Title:

Maternal thyroid dysfunction during pregnancy and the risk of adverse outcomes in the offspring: a systematic review and meta-analysis

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ABSTRACT

Context: Previous studies suggested a potential link of maternal thyroid dysfunction with adverse neurocognitive outcomes and impaired development of internal organs in offspring.

Objective: To review the association between maternal thyroid dysfunction and the risk of adverse outcomes in offspring.

Data Sources: PubMed, EMBASE and Cochrane Library.

Study Selections: Eligible studies reported the association between maternal thyroid hormone function and the risk of adverse outcomes in their children.

Data Extraction: Reviewers extracted data on study characteristics and results independently.

Data Synthesis: Estimates were pooled and reported as odds ratio (OR) with 95% confidence interval (CI). I^2 tests were applied to assess the heterogeneity across studies.

Results: We identified 29 eligible articles and found an association between maternal hyperthyroidism and attention deficit hyperactivity disorder (ADHD) (OR: 1.18, 95% CI: 1.04 - 1.34, I^2 = 0%) and epilepsy (OR: 1.19, 95% CI: 1.08 - 1.31, I^2 = 0%) in offspring; as well as an association of maternal hypothyroidism with increased risk of ADHD (OR: 1.14, 95% CI: 1.03 - 1.26, I^2 = 25%), autism spectrum disorder (OR: 1.41, 95% CI: 1.05 - 1.90, I^2 = 63%) and epilepsy (OR: 1.21, 95% CI: 1.06 - 1.39, I^2 = 0%) in offspring.

Conclusion: Routine measurement and timely treatment on thyroid function should be considered for pregnant women.

1. INTRODUCTION

Thyroid dysfunction is among the most prevalent endocrine disorders during pregnancy [1,2]. Hyperthyroidism occurs in about 0.2% of pregnant women, with Graves' disease being the major underlying cause [3]. Maternal hyperthyroidism is associated with severe adverse effects in both mother and fetus, including pre-eclampsia, preterm delivery, heart failure, and in-utero growth retardation (IUGR) [4,5]. Conversely, the incidence of hypothyroidism in pregnancy is estimated to be from 0.3% to 3%, and it is particularly common in regions with iodine deficiency [1]. Maternal hypothyroidism is associated with an increased risk of IUGR, miscarriage, pre-eclampsia, placental abruption, and fetal death [1,6,7]. In addition to hyperthyroidism and hypothyroidism, as high as 18% [8] of pregnant women are tested positive for thyroid peroxidase antibody (TPO-Ab) or thyroglobulin antibody (TgAb). TPO-Ab positivity regulates the effect of maternal thyroid status unfavourably on pregnancy and the developing fetus [8,9]. Thus, maintaining a normal thyroid status in pregnancy is important for both the mother and the offspring.

The growth and development of the fetus are totally dependent on maternal thyroid hormones until the onset of fetal thyroid function near mid-gestation [10]. Thus, the transferral of maternal thyroid hormones to the developing fetus is critical during the early stage of pregnancy [10-12]. The hypothesis of fetal programming [10,13] suggested that maternal thyroid dysfunction can disturb early fetal brain development and lead to subsequent onset of neurodevelopmental disorders during the childhood of the offspring. This makes it biologically plausible to investigate the potential association between maternal thyroid dysfunction during pregnancy and the long-term health outcome of the offspring [14,15]. Moreover, since the thyroid hormone receptor is widely expressed in multiple tissues, abnormal maternal thyroid status may also lead to non-neurodevelopmental disorders in the offspring, such as metabolic or endocrine

disorders [16,17], impaired cardiovascular function [18,19], and respiratory system [20,21]. Although maternal thyroid status may have a profound impact on the offspring, no systematic reviews were conducted to evaluate the relationship.

Therefore, we conducted a systematic review and meta-analysis of published studies to review and meta-analyze the association between maternal thyroid dysfunction during pregnancy and the risk of various adverse outcomes in the offspring.

2. METHODS

This systematic review was reported following The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22] in Appendix 1 (https://osf.io/k9jpf [23]).

2.1 Study search

We performed a systematic literature search in PubMed, EMBASE and Cochrane Library from inception to 1st November 2019, with an updated search conducted on 1st February 2020. Articles from previous reviews or included studies were also reviewed. No restrictions on study design or language were applied in the search, but only original research studies published in peer-reviewed journals were included. The search strategy was developed for PubMed and applied to other databases. The keywords were developed based on 3 concepts: namely (i) mothers and pregnancy, (ii) thyroid hormone status, and (iii) offspring. The full predefined search terms and search strategy are provided in the Supplementary Table 1 (https://osf.io/k9jpf [23]).

2.2 Study selection and data extraction

Only full-text articles reporting the association between maternal thyroid hormone function during pregnancy and the risk of adverse outcomes in their children were included in the present systematic review and meta-analysis. Such adverse outcomes included neurodevelopmental disorders [attention deficit hyperactivity disorder (ADHD), autism spectrum (ASD), epilepsy, language and speech impairment, depression, schizophrenia, and cerebral palsy], and other clinically diagnosed outcomes. However, markers of these clinical outcomes, such as fasting glucose and blood pressure, were excluded from this systematic

review and meta-analysis. Whereas, studies related to the thyroid function of the offspring which measured levels of thyroid-stimulating hormone (TSH), free thyroxine (FT4), and TPO-Ab were included. Non-human studies, commentary reviews or descriptive studies without adequate statistical analysis were excluded.

The titles and abstracts of the included articles were screened by two independent researchers (GG and ML). The two authors (GG and ML) independently decided on the inclusion and exclusion of the studies and conducted data extraction. Discrepancies were resolved by consensus. Information in the data extraction form included year and country of the publication, study design, sample size, exposure timing, maternal thyroid status, child outcomes with measurement tools, age of the children at assessment, summary statistics, and variables used for potential confounder adjustment. Relative risk (RR), incidence rate ratio (IRR) or comparable statistics from the fully adjusted model were extracted from each included study. Since the prevalence of clinical outcomes in offspring are all < 10%, odds ratio (OR) is similar to and considered as comparable to RR. For duplicated studies using the same cohort, the study with a larger sample size was included in the meta-analysis. As Andersen et al. 2018 [15] is an update of Andersen et al. 2013 [24] and Andersen et al. 2014 [25] with different study design and smaller sample size, Andersen et al. 2018 [15] was excluded from the systematic review and meta-analysis.

2.3 Quality assessment

The quality of the included studies was assessed using The Newcastle-Ottawa Scale (NOS) by two authors (GG and ML) independently. The NOS consists of three domains (selection,

comparability, and outcome), and provides a summary measure of quality for each study. Disagreements were resolved through discussion with IW and CLC.

2.4 Data analysis

All included studies were described narratively and presented in Table 1. Pooled OR was calculated using the inverse variance weighting model. Meta-analysis was conducted when data of two or more studies investigating the same exposure and outcome were available. The original studies' definition of maternal hyperthyroidism, hypothyroidism and hypothyroxinemia was adopted in this meta-analysis. Maternal thyroid parameters (FT4 and TSH) were fitted as continuous variables and meta-analyzed if they had the same unit (e.g. per SD). Where multiple cut-offs of FT4 or TPO-Ab were measured, we included results derived from all cut-offs. We extracted OR / HR from the adjusted model when applicable. We estimated the OR / HR based on the lower confidence limits in the original studies if only data with one decimal point was available. The heterogeneity of the studies was evaluated using I^2 tests. I^2 no more than 25% represented low heterogeneity; I^2 between 25% and 50% represented moderate heterogeneity; I^2 greater than 50% represented high heterogeneity. The overall effects were analyzed with a fixed-effects model if the heterogeneity was low; otherwise, a random-effects model was applied. Forest plots were generated for further visual inspection of heterogeneity. Statistical analyses were conducted using Review Manager (RevMan 5.3; Cochrane Collaboration, Oxford, UK).

3. RESULTS

3.1 Study selection

A total of 9975 records were identified by the electronic search engine. After removal of duplicates, 7914 items were evaluated based on title and abstract screening, of which 151 full-text articles were assessed for eligibility. Of these, 29 studies [14,16-21,24-45] met our inclusion criteria and were included in this study. The PRISMA flow diagram summarizing the search results is presented in Figure 1.

3.2 Characteristics of included studies

Study characteristics are summarized and shown in Table 1. All included studies were observational studies based on population-based prospective birth cohorts or national register-based retrospective cohorts. Among the 29 studies included, 22 articles investigated the association between maternal thyroid dysfunction and neurodevelopmental disorders in offspring. One of these 22 articles, together with the remaining 7 articles, also investigated non-neurodevelopmental outcomes. In all these 29 studies, the non-exposure group comprised pregnant mothers without thyroid dysfunction. Estimates of maternal thyroid status and offspring outcomes extracted from these 29 studies are provided in Tables 2 - 5. Pooled estimates and the forest plots are provided in Figures 2 - 4. The corresponding funnel plots are provided in Supplementary Figures 1 - 3 (https://osf.io/k9jpf [23]).

