stress exposure in rats, based on a time-cause study(Olivares et al., 2012). It might take more time to induce a significant variation of FT4(hypothyroidism). Further study is needed to explore the mechanism of stress-related pandemic on hypothyroidism.

The stratified analysis showed that the impact of the COVID-19 pandemic produced a lower FT4 level and higher risk of hypothyroidism in women with negative TPOAb， but disappeared in women with positive TPOAb. Previous research has reported that low thyroid hormone levels were related to the low humoral specific immune response in stressed animals, and assumed that stress conditions can alter thyroid axis function that in turn affects the immune response(Cremaschi et al., 2000). A combined stress could induce immunosuppression in the generation of adaptive immune responses(Zhang et al., 2018). However, the involved interaction between hypothyroidism and immune response in stressed pregnant women is needed to explore in future study.

5. Conclusions

Our study provided important evidence to health threats in pregnant women under mass quarantine during a severe pandemic. Maternal thyroid dysfunction represents a risk factor for maternal morbidity(Medici et al., 2014; Su et al., 2019; Wu et al., 2019) and neuropsychiatric disorders in both mother and offspring(Andersen et al., 2018a; Fetene et al., 2020; Fetene et al., 2019; Ibanez et al., 2015; Nelson et al., 2018; Saki et al., 2014; Stewart, 1991; Szpunar and Parry, 2018). Responding to the outbreak of COVID-19 using a mass confinement (downlock of cities) as a primary community control measure may produce a significant cost to public health resources(Brooks et al., 2020; Reynolds et al., 2008). Accessibility to public health service system and medical resources should be reformed or further improved under COVID-19 or other future severe pandemics. And further efforts should be made after the pandemic subsides because the impacts of maternal thyroid dysfunction persist in mothers and offspring over the long term.

6. Strength and Limitations

The strength of our study is to reveal the effects of stress-related pandemic of COVID-19 on FT4 and isolated hypothyroxinemia when considering the serum nutrients, which is related with outdoor activity and diets. The results further confirmed by acute variation of FT4 in response to daily reported new case of COVID-19. However, we did not detect maternal iodine levels during pregnancy which is important to the synthesis of thyroid hormones(Anees et al., 2015; Velasco et al., 2013; Yang et al., 2018; Yoganathan et al., 2015), because iodized salt has been supplied in China since 1996 (Teng et al., 2006), and current dietary iodine intake in a coastal city (e.g. Shanghai) has been considered sufficient enough for pregnant women. Additionally, information was not collected about the experiences of subjects placed under confinement such as compliance, difficulties, emotional response, psychological stress, as well as sleep problems using valid scales. Further studies analyzing the risk of hypothyroidism during a pandemic should assess subjects' stress levels and other psychological statuses. Additionally, pregnancy has a significant impact on the thyroid function(Ashoor et al., 2010; Salek et al., 2018), we did not measure other hormones (e.g. HCG) which may affect the thyroid function during pregnancy(Zhang et al., 2019). Therefore, gestational days were considered as an adjusting variable when analyzing the association between the COVID-19 pandemic and thyroid function in our study.

Funding

This study was supported by National Natural Science Foundation of China (81673179, , National Natural Science Foundation of China (11771146, 11831008, 81530086), the Science and Technology Commission of Shanghai Municipality (18140903100，19140903100), Shanghai Municipal Health Commission (2020YJZX0213), Pudong Municipal Health Commission (PW2020D-11).

Acknowledgements

The authors would like to thank the participated medical professors for collecting the data even under the COVID-19 pandemic

Conflict of interest declaration

No competing financial interests exist.

References

Alexander, E.K., Pearce, E.N., Brent, G.A., Brown, R.S., Chen, H., Dosiou, C., Grobman, W.A., Laurberg, P., Lazarus, J.H., Mandel, S.J., Peeters, R.P., Sullivan, S., 2017. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid 27, 315-389.

Aliev, M.G., Rzaeva, L.V., Rybakova, O.I., 1987. [Effect of chronic stress during pregnancy on the thyroid status of mother and progeny]. Probl Endokrinol (Mosk) 33, 74-78.

Andersen, S.L., Andersen, S., Liew, Z., Vestergaard, P., Olsen, J., 2018a. Maternal Thyroid Function in Early Pregnancy and Neuropsychological Performance of the Child at 5 Years of Age. J Clin Endocrinol Metab 103, 660-670.

Andersen, S.L., Andersen, S., Vestergaard, P., Olsen, J., 2018b. Maternal Thyroid Function in Early Pregnancy and Child Neurodevelopmental Disorders: A Danish Nationwide Case-Cohort Study. Thyroid 28, 537-546.

Anees, M., Anis, R.A., Yousaf, S., Murtaza, I., Sultan, A., Arslan, M., Shahab, M., 2015. Effect of maternal iodine supplementation on thyroid function and birth outcome in goiter endemic areas. Curr Med Res Opin 31, 667-674.

Ashoor, G., Kametas, N.A., Akolekar, R., Guisado, J., Nicolaides, K.H., 2010. Maternal thyroid function at 11-13 weeks of gestation. Fetal Diagn Ther 27, 156-163.

Avnon, T., Anbar, R., Lavie, I., Ben-Mayor Bashi, T., Paz Dubinsky, E., Shaham, S., Yogev, Y., 2020. Does vegan diet influence umbilical cord vitamin B12, folate, and ferritin levels? Arch Gynecol Obstet 301, 1417-1422.

Brooks, S.K., Webster, R.K., Smith, L.E., Woodland, L., Wessely, S., Greenberg, N., Rubin, G.J., 2020. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. Lancet.

Chen, J., Feng, Z.H., Ye, L., Cheng, Y.R., Zhou, M.Y., Li, Y., Du, C., Wang, L., Wang, M.W., 2020. Travel rush during Chinese Spring Festival and the 2019-nCoV. Travel Med Infect Dis, 101686.

Chen, W., Tian, Y., Li, Z., Zhu, J., 2021. Potential interaction between SARS-CoV-2 and thyroid: a review. Endocrinology 3.

Chua, M.S.Q., Lee, J.C.S., Sulaiman, S., Tan, H.K., 2020. From the frontlines of COVID-19 - How prepared are we as obstetricians: a commentary. BJOG.

Collins, A.B., Pawlak, R., 2016. Prevalence of vitamin B-12 deficiency among patients with thyroid dysfunction. Asia Pacific Journal of Clinical Nutrition 25, 221-226.

Consultation, W.H.O.E., 2004. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 363, 157-163.

Cremaschi, G.A., Gorelik, G., Klecha, A.J., Lysionek, A.E., Genaro, A.M., 2000. Chronic stress influences the immune system through the thyroid axis. Life Sci 67, 3171-3179.

Fetene, D.M., Betts, K.S., Alati, R., 2020. The role of maternal prenatal thyroid function on offspring depression: Findings from the ALSPAC cohort. Dev Psychopathol 32, 189-196.

Fetene, D.M., Betts, K.S., Scott, J.G., Alati, R., 2019. Maternal prenatal thyroid function and trajectories of offspring emotional and behavioural problems: findings from the ALSPAC cohort. Eur Child Adolesc Psychiatry.

Gianferante, D., Thoma, M.V., Hanlin, L., Chen, X., Breines, J.G., Zoccola, P.M., Rohleder, N., 2014. Post-stress rumination predicts HPA axis responses to repeated acute stress. Psychoneuroendocrinology 49, 244-252.

Groscolas, R., Leloup, J., 1989. The effect of severe starvation and captivity stress on plasma thyroxine and triiodothyronine concentrations in an antarctic bird (emperor penguin). Gen Comp Endocrinol 73, 108-117.

Guo, T.Y., Liu, L.J., Xu, L.Z., Zhang, J.C., Li, S.X., Chen, C., He, L.G., Chen, Y.M., Yang, H.D., Lu, L., Hashimoto, K., 2015. Alterations of the daily rhythms of HPT axis induced by chronic unpredicted mild stress in rats. Endocrine 48, 637-643.

Helmreich, D.L., Parfitt, D.B., Lu, X.Y., Akil, H., Watson, S.J., 2005. Relation between the hypothalamic-pituitary-thyroid (HPT) axis and the hypothalamic-pituitary-adrenal (HPA) axis during repeated stress. Neuroendocrinology 81, 183-192.

Helmreich, D.L., Tylee, D., 2011. Thyroid hormone regulation by stress and behavioral differences in adult male rats. Horm Behav 60, 284-291.