3.3 Neurodevelopmental disorders in the offspring (N = 22)

Most studies (N = 17) were conducted in European countries except five were conducted in India (N =1), Israel (N =1), and the United States (N = 3). There are 18 cohort studies and 4

case-control studies. Maternal thyroid dysfunctions discussed were hyperthyroidism, hypothyroidism, hypothyroxinemia and levels of maternal thyroid hormone [including TSH, FT4, and thyroperoxidase antibodies positive (TPO-Abs+)].

3.3.1 Hyperthyroidism

Seven studies investigated hyperthyroidism as exposure (Table 2), with ADHD (n_{study} = 2; $n_{sample\ size}$ = 15422) [25,29], ASD (n_{study} = 2; $n_{sample\ size}$ = 14204) [25,26], epilepsy (n_{study} = 2; $n_{sample\ size}$ = 25495) [14,24], and schizophrenia (n_{study} = 2; $n_{sample\ size}$ = 4638) [14,28] in offspring as the outcomes. The pooled OR of offspring ADHD, ASD, epilepsy, and schizophrenia was 1.18 (95% CI: 1.04 - 1.34), 1.17 (95% CI: 0.96 - 1.42), 1.19 (95% CI: 1.08 - 1.31), and 0.96 (95% CI: 0.53 - 1.72), respectively. The heterogeneity was estimated to be low (I^2 = 0%) in all outcomes. (Figure 2, Supplementary Figure 1 [https://osf.io/k9jpf [23]])

Only one study investigated the association between maternal hyperthyroidism and cerebral palsy, revealing a null association [42] (Table 2). Meta-analysis was not performed for this outcome.

3.3.2 Hypothyroidism

Among all maternal thyroid status, maternal hypothyroidism was the most frequently studied (N = 12). There are 4 ($n_{sample\ size}$ = 32827), 5 ($n_{sample\ size}$ = 419878), 2 ($n_{sample\ size}$ = 12465), 2 ($n_{sample\ size}$ = 2780), and 2 studies ($n_{sample\ size}$ = 29070) investigating ADHD [25,29,37,38], ASD [25-27,34,37], epilepsy [14,24], schizophrenia [14,28], and cerebral palsy [37,42] as the clinical outcomes respectively (Table 3). The pooled OR for offspring ADHD, ASD, epilepsy, schizophrenia,

and cerebral palsy was 1.14 (95% CI: 1.03 - 1.26), 1.41 (95% CI: 1.05 - 1.90), 1.21 (95% CI: 1.06 - 1.39), 3.02 (95% CI: 0.26 - 35.51), and 0.95 (95% CI: 0.64 - 1.40), respectively, with low (ADHD: I^2 = 25%; epilepsy / cerebral palsy: I^2 = 0%), to high (ASD: I^2 = 63%, schizophrenia: I^2 = 86%) heterogeneity detected for each outcome (Figure 3, Supplementary Figure 2 [https://osf.io/k9jpf [23]]).

Only one study by Frank et al. [33] investigated language and speech impairment as the clinical outcome but null association was observed in the study (HR: 0.75, 95% CI: 0.38 - 1.43, Table 3).

The definition of hypothyroidism in the included studies were mainly overt hypothyroidism. Only three studies performed an exploratory analysis of maternal subclinical hypothyroidism and investigated offspring ASD [26], schizophrenia [28], and ADHD [39] as the clinical outcomes, but null association was observed.

3.3.3 Hypothyroxinemia

Five studies investigated the association between maternal hypothyroxinemia and offspring neurodevelopmental disorders (Table 4). Three studies investigated ADHD as a clinical outcome. Modesto et al. [39] found children exposed to maternal hypothyroxinemia during pregnancy had higher ADHD scores compared with non-exposed children (β : 0.07, 95% CI: 0.003 - 0.14). Similarly, Oostenbroek et al. [40] found maternal hypothyroxinemia with FT4 < 5^{th} percentile was associated with a 1.70-fold (95% CI: 1.01 - 2.86) increase in odds of teacher-reported ADHD, although a null association was observed when parent-reported ADHD was

used as the outcome. Vermiglio et al. [44] reported a significantly higher prevalence of ADHD among the offspring of mothers with hypothyroxinemia in the moderately iodine-deficient region.

Only one single study was conducted for the association of maternal hypothyroxinemia with offspring ASD and schizophrenia (Table 4). Roman et al. [43] reported severe maternal hypothyroxinemia (FT4 < 5th percentile) was associated with increased odds of pervasive developmental problems in offspring (OR: 2.60, 95% CI: 1.30 - 5.18). Gyllenberg et al. [28] reported a positive association between maternal hypothyroxinemia and offspring schizophrenia (OR: 1.75, 95% CI: 1.22 - 2.50).

3.3.4 Thyroid hormone levels

Eleven studies investigated the association between maternal thyroid hormone parameters and offspring neurodevelopmental disorders (Table 5). Fetene et al. [32] found null association between maternal TPO-Ab+ with offspring ADHD, but Ghassabian et al. [36] observed an association between elevated titers of TPO-Abs and the risk of ADHD (OR = 1.77, 95% CI: 1.15-2.72, Table 5). Two studies [26,43] investigated the association of maternal TPO-Ab+ with offspring ASD ($n_{\text{sample size}}$ = 5959), and the pooled OR is 1.30 (95% CI: 0.58 - 2.94, I^2 = 60%) (Figure 4, Supplementary Figure 3 [https://osf.io/k9jpf [23]]). Notably, the two studies used different cut-off points to define TPO-Ab+.

Four studies investigated the association of maternal FT4 level with offspring ADHD. Chevrier et al. [30] and Modesto et al. [39] found a null association between maternal FT4 level and offspring

scores on ADHD (Table 5). The other two studies [32,40] included offspring ADHD as a binary outcome and also found the level of maternal FT4 was not associated with ADHD in children.

Six studies investigated the association of maternal TSH level with offspring ADHD. Chevrier et al. [30] found doubling in TSH levels was associated with a 0.65 point decrease (95% CI = -1.26 to -0.04) on the ADHD subscale of the Child Behaviour Checklist (CBCL), but there was no significant association between maternal TSH level and child's performance on the Conner's Kiddie Continuous Performance Test (KCPT). Ghassabian et al. [35] reported that per SD increase in plasma level of TSH was associated with higher CBCL externalizing (ADHD) scores. On the other hand, Modesto et al. [39] found null association between maternal TSH level and offspring scores on ADHD using Conner's Parent Rating Scale-Revised Short Form. Three studies [32,40,41] fitted maternal TSH level as continuous variables and included offspring ADHD as a binary outcome. Fetene et al. [32] observed null association between maternal TSH level and offspring ADHD. Similarly, Oostenbroek et al. [40] observed null association between maternal TSH level and offspring ADHD, either reported by teachers or by parents. However, Pakkila et al. [41] found an association for each log increase in maternal TSH with ADHD symptoms in both boys (OR: 1.17, 95% CI: 1.00 - 1.36) and girls (OR: 1.39, 95% CI: 1.07 - 1.80, Table 5).

Only one single study was conducted for the following comparisons between maternal thyroid hormone levels and offspring neurodevelopmental disorders. Roman et al. [43] investigated the association of maternal FT4 and TSH levels with offspring ASD while null association was observed. Fetene et al. [31] was the only study investigating offspring depression as a clinical outcome. They reported a null association of maternal TPO-Ab+ and TSH levels with offspring depression. Meanwhile, a significant association of maternal FT4 level with higher odds of

depression in offspring was observed (OR: 1.21, 95% CI: 1.00 - 1.47). Gyllenberg et al. [28] investigated the association of maternal FT4 and TSH levels with offspring schizophrenia. They found the odds of schizophrenia decreased by 54% per log unit increase of maternal FT4 (95% CI: 0.31 - 0.94), but the association between log-transformed level of TSH and schizophrenia was not significant (Table 5).

3.4 Non-neurodevelopmental outcomes (N = 8)

Since most of the non-neurodevelopmental outcomes were observed in one single study (Supplementary Table 2, https://osf.io/k9jpf [23]), meta-analysis was not conducted, and the individual studies were described in Supplementary Text (https://osf.io/k9jpf [23]).

3.5 Quality assessment

Study quality assessments were presented in Appendix 2 (https://osf.io/k9jpf [23]). Most studies (accounted for 60% of total included studies) were of good quality except for nine studies. The overall quality of these nine studies was low because of the small sample size, poor identification of exposure and outcomes, or they did not adjust for any potential covariates in the model. Six out of the nine studies were not included in meta-analysis. For the remaining three, we performed additional sensitivity analyses by removing lower-quality studies in the meta-analysis. An exception is the association analysis between maternal TPO-Ab+ and offspring ASD where only two studies were included in the meta-analysis, indicating cautious interpretation may be required. Similar results were observed in all the sensitivity analyses when compared to the original analysis without excluding lower-quality studies (Figure 3).

4. DISCUSSION

This is a comprehensive systematic review with meta-analysis providing evidence for the association between maternal thyroid status and various offspring clinical outcomes. In general, maternal hyperthyroidism during pregnancy was significantly associated with increased risk of offspring ADHD, epilepsy, and hyperthyroidism. Whereas, maternal hypothyroidism during pregnancy was significantly associated with increased risk of ADHD, ASD, epilepsy, and hypothyroidism. These findings suggest that either maternal hyper- or hypo-thyroidism could affect neurodevelopment and thyroid health in the offspring.

4.1 Maternal thyroid dysfunction and neurodevelopmental disorders in offspring

Most studies included in this systematic review and meta-analysis studied maternal hypothyroidism as exposure. Although not a highly prevalent condition during pregnancy, maternal hypothyroidism is known to be associated with increased risk of spontaneous miscarriage, stillbirth, and perinatal death. Regarding the ascertainment of thyroid status, 13 out of 22 studies measured maternal exposure using thyroid function test, while the other nine studies used clinical diagnosis or prescription records from hospitals. The majority of the studies employed laboratory tests to measure maternal thyroid levels during the first and early second trimesters. Notably, most studies available did not adjust for treatment status, while this potential factor can play a role in the association. A recently published article by Rotem et al. [46], which is out of our investigation period, examined the association between maternal thyroid disorders and the risk of ASD in offspring, taking into account gestational thyroid hormone level and thyroid medications use. They found that maternal thyroid disorders, especially hypothyroidism, were associated with increased ASD risk in the offspring. This observation is indeed in line with our meta-analysis, showing hypothyroidism was significantly associated

with offspring ASD. Nevertheless, they proposed that the association between maternal thyroid status and offspring ASD was independent of maternal gestational thyroid hormones and unaffected by medication treatment. By including a more comprehensive range of confounding factors and biologically relevant covariates (e.g. thyroxine treatment), future studies are warranted to re-visit the association between maternal thyroid dysfunction and various health outcomes in offspring. Together with larger sample size and longer follow-up time, future work may particularly focus on the underlying mechanisms, which is largely unknown.

Notably, in the setting of register-based study cohorts using diagnosis codes or prescription records for exposure measurement, most included studies were unable to identify individuals with subclinical hypothyroidism. Only three studies investigated the association between maternal subclinical hypothyroidism and clinical outcomes in offspring while null associations were reported. The current data did not show a consistent association between subclinical hypothyroidism during pregnancy and adverse pregnancy outcomes [8,47-49] but this was observed in a limited number of studies with small sample size. In fact, subclinical hypothyroidism is more common than overt hypothyroidism[8,50] Future studies are required to examine individuals with subclinical hypothyroidism. On the other hand, we observed in this review that there was some evidence of association between maternal hypothyroxinemia and offspring ADHD, ASD and schizophrenia. To date, treatment for thyroid dysfunction during pregnancy is still a controversial issue [48,49]. The potential risks of maternal hypothyroxinemia on the offspring unraveled in this review may raise the awareness of the need to devise an optimum clinical management strategy for pregnant women, such as levothyroxine treatment.

The most commonly studied outcome is neurodevelopmental disorders in offspring, and there is a plausible explanation of the impact of maternal thyroid status during the first and early stages of second trimesters on the neurodevelopment in offspring [51-53]. The fetal thyroid heavily depends on the maternal supply of thyroid hormone before the onset of thyroid function in the fetus which occurs around 16 - 20 weeks of gestation, and there is a significant transfer of thyroid hormones from the mother to the fetus [10,12]. The supply of thyroid hormone to the fetus leads to increased FT4 and decreased TSH concentrations from around the eighth week till the first half of pregnancy in the pregnant mothers, resulting in different reference intervals for TSH and FT4 when compared with the non-pregnant status [54]. Besides, Oostenbroek et al. [40] investigated maternal thyroid hormone levels throughout the whole duration of pregnancy. They partially confirmed early disruption in maternal thyroid function may be associated with ADHD but found a null association with other behavioral problems. In this systematic review and meta-analysis, we provided evidence that maternal hyper- and hypo-thyroidism are associated with increased risk of a range of neurodevelopmental disorders, suggesting that the impact of maternal thyroid status may not be limited to ADHD only in offspring.

The impact of maternal thyroid status after the early stage of the second trimester is less frequently studied. Chevrier et al. [30] was the only one who measured maternal thyroid hormone during the third trimester. They reported a higher maternal TSH level was associated with a lower risk of having ADHD symptoms in offspring. Whereas, some studies identified a positive association between higher maternal thyroid hormone levels in the first two trimesters and increased risk of ADHD in offspring [35,41]. This indicated a balanced level of maternal thyroid hormone at each stage of pregnancy would be optimal for fetus neurodevelopment. However, the presence of abnormal thyroid status in the third trimester could be a marker of abnormal

thyroid status in earlier trimesters. Nevertheless, the effect of timing of maternal thyroid function measurement requires further studies.

4.2 Strength and limitations

Previously, three published systematic reviews investigated the association between maternal thyroid hormone abnormalities and the risk of neurodevelopmental disorders in the offspring [55-57]. Two systematic reviews examined the relationship between maternal thyroid dysfunction and psychiatric disorders (mainly focused on ADHD) [58,59]. Compared to these previous reviews, our study had a wider scope in respect of both the exposure and the outcome. Moreover, we only included outcomes that are clinically diagnosed or ascertained by well-established measurement tools. The setting of our inclusion criteria is more likely to produce consistent and reliable conclusions.

Nevertheless, there are limitations. First, we observed marginally significant association in the meta-analysis, which could be due to the limited number of studies, and the small sample size in each study, echoing the presence of the research gap and arousing the need to have more studies in this important but underexplored area. Cautious interpretation is also required in the current meta-analysis. Second, the definitions of thyroid dysfunction were heterogeneous across studies, as there was no consensus in the definition of thyroid dysfunction during pregnancy at the time of this current study. Third, the definition of the clinical outcomes was not standardized in the included studies. Although we only included outcomes that were

clinically diagnosed or assessed by validated tools, ten out of 22 studies that examined neurodevelopmental outcomes in offspring used behavior checklist rather than diagnosis or prescription records to identify the outcomes. The questionnaires adopted were reported by parents [30-32,35,36,39-41,43], teachers [40], self-report [31,32], or by clinical observation [44], leading to the discrepancy of the estimates. Fourth, the timing for the measurement of offspring outcomes plays a key role in revealing the association. Outcomes such as schizophrenia and depression usually develop at a late stage in childhood or even adolescence. Thus, a long follow-up time is essential to detect the potential association. Fifth, clinical outcomes ascertained using the diagnosis code or prescription records could lead to overestimation by misclassification. As these limitations may increase heterogeneity between studies, cautious interpretation is required regarding the findings of meta-analyses with high heterogeneity.

4.3 Clinical interpretations

Although measurement of maternal thyroid hormone levels during pregnancy can be used for determining maternal thyroid status, current guidelines from the American Thyroid Association and the European Thyroid Association differ in their recommendations regarding the screening of thyroid hormone during pregnancy [2,50]. The current systematic review and meta-analysis highlighted the potential association between maternal thyroid dysfunction during pregnancy and various disorders in the offspring, suggesting the importance of prevention during pregnancy in maintaining the health of the offspring. To cater for fetal iodine requirement, increase in maternal thyroid hormone production and renal iodine clearance, there is an elevated iodine requirement during pregnancy. Having sufficient iodine intake during pregnancy is one of the effective preventive measures of maternal thyroid dysfunction. In cases of pregnant mothers who are diagnosed with abnormal thyroid function, they should be

promptly treated and carefully monitored throughout pregnancy to avoid hyper- and hypo-thyroidism. Regarding the thyroid hormone supplementation during pregnancy, a recent systematic review and meta-analysis [60] of randomized controlled trials (RCTs) and retrospective studies including 7970 patients demonstrated that LT4 supplementation had beneficial effects in pregnant women with subclinical hypothyroidism and / or thyroid autoimmunity by reducing their risks of pregnancy loss and preterm birth. Consistent results were obtained by subgroup analysis of RCTs. Depending on the types of pregnancy [naturally conceived pregnancies, versus pregnancy achieved by assisted reproduction technology (such as in vitro fertilization and intracytoplasmic sperm injection)], LT4 supplementation may reduce the risk of pregnancy loss or / and preterm birth better in women with thyroid autoimmunity or subclinical hypothyroidism. On the other hand, a meta-analysis [61] of RCTs demonstrated that euthyroid women with individualized initial dosages of LT4 had lower risk of miscarriage, while those with fixed dosages of LT4 showed no significant difference. In addition, euthyroid women with thyroid autoimmunity given initial LT4 treatment in early pregnancy had a lower risk of preterm birth when compared with those receiving placebo or no treatment. According to the aforementioned findings, detailed treatment strategies (such as timing and dosage of initial treatment) should be developed for pregnant women based on their types of pregnancy and thyroid status. After such strategies are developed, individualized therapeutic strategy of LT4 supplementation might be encouraged for pregnant women with euthyroidism, subclinical hypothyroidism or thyroid autoimmunity. Nevertheless, the number of RCTs to date is limited, and the sample size of available studies are small. Future large RCTs are warranted in this area.