Hohtari, H., Pakarinen, A., Kauppila, A., 1987. Serum concentrations of thyrotropin, thyroxine, triiodothyronine and thyroxine binding globulin in female endurance runners and joggers. Acta Endocrinol (Copenh) 114, 41-46.

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., Xiao, Y., Gao, H., Guo, L., Xie, J., Wang, G., Jiang, R., Gao, Z., Jin, Q., Wang, J., Cao, B., 2020.

Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395, 497-506.

Ibanez, G., Bernard, J.Y., Rondet, C., Peyre, H., Forhan, A., Kaminski, M., Saurel-Cubizolles, M.J., Group, E.M.-C.C.S., 2015. Effects of Antenatal Maternal Depression and Anxiety on Children's Early Cognitive Development: A Prospective Cohort Study. PLoS One 10, e0135849.

Khan, I.H., Chowdhury, T., Khan, S.O., 2020. Considering the Role of Psychological Stress on Sleep Quality in Individuals with Subclinical Hypothyroidism [Letter]. Risk Manag Healthc Policy 13, 3-4.

Kuhlman, K.R., Repetti, R.L., Reynolds, B.M., Robles, T.F., 2018. Interparental conflict and child HPA-axis responses to acute stress: Insights using intensive repeated measures. J Fam Psychol 32, 773-782.

Lang, X., Hou, X., Shangguan, F., Zhang, X.Y., 2020. Prevalence and clinical correlates of subclinical hypothyroidism in first-episode drug-naive patients with major depressive disorder in a large sample of Chinese. J Affect Disord 263, 507-515.

Langer, P., Vigas, M., Kvetnansky, R., Foldes, O., Culman, J., 1983. Immediate increase of thyroid hormone release during acute stress in rats: effect of biogenic amines rather than that of TSH? Acta Endocrinol (Copenh) 104, 443-449.

Lee, S.Y., Cabral, H.J., Aschengrau, A., Pearce, E.N., 2019. Associations between Maternal Thyroid Function in Pregnancy and Obstetric and Perinatal Outcomes. J Clin Endocrinol Metab.

Medici, M., Korevaar, T.I., Schalekamp-Timmermans, S., Gaillard, R., de Rijke, Y.B., Visser, W.E., Visser, W., de Muinck Keizer-Schrama, S.M., Hofman, A., Hooijkaas, H., Bongers-Schokking, J.J., Tiemeier, H., Jaddoe, V.W., Visser, T.J., Peeters, R.P., Steegers, E.A., 2014. Maternal early-pregnancy thyroid function is associated with subsequent hypertensive disorders of pregnancy: the generation R study. J Clin Endocrinol Metab 99, E2591-2598.

Musa, I.R., Rayis, D.A., Ahmed, M.A., Khamis, A.H., Nasr, A.M., Adam, I., 2018. Thyroid Function and 25 (OH) Vitamin D Level among Sudanese Women in Early Pregnancy. Open Access Maced J Med Sci 6, 488-492.

Nelson, S.M., Haig, C., McConnachie, A., Sattar, N., Ring, S.M., Smith, G.D., Lawlor, D.A., Lindsay, R.S., 2018. Maternal thyroid function and child educational attainment: prospective cohort study. BMJ 360, k452.

Olivares, E.L., Silva-Almeida, C., Pestana, F.M., Sonoda-Cortes, R., Araujo, I.G., Rodrigues, N.C., Mecawi, A.S., Cortes, W.S., Marassi, M.P., Reis, L.C., Rocha, F.F., 2012. Social stress-induced hypothyroidism is attenuated by antidepressant treatment in rats. Neuropharmacology 62, 446-456.

Pakkila, F., Mannisto, T., Hartikainen, A.L., Suvanto, E., 2018. Maternal Thyroid Function During Pregnancy and the Child's Linguistic and Sensory Development in the Northern Finland Birth Cohort 1986. Front Endocrinol (Lausanne) 9, 127.

Qiu, J.S., B.; Zhao, M; Wang, Z.; Xie, B.; Xu, Y., A nationwide survey of psychological distress among Chinese people in the COVID-19 epidemic: implications and policy recommendations. General Psychiatry 2020,33, e100213.

Reynolds, D.L., Garay, J.R., Deamond, S.L., Moran, M.K., Gold, W., Styra, R., 2008. Understanding, compliance and psychological impact of the SARS quarantine experience. Epidemiol Infect 136, 997-1007.