5. CONCLUSION

Our review suggested that maternal thyroid dysfunction during pregnancy is a potential risk factor for neurodevelopmental disorders (including ADHD, ASD, epilepsy), other cardiometabolic and respiratory conditions, and thyroid dysfunction in offspring during childhood. Currently, the optimum management strategy of maternal thyroid dysfunction during pregnancy is still largely unexplored. In view of these findings, routine measurement of thyroid function test during early pregnancy should be considered for all pregnant women. Further studies are warranted to delineate the association of thyroid status, especially levels of anti-TPO antibodies, in pregnancy and fetal outcome.

DISCLOSURE SUMMARY

KKCM is the recipient of the CW Maplethorpe Fellowship and personal fees from IQVIA Ltd., unrelated to the submitted work. PI has received funding from the Hong Kong Research Grants Council, Health & Medical Research Fund and Hong Kong Jockey Club Charities Trust, unrelated to the submitted work. ICKW reports research funding outside the submitted work from Amgen, Bristol-Myers Squibb, Pfizer, Janssen, Bayer, GSK, Novartis, the Hong Kong RGC, and the Hong Kong Health and Medical Research Fund, National Institute for Health Research in England, European Commission, National Health and Medical Research Council in Australia, and also received speaker fees from Janssen and Medicine in the previous 3 years, unrelated to the submitted work. The other authors declare no conflict of interest.

AUTHOR NOTES

CLC contributed to the conception of the work and designed the study. GMG and MTYL decided on the inclusion and exclusion of studies, and conducted data extraction. GMG performed the meta-analysis, wrote the first draft of the manuscript, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. KKCM, WCL, PI, GHYL, ICKW and AWCK interpreted, critically evaluated, and improved the study design and manuscript, and shared the responsibility for the final manuscript and the decision to submit.

Figure 1. PRISMA flow diagram of included studies

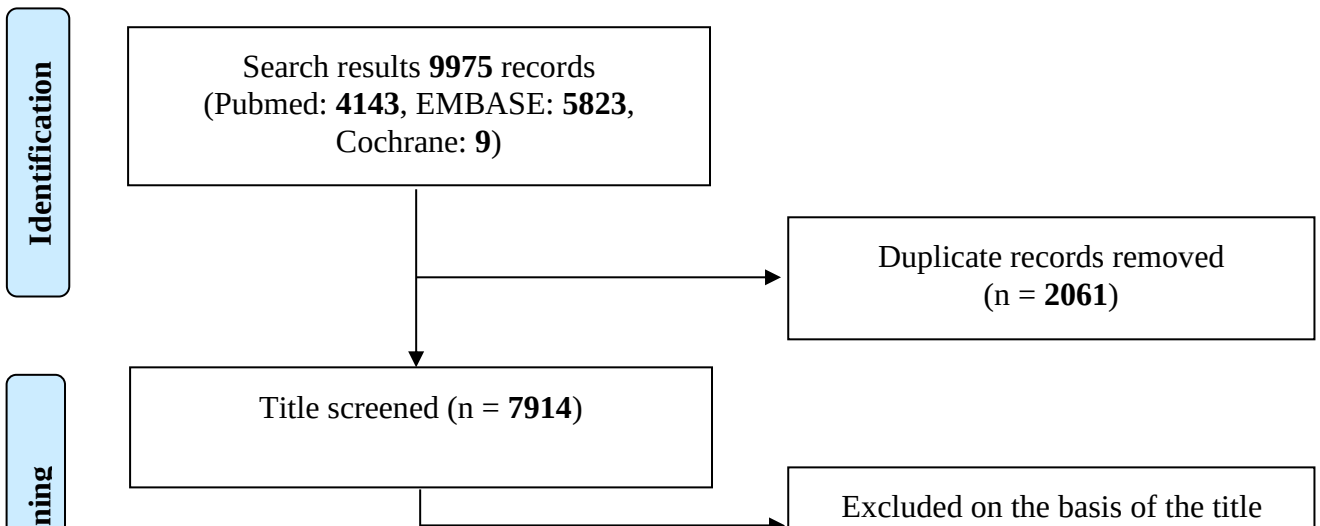
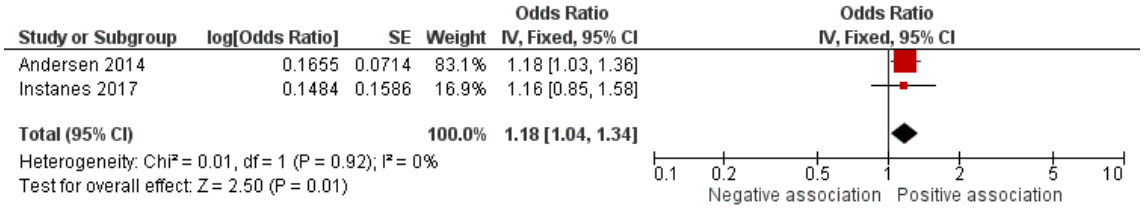
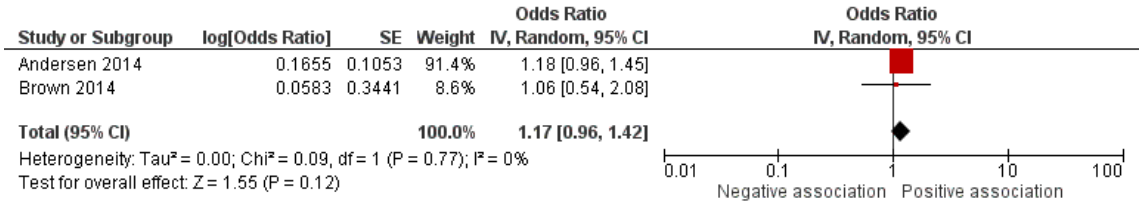


Figure 2. Meta-analysis of studies on the association between maternal hyperthyroidism and a. ADHD, b. ASD, c. epilepsy, and d. schizophrenia in the offspring.

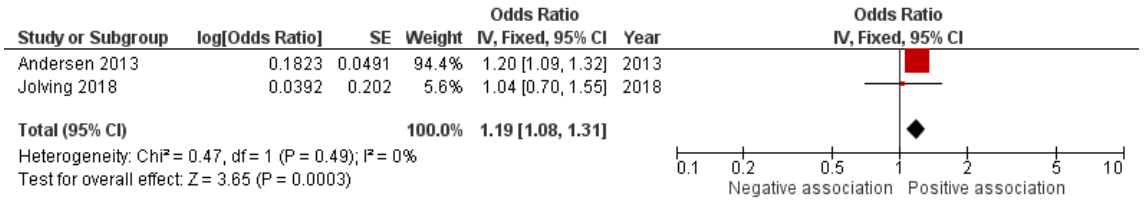
a. ADHD



b. ASD



c. epilepsy



d. schizophrenia

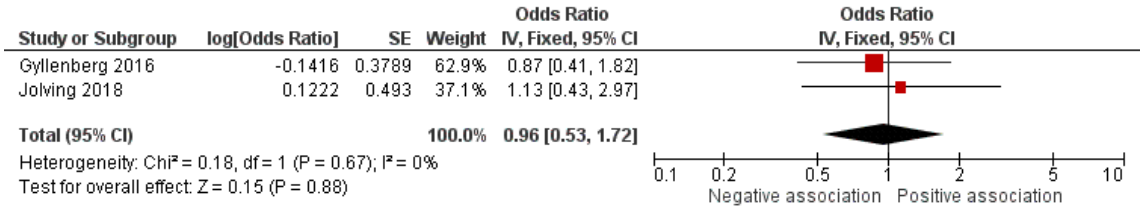
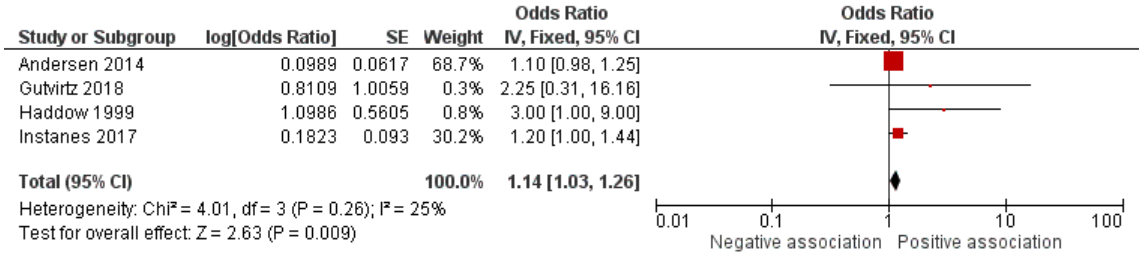


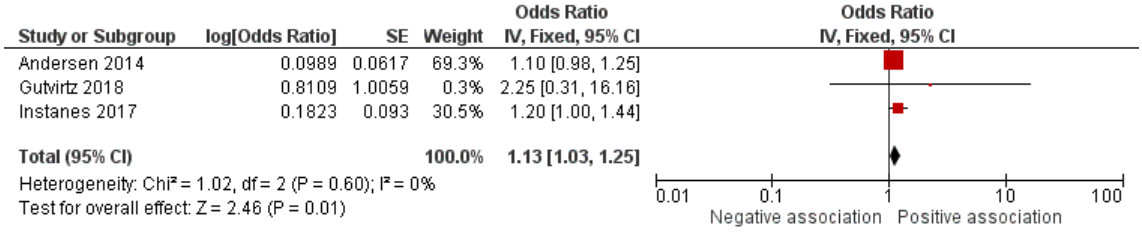
Figure 3. Meta-analysis of studies on the association between maternal hypothyroidism and a. ADHD, b. ASD, c. epilepsy, d. schizophrenia, and e. cerebral palsy in the offspring. Sensitivity analysis was conducted by i.) including or ii.) removing the comparatively lower quality study.

a. ADHD

i.)

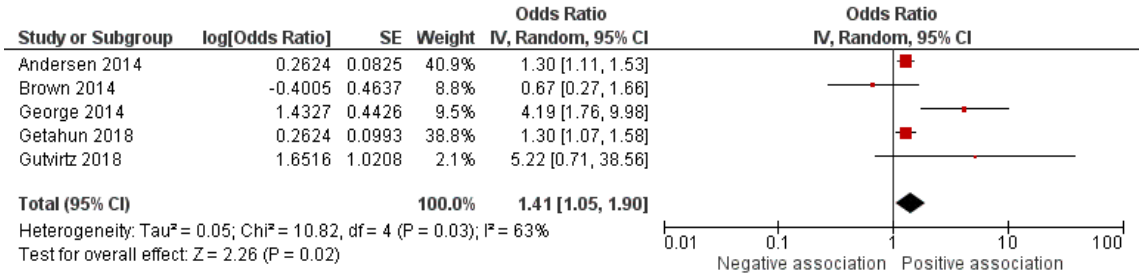


ii.) removing Haddow 1999 et al.

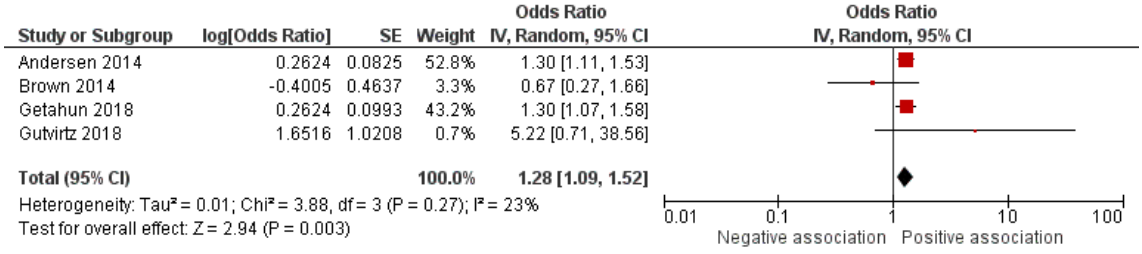


b. ASD

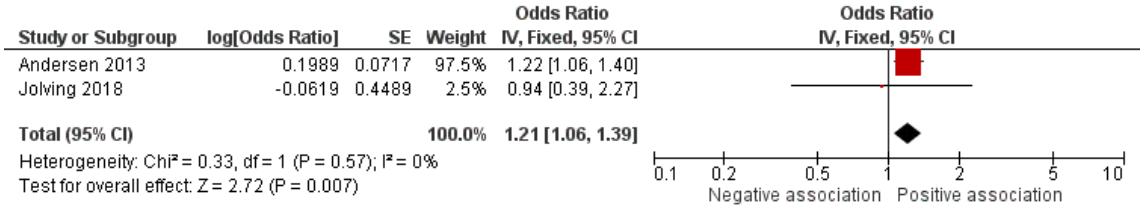
i.)



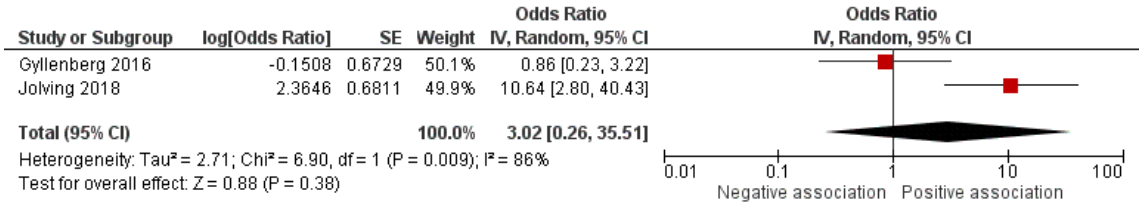
ii.) removing George 2014 et al.



c. epilepsy



d. schizophrenia



e. cerebral palsy

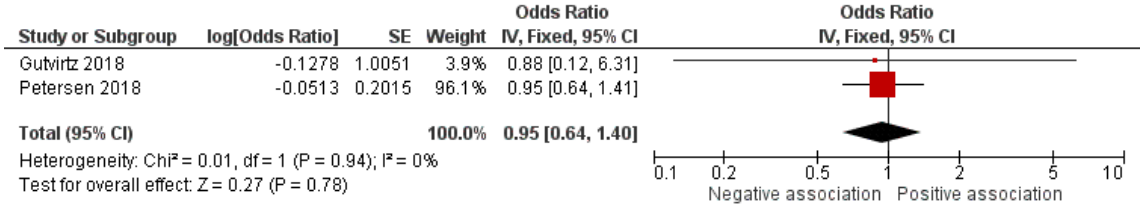


Figure 4. Meta-analysis of studies on the association between maternal TPO-Ab+ and offspring ASD

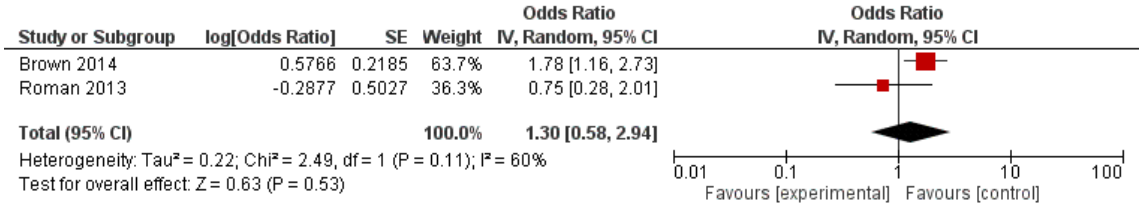


Table 1. Characteristics of studies with maternal thyroid dysfunction exposure and adverse outcomes in the offspring

Item	Author (Year), Country	Study design (Sample size)	Exposure measurement [a] (Timing), *Measurement kit for laboratory assays*	Mean maternal age (years ± SD)	Outcome measurement [b]	Age of children (years)	Adjusted variables in the model
1	Brown et al. (2015), Finland	case-control (1,920)	TFT: TSH, FT4, TPO-Ab (1st and early 2nd trimesters), *Abbott Diagnostics, Abbott Park, IL*	$TPO\text{-}Ab^+$: 29.62 ± 4.65 $TPO\text{-}Ab^-$: 29.22 ±5.30	ASD: Dx from FHDR, assessed with the ADI-R	N.A.	no adjusted covariate
2	Grattan et al. (2014), Canada	case-control (998)	self-report maternal history of hypothyroidism with a standardised questionnaire (during pregnancy)	N.A.	CHD: Dx using echocardiography	range 0 to 18, median of 2.7	age and risk of child chromosomal disorder, maternal diabetes mellitus, maternal age, and family history of CHD
3	George et al. (2014), India	case-control (343)	self-report Dx by interview (during pregnancy)	N.A.	ASD: Dx from autism clinic of Child Development Centre, using a Childhood Autism Rating Scale, score over 30	range 2 to 6	antenatal and natal risk factors for autism
4	Gyllenberg et al. (2016), Finland	case-control (2,020)	TFT: TSH, FT4 (1st trimester) *Abbott Diagnostics, Abbott Park, IL*	cases: 28.5 ± 5.5 control: 28.2 ± 5.1	schizophrenia: FHDR, using ICD-10: F20 and ICD-10: F25	N.A.	maternal psychiatric history, maternal smoking, degree of urbanization of birth municipality, birth province, twinning
5	Instanes et al. (2017), Norway	case-control (2,332,657)	Dx based on medical registry diagnosis records from MBRN and NorPD (before or during pregnancy)	N.A.	ADHD: Rx of ADHD medications methylphenidate (ATC code NO6BA04),	> 3	year of birth, parity, mother's age at birth, mother's educational level, mother's marital status, maternal and