Roos, L.G., Janson, J., Sturmbauer, S.C., Bennett, J.M., Rohleder, N., 2019. Higher trait reappraisal predicts stronger HPA axis habituation to repeated stress. Psychoneuroendocrinology 101, 12-18.

Saki, F., Dabbaghmanesh, M.H., Ghaemi, S.Z., Forouhari, S., Ranjbar Omrani, G., Bakhshayeshkaram, M., 2014. Thyroid function in pregnancy and its influences on maternal and fetal outcomes. Int J Endocrinol Metab 12, e19378.

Salek, T., Dhaifalah, I., Langova, D., Havalova, J., 2018. Maternal thyroid-stimulating hormone reference ranges for first trimester screening from 11 to 14 weeks of gestation. J Clin Lab Anal 32, e22405.

Singh, S., Geddam, J.J.B., Reddy, G.B., Pallepogula, D.R., Pant, H.B., Neogi, S.B., John, N., Kolli, S.R., Doyle, P., Kinra, S., Ness, A., Murthy, G.V.S., 2017. Folate, vitamin B12, ferritin and haemoglobin levels among women of childbearing age from a rural district in South India. BMC Nutr 3, 50.

Stewart, D.E., 1991. Thyroid function and postpartum depression. Am J Psychiatry 148, 816.

Su, X., Zhao, Y., Cao, Z., Yang, Y., Duan, T., Hua, J., 2019. Association between isolated hypothyroxinaemia in early pregnancy and perinatal outcomes. Endocr Connect 8, 435-441.

Szpunar, M.J., Parry, B.L., 2018. A systematic review of cortisol, thyroid-stimulating hormone, and prolactin in peripartum women with major depression. Arch Womens Ment Health 21, 149-161.

Teng, W., Shan, Z., Teng, X., Guan, H., Li, Y., Teng, D., Jin, Y., Yu, X., Fan, C., Chong, W., Yang, F., Dai, H., Yu, Y., Li, J., Chen, Y., Zhao, D., Shi, X., Hu, F., Mao, J., Gu, X., Yang, R., Tong, Y., Wang, W., Gao, T., Li, C., 2006. Effect of iodine intake on thyroid diseases in China. N Engl J Med 354, 2783-2793.

Velasco, I., Martin, J., Gallego, M., Gutierrez-Repiso, C., Santiago, P., Lopez-Siguero, J.P., Mesa, E.G., Peral, J.H., Perez, V., Garcia-Fuentes, E., Soriguer, F., 2013. Maternal-fetal thyroid function at the time of birth and its relation with iodine intake. Thyroid 23, 1619-1626.

Wang, C., Horby, P.W., Hayden, F.G., Gao, G.F., 2020. A novel coronavirus outbreak of global health concern. Lancet 395, 470-473.

Winsa, B., Adami, H.O., Bergstrom, R., Gamstedt, A., Dahlberg, P.A., Adamson, U., Jansson, R., Karlsson, A., 1991. Stressful life events and Graves' disease. Lancet 338, 1475-1479.

Wu, M.Q., Liu, J., Wang, Y.Q., Yang, Y., Yan, C.H., Hua, J., 2019. The Impact of Subclinical Hypothyroidism on Adverse Perinatal Outcomes and the Role of Thyroid Screening in Pregnancy. Front Endocrinol (Lausanne) 10, 522.

Wu, Y.C., Chen, C.S., Chan, Y.J., 2020. The outbreak of COVID-19: An overview. J Chin Med Assoc 83, 217-220.

Yang, J., Liu, Y., Liu, H., Zheng, H., Li, X., Zhu, L., Wang, Z., 2018. Associations of maternal iodine status and thyroid function with adverse pregnancy outcomes in Henan Province of China. J Trace Elem Med Biol 47, 104-110.

Ying, H., Tang, Y.P., Bao, Y.R., Su, X.J., Cai, X., Li, Y.H., Wang, D.F., 2016. Maternal TSH level and TPOAb status in early pregnancy and their relationship to the risk of gestational diabetes mellitus. Endocrine 54, 742-750.

Yoganathan, T., Hettiarachchi, M., Arasaratnam, V., Liyanage, C., 2015. Maternal iodine status and the thyroid function of pregnant mothers and their neonates in Jaffna District of Sri Lanka. Indian J Endocrinol Metab 19, 817-823.