Item	Author (Year), Country	Study design (Sample size)	Exposure measurement [a] (Timing), *Measurement kit for laboratory assays*	Mean maternal age (years ± SD)	Outcome measurement [b]	Age of children (years)	Adjusted variables in the model
					atomoxetine (ATC code N06BA09) and racemic amphetamine (ATC code N06BA01) extracted from the NorPD		paternal use of ADHD medication
6	Andersen et al. (2014), Denmark	cohort (857,014)	Dx & Rx from DNHR and DNPR (before and after delivery)	N.A.	ADHD, ASD: Dx & Rx from DNHR, DPCR and DNPR ADHD: ICD-10: F90; if no Dx then at least two Rx of ADHD medication (ATC N06NA) ASD: ICD-10: F84	range 3 to 18	gender of the child, year of birth of the child, maternal age, maternal origin, maternal residence, maternal marriage status, income, and parity
7	Andersen et al. (2013), Denmark	cohort (1,699,693)	Dx from DNHR (before and after delivery);	N.A.	epilepsy: Dx after the neonatal period, data from DNHR using ICD-8: 345.09–345.99 and ICD-10: G40.0–G41.9	median of 5.3	gender of the child, birth year, maternal age, parity including index pregnancy, maternal marriage status, income, maternal origin, maternal residence, and maternal diagnosis of febrile seizure and/or epilepsy registered in the DNHR
8	Chevrier et al. (2011), U.S.	cohort (287)	TFT: TSH, FT4 (26.9 ± 3.4 weeks gestation); *Siemens Healthcare Diagnostics, Deerfield, IL;*	N.A.	ADHD: maternal report on the Attention Problems scale of the CBCL or	5	maternal age, income, employment status at 6 months, country of birth, diet quality index, delivery complications,

Item	Author (Year), Country	Study design (Sample size)	Exposure measurement [a] (Timing), *Measurement kit for laboratory assays*	Mean maternal age (years ± SD)	Outcome measurement [b]	Age of children (years)	Adjusted variables in the model
					child performance on the KCPT		PPV (Peabody Picture Vocabulary Test) score, child 5minute APGAR, hospitalization at 1 year; the number of children in the home at 1 and 2 years, home density at 2 years, the family structure at 1 year; the season of assessment.
9	Cowett et al. (1975), U.S.	cohort (1,394)	butanol-extractable iodine determination and clinical history (during pregnancy)	N.A.	respiratory distress syndrome: clinical evidence of respiratory distress syndrome (N.A.)	N.A.	no adjusted covariate
10	Eshkoli et al. (2019), Israel	cohort (217,910)	Dx based on the maternal report as well as on a routine review of all computerized medical records from the hospital and ambulatory setting from SUMC (during pregnancy)	hypothyroidism: 30.8 ±5 euthyroid: 28.2 ± 5	pediatric endocrine morbidity: Dx using ICD-9 codes	N.A.	gestational and pregestational diabetes mellitus, chronic, gestational or pre-eclampsia, delivery before 37 weeks of gestation
11	Fetene et al. (2019), U.K.	cohort (2,920)	TFT: TSH, FT4 (1st trimester); *Abbott Diagnostics, Abbott Park, IL*	28.9 ± 4.6	depression: DAWBA coded according to parent-reported or self-reported DMS-IV criteria	7.5 for parent-reported depression; 15 for self-reported depression	maternal age, BMI, gender, birth weight, maternal smoking, maternal depression, gestational hypertension, and zinc and iodine intake during pregnancy

Item	Author (Year), Country	Study design (Sample size)	Exposure measurement [a] (Timing), *Measurement kit for laboratory assays*	Mean maternal age (years ± SD)	Outcome measurement [b]	Age of children (years)	Adjusted variables in the model
12	Fetene et al. (2018), U.K.	cohort (2,912)	TFT: TSH, FT4, TPO-Ab (1st trimester); *Abbott Diagnostics, Abbott Park, IL*	28.9 ± 4.6	ADHD: DAWBA coded according to parent-reported or self-reported DSM-IV criteria	7.5 for parent-reported ADHD; 15 for self-reported ADHD	maternal age, BMI, sex, gestational hypertension, antenatal depression, maternal smoking, partner smoking, maternal alcohol use, birth weight, maternal iodine, and zinc intake during pregnancy
13	Frank et al. (2019), Norway	cohort (1,204)	Rx records from MBRN and NorPD based on ATC classification System (during pregnancy)	N.A.	language impairment: ICD-10: F80 and parent-reported symptoms of language and communication skill deficits	8	maternal age, educational level, income, parity, BMI at conception, use of folic acid and other supplements, lifetime history of major depression, comedication for somatic and mental comorbidities, and smoking and alcohol use during pregnancy
14	Getahun et al. (2018), U.S.	cohort (397,201)	Dx using ICD-9: 244.X and medication prescribed to treat the condition (during pregnancy);	N.A.	ASD: at least one documented DSM-IV code for ASD on any two separate visits	range 2 to 17	maternal age, education, smoking during pregnancy, prenatal care, parity, year of diagnosis, median household income, child's sex and race/ethnicity
15	Ghassabian et al. (2012), Netherland	cohort (3,139)	TFT: TSH, FT4, TPO-Ab (13.5±1.8 weeks of gestation);	$TPO\text{-}Ab^{+}$: 31.2 ± 4.3 $TPO\text{-}Ab^{-}$: 31.1 ± 4.3	ADHD: CBCL completed by parents, using scales consistent with	3	child's gender and ethnicity, maternal age, cigarette smoking, and

Item	Author (Year), Country	Study design (Sample size)	Exposure measurement [a] (Timing), *Measurement kit for laboratory assays*	Mean maternal age (years ± SD)	Outcome measurement [b]	Age of children (years)	Adjusted variables in the model
			Vitros ECI Immunodiagnostic System Ortho Clinical Diagnostics, Rochester, NY		diagnostic categories of DSM-IV		time of thyroid sampling during pregnancy
16	Ghassabian et al. (2011), Netherland	cohort (3,736)	TFT: TSH, FT4 (13.3±1.7 weeks of gestation)	30.9 ± 4.5	ADHD: CBCL completed by parents, using externalizing (attention problems and aggressive behaviour) scale consistent with diagnostic categories of DSM	1.5 and 3	maternal age, education level, and psychopathology, child's gender, ethnicity, mode of delivery, and gestational age at the time of maternal thyroid sampling
17	Gutvirtz et al. (2019), Israel	cohort (217,910)	Dx based on the maternal report as well as medical records from the hospital and/or ambulatory settings, data from SUMC (during pregnancy)	hypothyroidism: 30.8 ± 5.2 no hypothyroidism: 28.2 ± 5.7	ADHD, ASD, cerebral palsy: computerized pediatric hospitalization database of SUMC and the computerized perinatal database of the Obstetrics and Gynecology department	< 18	maternal age, birth weight, pre-gestational and gestational diabetes and hypertensive disorders of pregnancy (pregestational, gestational hypertension and pre-eclampsia)
18	Haddow et al. (1999), U.S.	cohort (186)	TFT: TSH, FT4, TPO-Ab (2^{nd} trimester); *TSH: Diagnostic Products, LA;* *FT4: Wallac Oy, Turku, Finland;* *TPO-Ab: Kronus, San Clemente, Calif;*	N.A.	ADHD: the Conners' Continuous Performance Test to measure sustained vigilance and WISC-III scores	8	no adjusted covariate

Item	Author (Year), Country	Study design (Sample size)	Exposure measurement [a] (Timing), *Measurement kit for laboratory assays*	Mean maternal age (years ± SD)	Outcome measurement [b]	Age of children (years)	Adjusted variables in the model
19	Heikkinen et al. (2017), Finland	cohort (3,229)	TFT: thyrotropin, FT4, TPO-Ab, Tg-Abs (before 20th week of gestation); *Abbott Diagnostics, Abbott Park, IL*	euthyroid: 28.1 ± 5.3 hypothyroid: 28.4 ± 5.5 hyperthyroid: 30.0 ± 5.4 hypothyroxinemia: 30.0 ± 6.3 TPO-Ab-: 28.2 ± 5.4 TPO-Ab+: 28.6 ± 5.0	cardiometabolic risk factor: blood sampling	16	maternal age, smoking, parity, and overweight/obesity
20	Jolving et al. (2018), Denmark	cohort (2,618)	Dx of autoimmune hyperthyroidism/Graves' disease (ICD-8 codes: 242.00, 242.01, 242.08, 242.09; ICD-10 code: E05.0) or autoimmune hypothyroidism/Hashimoto's thyroiditis (ICD-8 code: 244.01; ICD-10 codes: E06.3, E06.3A and E06.3B) (within one year before delivery)	N.A.	15 disease groups covering major non-malignant somatic and psychiatric disease categories	> 5	sex of the child, year of birth, maternal age at birth, delivery mode, multiple births, birth order, preterm birth, small for gestational age, and maternal comorbidity of the outcome disease
21	Liu et al. (2018), Denmark	cohort (14,302)	Dx using ICD-8 codes: 243.99–244.09; or E03 and ICD-10 code E89.0; Rx using ATC: H03A; data from DNPR (before 5 years after delivery);	N.A.	asthma: Dx using ICD-10: J45 and J46; Rx using ATC codes of inhaled β2-agonists (R03AC02–04, -12, and -13), inhaled glucocorticoids	> 5	maternal age, primiparity, smoking during pregnancy, education status, income status, calendar year of birth, maternal diabetes, maternal asthma, paternal asthma at delivery, and