Zhang, J., Huang, J., Aximujiang, K., Xu, C., Ahemaiti, A., Wu, G., Zhong, L., Yunusi, K., 2018. Thyroid Dysfunction, Neurological Disorder and Immunosuppression as the Consequences of Long-term Combined Stress. Sci Rep 8, 4552.

Zhang, Y., Zhang, C., Yang, X., Yang, S., Meng, Y., Liu, Z., Peeters, R.P., Huang, H.F., Korevaar, T.I.M., Fan, J., 2019. Association of Maternal Thyroid Function and

Thyroidal Response to Human Chorionic Gonadotropin with Early Fetal Growth. Thyroid 29, 586-594.

Zhong, P., Guo, S., Chen, T., 2020. Correlation between travellers departing from Wuhan before the Spring Festival and subsequent spread of COVID-19 to all provinces in China. J Travel Med.

Zhu, Z.B., Zhong, C.K., Zhang, K.X., Dong, C., Peng, H., Xu, T., Wang, A.L., Guo, Z.R., Zhang, Y.H., 2020. [Epidemic trend of corona virus disease 2019 (COVID-19) in mainland China]. Zhonghua Yu Fang Yi Xue Za Zhi 54, E022.

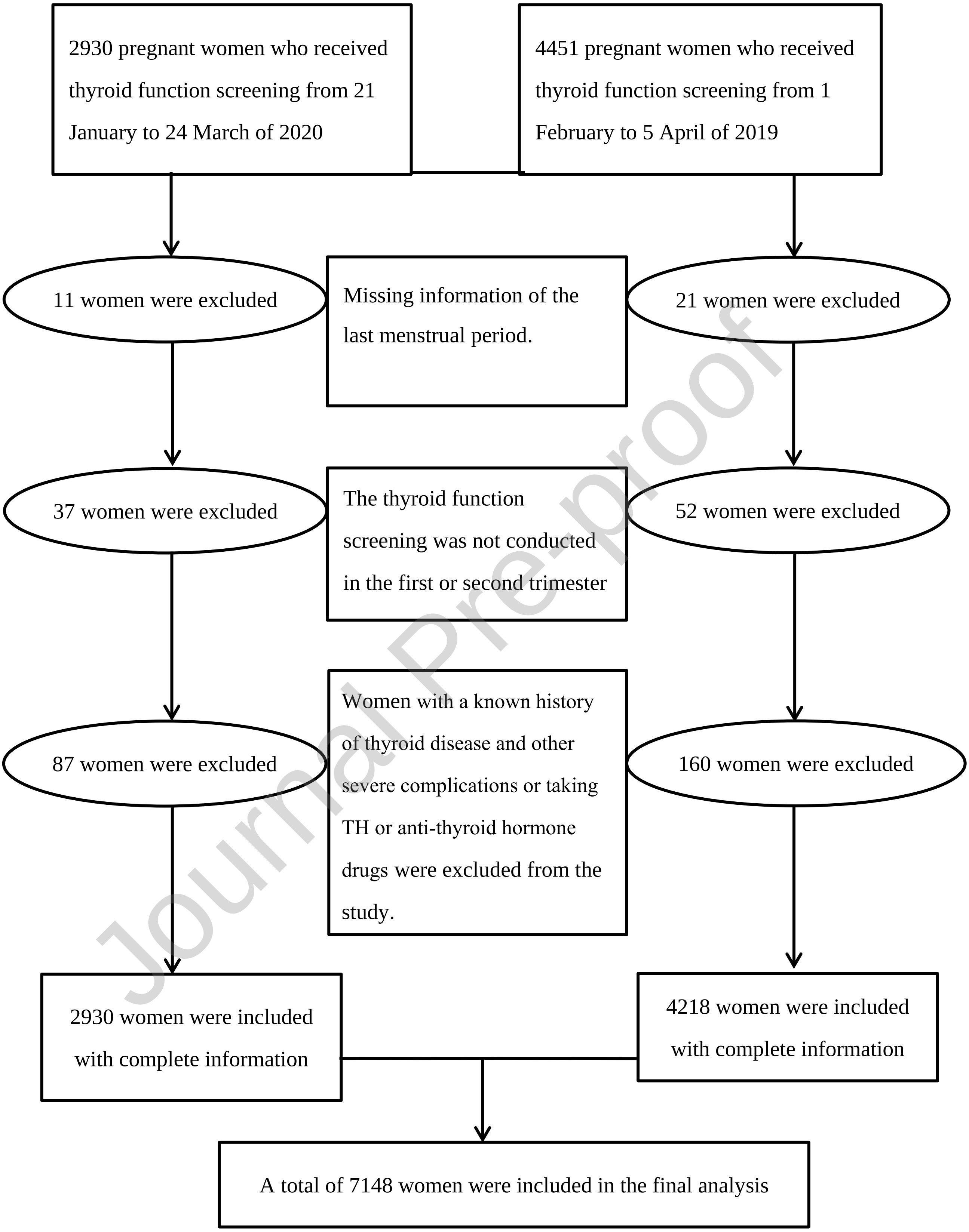

Fig. 1. Flowchart of the study population

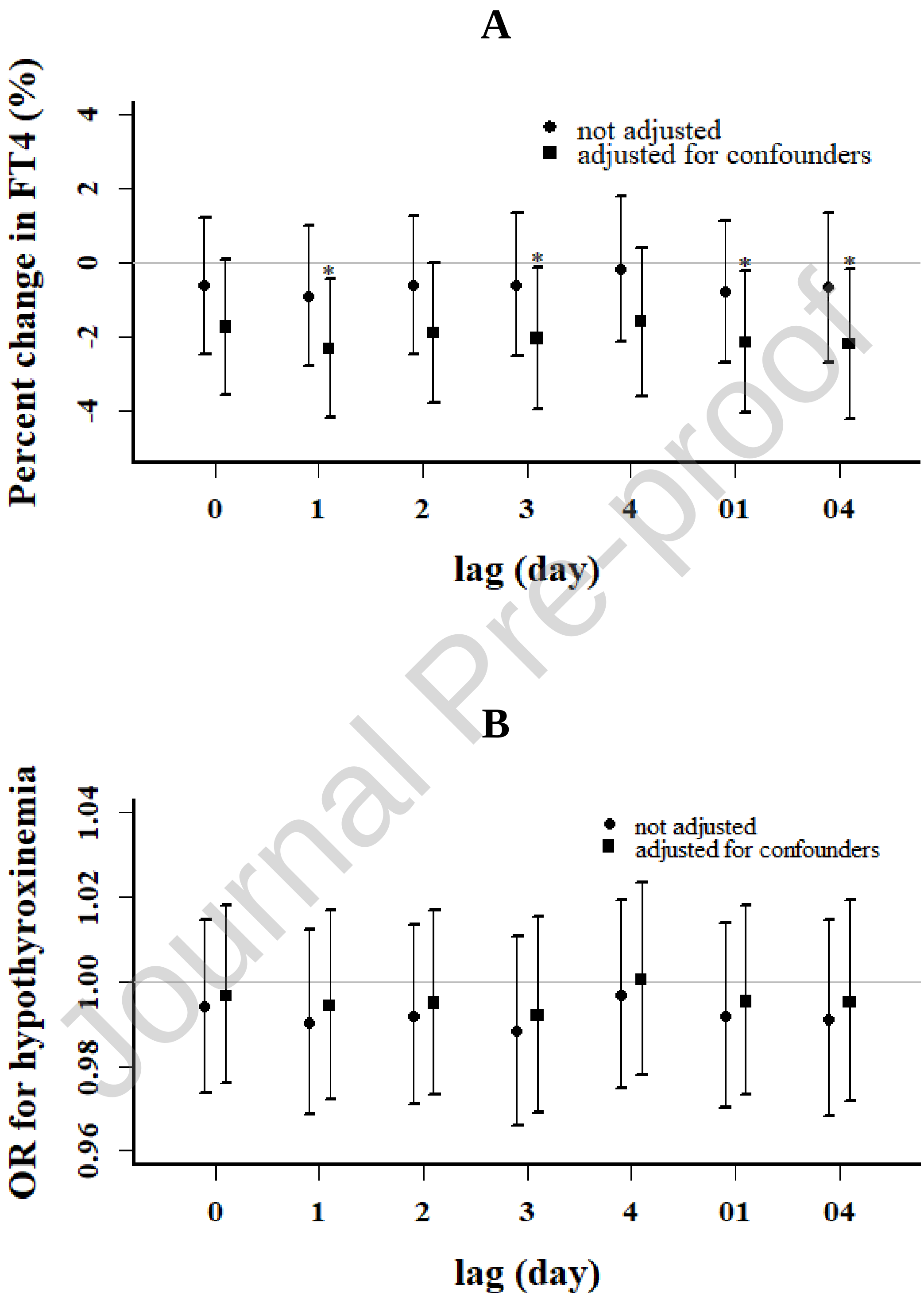

Fig. 2. The effects of daily new reported cases of COVID-19 on maternal FT4(A) and isolated hypothyroxinemia(B) classified by different lag days when adjusting or not adjusting for 25 (OH)vitamin D,vitamin B12, folate，ferritin and gestational days, maternal socio-demographic characteristics and health conditions (n=2930).

Table 1
Maternal socio-demographic characteristics and health conditions in study populatioon(n=7148)

Characteristics	Total	Under COVID-19 epidemic status (M,SD) or n(%)		Gestational age (M,SD) or n(%)	
		No	Yes	First trimester	Second trimester
Maternal age at enrollment n (%)					
<20	11(0.2)	6(0.1)	5(0.2)	4(0.1)	7(0.4)
20-34	6078(85.0)	3622(85.9)	2456(83.8)	4479(84.8)	1599(85.7)
⩾35	1059(14.8)	590(14.0)	469(16.0)	800(15.1)	259(13.9)
Occupation n (%)					
Employed	5539(77.5)	3326(78.9)	2213(75.5)	4264(80.7)	1275(68.4)
Unemployed	1609(22.5)	892(21.2)	717(24.5)	1019(19.3)	590(31.6)
Marital status n (%)					
Married	6559(91.8)	4010(95.1)	2549(87.0)	4898(92.7)	1661(89.1)
Not married	589(8.2)	208(4.9)	381(13.0)	385(7.3)	204(10.9)
Pre-pregnancy BMI[a] n (%)					
Underweight	847(11.9)	507(12.0)	340(11.6)	612(11.6)	235(12.6)
Normal	5478(76.6)	3253(77.1)	2225(75.9)	4075(77.1)	1403(75.2)
Overweight or obesity	823(11.5)	458(10.9)	365(12.5)	596(11.3)	227(12.2)
Parity n (%)					
Nulliparous	5261(73.6)	3064(72.6)	2197(75.0)	3970(75.1)	1291(69.2)
Multiparous	1887(26.4)	1154(27.4)	733(25.0)	1313(24.9)	574(30.8)