Item	Author (Year), Country	Study design (Sample size)	Exposure measurement [a] (Timing), *Measurement kit for laboratory assays*	Mean maternal age (years ± SD)	Outcome measurement [b]	Age of children (years)	Adjusted variables in the model
					(R03BA01, -02 and -05), fixed-dose combination of inhaled β2-agonists and glucocorticoids (R03AK06 and -07), leukotriene receptor antagonists (R03DC03), and anti-IgE therapies (R03DX05)		the index child's age at observation during the study period
22	Modesto et al. (2015), Finland	cohort (3,873)	TFT: thyrotropin, FT4 (range 6.6 to 17.9 weeks, mean of 13.6 weeks gestation;); *FT4 & TSH: Vitros ECiimmunodiagnostic system; Ortho Clinical Diagnostics; TPO-Ab: Phadia 250; Thermo Scientific;*	30.0 ± 5.0	ADHD: Conner's Parent Rating Scale-Revised Short Form with ADHD index	range 7.5 to 10.5, mean (SD) of 8.1 (0.2)	child age, sex, and ethnic background and maternal educational level, age, history of smoking, psychopathologic symptoms during pregnancy, parity, marital status, household income, BMI and time of blood sampling in pregnancy
23	Oostenbroek et al. (2017), Netherland	cohort (2,000)	TFT: TSH, FT4, TPO-Ab (median of 12.9 weeks gestation); *FT4 & TSH: Beckman Coulter Inc (Fullerton, California) TPO-Ab+: E-CK-96; ZenTech, Angleur, Belgium;*	hypothroxinemic: 32.2 ± 4.4 non-hypothyroxinemic: 31.8 ± 4.3	ADHD: parent and teacher reports of SDQ using borderline clinical cut-off	range 5 to 6, mean (SD) of 5.1 (0.2)	ethnicity, years of education, pregnancy BMI, hypertension, smoking during pregnancy of at least 1 cigarette per day and anxiety level

Item	Author (Year), Country	Study design (Sample size)	Exposure measurement [a] (Timing), *Measurement kit for laboratory assays*	Mean maternal age (years ± SD)	Outcome measurement [b]	Age of children (years)	Adjusted variables in the model
24	Pakkila et al. (2013), Finland	cohort (3,673)	TFT: TSH, FT4, TPO-Ab (10.7±2.8 weeks gestation) *Architect i2000 automatic analyzer (Abbott Diagnostics)*	N.A.	same serum thyroid biomarkers level as mothers: TFT	8	maternal continuous TPO-Ab levels
25	Pakkila et al. (2014), Finland	cohort (5,131)	TFT: TSH, FT4, TPO-Ab (10.7±2.8 weeks gestation); *Abbott Architect i2000 method (Abbott Diagnostics)*	N.A.	ADHD: Parents reported Rutter B2 Scale-Finnish version	8	having more than two children in the family, maternal smoking, maternal education, and maternal age
26	Petersen et al. (2018), Denmark	cohort (1,270,079)	hypothyroidism: Dx based on ICD-8 243.99 and 244.00-244.09, ICD-10: E00, E03.0-E03.9 AND E89.0, excluding 244.02, E03.0A, E03.1B, and E03.4; Rx based on thyroid hormone, ACT: h03A hyperthyroidism: Dx based on ICD-8 as 242.00–242.29 and by ICD-10 as E05.0-E05.9, excluding E05.4, E05.8A, and E05.9A; Rx based on anti-thyroid medication, ACT: H03A (before and during pregnancy, and within 5 years after pregnancy)	N.A.	cerebral palsy: Dx through the Danish National Cerebral Palsy Registry	range 1 to 6	birth year, maternal age, maternal diabetes, and maternal socioeconomic status and smoking and alcohol consumption in pregnancy
27	Roman et al. (2013), Netherland	cohort (4,039)	TFT: TSH, FT4, TPO-Ab (range 5.9 to 7.913.4±1.9 weeks gestation); *FT4&TSH: Vitros ECI Immunodiagnostic System;*	31.2 ± 4.7	ASD: parents reported CBCL using pervasive developmental problems scale	6	child's sex, ethnicity, gestational age at birth, birth weight, maternal age, educational level, smoking history, prenatal psychopathology, thyroid

Item	Author (Year), Country	Study design (Sample size)	Exposure measurement [a] (Timing), *Measurement kit for laboratory assays*	Mean maternal age (years ± SD)	Outcome measurement [b]	Age of children (years)	Adjusted variables in the model
			Ortho Clinical Diagnostics, Rochester, NY; *TPO-Ab: Phadia 250 immunoassay; Phadia, Uppsala, Sweden;*				medication during pregnancy, parity, marital status, maternal folate and C-reactive protein levels in early pregnancy, time of thyroid sampling during pregnancy, and paternal age.
28	Vermiglio et al. (2004), Italy	cohort (27)	TFT: TSH, FT4 (5 to 10, 11 to 14, 18 to 20 weeks gestation)	N.A.	ADHD: DMS-IV-TR items by clinical observation	range 8 to 10	no adjusted covariate
29	Wasserman et al. (2008), U.S.	cohort (1,731)	TFT: TPO-Ab (3^{rd} trimester)； *QUANTA Lite TPO; INOVA Diagnostics, San Diego, California*	24.1 (range: 11 to 46)	sensorineural hearing loss: Dx according to pediatric case definition	8	maternal age, race and treated clinical hypothyroidism

[a] Exposure refers to maternal thyroid status. Timing refers to the time of the diagnosis or prescription or the function test conducted. TFT indicates thyroid function test; Dx indicates the diagnosis of thyroid diseases; Rx indicates prescription for thyroid diseases;

[b] Outcomes refer to diagnosed or assessed disorders in the offspring. Dx indicates diagnosis and Rx indicates prescriptions;

Abbreviations: ADHD, attention deficit hyperactivity disorder; ADI-R, Autism Diagnostic Interview-Revised; ASD, autism spectrum disorders; ATC: Anatomical Therapeutic Chemical Classification System; BMI: Body Mass Index; CBCL, Child Behavior Checklists; CHD: congenital heart defect; DAWBA, Developmental and Well-Being Assessment; DMS-IV-TR, Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition- Text Revision; DNHR, Danish National Hospital Registry; DNPR, Danish National Prescription Registry, DPCR, Danish Psychiatric Central Register; FHDR, Finnish Hospital, and Outpatient Discharge Registry; FT4, free thyroxine; ICD: International Classification of Diseases; KCPT: Kiddie Continuous Performance Test; MBRN: Medical Birth Registry of Norway; NorPD: Norwegian Prescription Database; N.A., not available.; SD: Standard deviation; SDQ: Strengths and Difficulties Questionnaire; SUMC, Soroka University Medical Center; TgAb, thyroglobin antibodies; TPO-Ab(+/-), thyroid peroxidase antibodies (positive / negative); TSH, thyroid stimulating hormone; WISC-III: Wechsler Intelligence Scale for Children- Third edition

Table 2. Estimated associations between maternal hyperthyroidism and offspring neurodevelopmental disorders

Item	Author (year)	Outcome measurement	Estimate (95% CI)
ADHD as outcome			
1	Andersen et al. (2014)	ICD-10 diagnosis and prescription of drugs	HR = 1.18 (1.03, 1.36)
2	Instanes et al. (2017)	Prescription of drugs	OR = 1.2 (0.9, 1.5)
ASD as outcome			
1	Andersen et al. (2014)	ICD-10 diagnosis	HR = 1.18 (0.96, 1.45)
2	Brown et al. (2015)	ICD-10 diagnosis assessed with the Autism Diagnostic Interview-Revised	OR = 1.06 (0.54, 2.10)
Epilepsy as outcome			
1	Andersen et al. (2013)	ICD-10 diagnosis	HR = 1.20 (1.09, 1.32)
2	Jolving et al. (2018)	ICD-10 diagnosis	HR = 1.04 (0.70, 1.55)
Cerebral palsy as outcome			
1	Petersen et al. (2018)	ICD-8 and ICD-10 diagnosis	OR = 1.11 (0.94, 1.66)
Schizophrenia as outcome			
1	Gyllenberg et al. (2016)	ICD-10 diagnosis	OR = 0.87 (0.41, 1.82)
2	Jolving et al. (2018)	ICD-10 diagnosis	HR = 1.13 (0.43, 3.01)

Abbreviations: ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorders; ICD: International Classification of Diseases

Table 3. Estimated associations between maternal hypothyroidism and offspring neurodevelopmental disorders