VB_{12} pg/ml M(SD)	362.078(158.402)	380.386,(158.018)	335.723(155.232)	380.285(161.392)	310.502(137.089)
Ferritin ng/ml M(SD)	57.800(46.592)	55.647(43.261)	60.900(50.854)	59.938(47.323)	51.745(43.907)
Folate ng/ml M(SD)	19.358(5.055)	18.82(5.119)	20.128(4.862)	19.905(4.684)	17.808(5.706)
25 (OH) Vitamin D ng/ml M(SD)	38.883(19.942)	38.831(19.471)	38.956(20.605)	38.466(19.299)	40.063(21.621)

[a]Prepregnancy BMI presented as three categories (underweight: <18.5 kg/m^2, normal: ≥18.5 and <25kg/m^2, Overweight or obesity: ≥25 kg/m^2)

Table 2
Thyroid function by COVID-19 pandemic status and gestational age(n=7148)

Characteristics	Total	Under COVID-19 epidemic status		Gestational age	
		No	Yes	First trimester	Second trimester
FT4 (pmol/L) M(SD)	17.791(2.657)	17.872, 2.515	17.673, 2.845	18.122, 2.631	16.852, 2.502
TSH (mIU/L) M(SD)	1.485(2.088)	1.468, 1.082	1.511, 2.992	1.386, 1.083	1.768, 3.645
TPOAb n(%)					
Negative (≤ 60 IU/ml)	6294(88.1)	3764(89.0)	2530(86.0)	4664(88.0)	1630(87.0)
Positive (>60 IU/ml)	854(11.9)	454(11.0)	400(14.0)	619(12.0)	235(13.0)
Isolated hypothyroxinemia n(%)[a]					
Yes	6750(94.4)	193(4.6)	205(7.0)	298(5.6)	100(5.4)
No	398(5.6)	4025(95.4)	2725(93.0)	4985(94.4)	1765(94.6)

[a]A trimester-specifiic criteria was used with FT4 < 5 percentile and TSH between 2.5 and 97.5 pencentile

Table 3
The impact of COVID-19 pandemic status on serum FT4 level (n=7148)

	Crude β[a] (95% CI)	Adjusted β[b] (95% CI)	Adjusted β[c] (95% CI)
Total subjects			
First and second trimesters	-0.199(-0.324,-0.074)**	-0.241(-0.367,-0.114)***	-0.131(-0.257,-0.006)*
First trimester	-0.178(-0.323,-0.033)*	-0.213(-0.360,-0.065)**	-0.176(-0.326,-0.026)*
Second trimester	-0.046(-0.274,0.182)	-0.120(-0.353,0.112)	-0.208(-0.435,0.018)
Subjects with negative TPOAb			
First and second trimesters	-0.229(-0.362,-0.097)***	-0.261(-0.395,-0.126)***	-0.147(-0.280,-0.015)*
First trimester	-0.177(-0.331,-0.022)*	-0.206(-0.363,-0.048)*	-0.176(-0.336,-0.016)*
Second trimester	-0.144(-0.378, 0.091)	-0.195(-0.433,0.044)	-0.269(-0.501, -0.037)*
Subjects with positive TPOAb			
First and second trimesters	0.051(-0.332,0.434)	-0.070(-0.455,0.314)	0.002(-0.387,0.391)
First trimester	-0.120(-0.549,0.310)	-0.220(-0.649,0.210)	-0.151(-0.592,0.289)
Second trimester	0.570(-0.230,1.370)	0.325(-0.489,1.139)	0.287(-0.533,1.107)

[a]Not adjusted for other variables
[b]Adjusted for 25 (OH) vitamin D, vitamin B12, folate and ferritin
[c]Adjusted for 25 (OH) vitamin D,vitamin B12, folate and ferritin and gestational days, maternal socio-demographic characteristics and health conditions
*p<0.05, **p<0.01,***p<0.001

Table 4
The impact of COVID-19 pandemic status on isolated hypothyroxinemia(n=7148)

	Crude OR[a] (95% CI)	Adjusted OR[b](95% CI)	Adjusted OR[c] (95% CI)
Total subjects			
First and second trimesters	1.569(1.281,1.922)***	1.588(1.289,1.956)***	1.547(1.251,1.913)***
First trimester	1.686(1.334,2.132)***	1.701(1.337,2.165)***	1.651(1.289,2.114)***
Second trimester	1.285(0.858,1.926)	1.301(0.852,1.989)	1.508(0.965,2.362)
Subjects with negative TPOAb			
First and second trimesters	1.705(1.369,2.125)***	1.729(1.379,2.169)***	1.702(1.352,2.144)***
First trimester	1.741(1.350,2.247)***	1.767(1.360,2.296)***	1.756(1.343,2.297)***
Second trimester	1.618(1.047,2.517)*	1.608(1.015,2.561)*	1.940(1.189,3.190)**
Subjects with positive TPOAb			
First and second trimesters	0.923(0.541,1.562)	0.941(0.545,1.613)	0.804(0.451,1.415)
First trimester	1.313(0.719,2.411)	1.313(0.707,2.450)	1.032(0.534,1.991)
Second trimester	0.261(0.058,0.861)*	0.300(0.065,1.024)	0.310(0.063,1.125)

[a]Not adjusted for other variables
[b]Adjusted for 25 (OH) vitamin D, vitamin B12, folate and ferritin
[c]Adjusted for 25 (OH) vitamin D,vitamin B12, folate and ferritin and gestational days, maternal socio-demographic characteristics and health conditions
*p<0.05, **p<0.01,***p<0.001

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Not applicable

Highlights

- We observed a lower maternal FT4 level and a higher risk of hypothyroxinemia during the pandemic when adjusting for the nutrients which are related with diets and outdoor activity.
- There was a relationship with more new reported cases of COVID-19 following lower maternal FT4 level.
- The thyroid dysfunction during pregnancy due to the COVID-19 pandemic could suggest a long-term risk to maternal and offspring health.