Item	Author (year)	Outcome measurement	Estimate (95% CI)
ADHD as outcome			
1	Andersen et al. (2014)	Prescription of drugs	HR = 1.10 (0.98, 1.25)
2	Gutvirtz et al. (2018)	ICD-9 diagnosis	HR = 2.25 (0.31, 16.16)
3	Haddow et al. (1999) [a]	Conner's Continuous Performance Test > 8 [a]	OR = 3 (1, 5)
		WISC-III freedom from distractibility score [b]	Mean difference ± SE = -3 ± 2
4	Instanes et al. (2017)	Prescription of drugs	OR = 1.2 (1.0, 1.4)
ASD as outcome			
1	Andersen et al. (2014)	ICD-10 diagnosis	HR = 1.30 (1.11, 1.53)
2	Brown et al. (2015)	ICD-10 diagnosis assessed with the Autism Diagnostic Interview-Revised	OR = 0.67 (0.27, 1.63)
3	Getahun et al. (2018)	Clinical diagnosis	HR = 1.31 (1.13, 1.53)
4	Gutvirtz et al. (2018)	ICD-9 diagnosis	HR = 5.22 (0.70, 38.56)
5	George et al. (2014)	Clinical diagnosis	OR = 4.25 (1.38, 13.07)
Epilepsy as outcome			
1	Andersen et al. (2013)	ICD-10 diagnosis	HR = 1.22 (1.06, 1.40)
2	Jolving et al. (2018)	ICD-10 diagnosis	HR = 0.94 (0.39, 2.27)
Language and speech impairment as outcome			
1	Frank et al. (2019)	ICD-10 diagnosis	HR = 0.75 (0.38, 1.43)
Schizophrenia as outcome			
1	Gyllenberg et al. (2016)	ICD-10 diagnosis	OR = 0.86 (0.23, 3.24)
2	Jolving et al. (2018)	ICD-10 diagnosis	HR = 10.64 (2.80, 40.41)
Cerebral palsy as outcome			
1	Gutvirtz et al. (2018)	ICD-9 diagnosis	HR = 0.88 (0.13, 6.31)
2	Petersen et al. (2018)	ICD diagnosis	OR = 0.95 (0.64, 1.39)

Haddow et al. used Continuous Performance Test score and WISC-III freedom-from-distractibility score to measure offspring ADHD. [a] A higher score indicates more problems in this scale. The author took score 8 as cut-off point and this row provides OR for the children of

mothers with hypothyroidism as compared with the control children; [b] This row provides the difference as the value in the case minus the average of the values in the control; the value expressed as means ± SE of the individual differences in each matched set;

Abbreviations: ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorders; ICD: International Classification of Diseases; WISC-III: Wechsler Intelligence Scale for Children- Third edition

Table 4. Estimated associations between maternal hypothyroxinemia and offspring neurodevelopmental disorders

Item	Author (year)	Definition of maternal hypothyroxinemia	Outcome measurement	Estimate (95% CI)
ADHD as outcome				
1	Modesto et al. (2015)	TSH levels of 0.1 to 2.5 mIU/L and FT4 levels below the 5 ^{the} percentile of the sample	Conner's Parent Rating Scale-Revised Short Form	β = 0.07 (0.003, 0.14)
2	Oostenbroek et al. (2017)	FT4 level below the 10^{th} or 5^{th} percentile of distribution in the maternal FT4 level	Strengths and Difficulties Questionnaire	Teacher-reported: OR $_{FT4 < 10^{th} \text{ percentile}}$ = 1.47 (0.99, 2.20) OR $_{FT4 < 5^{th} \text{ percentile}}$ = 1.70 (1.01, 2.86) Parent-reported: OR $_{FT4 < 10^{th} \text{ percentile}}$ = 0.85 (0.50, 1.46) OR $_{FT4 < 5^{th} \text{ percentile}}$ = 0.78 (0.36, 1.66)
3	Vermiglio et al. (2004)	normal TSH concentrations (0.4 - 4.0 μ U/ml) with low serum FT4 value as compared with the range values calculated at the same stage of pregnancy	DMS-IV-TR items by clinical observation	χ^2 = 2.34, p = 0.01
ASD as outcome				
1	Roman et al. (2013)	mild: normal TSH levels of 0.03 to 2.5 mIU/L and FT4 levels below the 10^{th} percentile of the sample (< 11.82 pmol/L); severe: FT4 levels below the 5^{th} percentile of the sample (< 10.99 pmol/L)	Pervasive Developmental Problems subscale from CBCL	OR $_{FT4 < 10^{th} \text{ percentile}}$ = 1.41 (0.78, 2.57) OR $_{FT4 < 5^{th} \text{ percentile}}$ = 2.60 (1.30, 5.18)
Schizophrenia as outcome				
1	Gyllenberg et al. (2016)	TSH levels over 5^{th} to 95^{th} percentile and FT4	ICD-10 diagnosis	OR = 1.75 (1.22, 2.50)

		levels below 10th percentile of the sample		

Abbreviations: ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorders; CBCL, Child Behavior Checklists; DMS-IV-TR, Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition- Text Revision; FT4, free thyroxine; TSH, thyroid stimulating hormone

Table 5. Estimated associations between maternal thyroid hormone parameters and offspring neurodevelopmental disorders

Item	Author (year)	Outcome measurement	Estimate (95% CI)
Maternal TPO-Ab+			
ADHD as outcome			
1	Fetene et al. (2018)	DAWBA	OR = 1.00 (0.84, 1.20) per SD
2	Ghassabian et al. (2012)	CBCL (Maternal and paternal rating)	OR = 1.77 (1.15, 2.72), TPO-Ab+ defined as >100 IU/ml
ASD as outcome			
1	Brown et al. (2015) [a]	ICD-10 diagnosis	OR = 1.78 (1.16, 2.75), TP-Ab+ defined as >156 IU/ml
2	Roman et al. (2013) [b]	Pervasive Developmental Problems subscale from CBCL	OR = 0.78 (0.28, 2.16), TPO-Ab+ defined as >100 IU/ml
Depression as outcome			
1	Fetene et al. (2019)	DAWBA	OR = 1.02 (0.85, 1.23) per SD
Maternal FT4 level			
ADHD as outcome			
1	Chevrier et al. (2011)	CBCL	β = -0.10 (-2.03, 1.82) per 1 ng/dL
		KCPT	β = 7.52 (-4.86, 19.91) per 1 ng/dL
2	Modesto et al. (2015)	Conner's Parent Rating Scale-Revised Short Form	β = -0.01 (-0.02, 0.01) per SD
3	Fetene et al. (2018)	DAWBA	OR = 1.10 (0.89, 1.36) per SD
4	Oostenbroek et al. (2017)	SDQ	Teacher-reported: OR = 0.95 (0.85, 1.05) per 1 pmol/L Parent-reported: OR = 1.01 (0.90, 1.13) per 1 pmol/L
ASD as outcome			
1	Roman et al. (2013)	Pervasive Developmental Problems subscale from CBCL	OR = 0.95 (0.77, 1.17) per SD
Depression as outcome			
1	Fetene et al. (2019)	DAWBA	OR = 1.21 (1.00, 1.47) per SD
Schizophrenia as outcome			
1	Gyllenberg et al. (2016)	ICD-10 diagnosis	OR = 0.54 (0.31, 0.94) per LN unit

Maternal TSH level			
ADHD as outcome			
1	Chevrier et al. (2011)	CBCL	β = -0.65 (-1.26, -0.04) per LN unit
		KCPT	β = -0.75 (-4.61, 3.12) per LN unit
2	Ghassabian et al. (2011)	CBCL	β = 0.08 (0.01, 0.15) per SD
3	Modesto et al. (2015)	Conner's Parent Rating Scale-Revised Short Form	β = -0.01 (-0.02, 0.01) per SD
4	Fetene et al. (2018)	DAWBA	OR = 0.83 (0.37, 1.85) per SD
5	Oostenbroek et al. (2017)	SDQ	Teacher-reported: OR = 1.02 (0.96, 1.09) per mU/L Parent-reported: OR = 1.01 (0.92, 1.11) per mU/L
6	Pakkila et al. (2014)	Rutter B2 Scale-Finnish version	OR_{boys} = 1.17 (1.00, 1.36) per LN unit OR_{girls} = 1.39 (1.07, 1.80) per LN unit
ASD as outcome			
1	Roman et al. (2013)	Pervasive Developmental Problems subscale from CBCL	OR = 0.92 (0.72, 1.17) per SD
Depression as outcome			
1	Fetene et al. (2019)	DAWBA	OR = 1.14 (0.98, 1.32) per SD
Schizophrenia as outcome			
1	Gyllenberg et al. (2016)	ICD-10 diagnosis	OR= 0.93 (0.84, 1.02) per LN unit

[a.] The cut-off point for TPO-Ab+ corresponded to serum concentrations >156 IU/ml

[b.] The cut-off point for TPO-Ab+ corresponded to plasma concentrations ⩾ 100 IU/ml

Abbreviations: ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorders; CBCL, Child Behavior Checklist; DAWBA: Developmental and Well-Being Assessment; FT4, free thyroxine; SDQ: Strengths and Difficulties Questionnaire; TPO-Ab: thyroid peroxidase antibodies; TSH, thyroid stimulating hormone

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