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Maternal Thyroid Dysfunction During Pregnancy as an Etiologic Factor in Autism Spectrum Disorder: Challenges and Opportunities for Research

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Background: Autism spectrum disorder (ASD) is a neurodevelopmental condition with unknown etiology. Both genetic and environmental factors have been associated with ASD. Environmental exposures during the prenatal period may play an important role in ASD development. This narrative review critically examines the evidence for a relationship between maternal thyroid dysfunction during pregnancy and ASD in the child.
Summary: Studies that assessed the associations of hypothyroidism, hyperthyroidism, hypothyroxinemia, thyroid hormone concentrations, or autoimmune thyroid disease with ASD outcomes were included. Most research focused on the relationship between hypothyroidism and ASD. Multiple population-based studies found that maternal hypothyroidism was associated with higher likelihood of an ASD diagnosis in offspring. Associations with other forms of maternal thyroid dysfunction were less consistent. Findings may have been affected by misclassification bias, survival bias, or publication bias. Studies using medical records may have misclassified subclinical thyroid dysfunction as euthyroidism. Two studies that assessed children at early ages may have misclassified those with ASD as typically developing. Most studies adjusted for maternal body mass index (BMI) and/or mental illness, but not interpregnancy interval or pesticide exposure, all factors associated with fetal survival and ASD. Most studies reported a combination of null and statistically significant findings, although publication bias is still possible.
Conclusions: Overall, evidence supported a positive association between maternal thyroid dysfunction during pregnancy and ASD outcomes in the child, especially for hypothyroidism. Future studies could reduce misclassification bias by using laboratory measures instead of medical records to ascertain thyroid dysfunction and evaluating children for ASD at an age when it can be reliably detected. Survival bias could be further mitigated by adjusting models for more factors associated with fetal survival and ASD. Additional research is needed to comprehensively understand the roles of maternal levothyroxine treatment, iodine deficiency, or exposure to thyroid-disrupting compounds in the relationship between maternal thyroid dysfunction and child ASD outcomes.

Keywords: autism spectrum disorder, thyroid dysfunction, hypothyroidism, hyperthyroidism, prenatal exposure, delayed effects

Introduction

Prevalence and etiology of autism spectrum disorder

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by difficulties in social communication, such as challenges in understanding social cues or lack of interest in social behaviors, and the presence of restricted interests and/or repetitive behaviors.[1] These characteristics usually develop early in life and can be accompanied by differences in intellectual ability, sensory sensitivities, and other copresenting characteristics.[1] Studies suggest that ASD is sometimes associated with heightened

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attention to detail and strong abilities in pattern recognition and visual search tasks.[2–4] In 2020, the U.S. prevalence of ASD was estimated to be 21.5 per 1000 children aged 4 years.[5] Globally, prevalence estimates vary considerably both within and between regions.

Based on the data collected in the last decade, ASD prevalence is estimated to range from 0.24% to 2.68% in Europe, 0.08% to 1.40% in Southeast Asia, 0.01% to 2.50% in the Americas, and 0.01% to 4.36% in the Western Pacific region.[6] Regional differences in prevalence likely reflect differences in reporting and diagnostic practices and may not be indicative of differences in factors that increase the likelihood of ASD.[6] Currently, the gold standard assessments for diagnosing ASD are the Autism Diagnostic Observation Schedule (ADOS), a series of professional observational examinations,[7] and the Autism Diagnostic Interview-Revised (ADI-R),[8] a parental interview.[9]

The etiology of ASD is poorly understood, despite decades of investigation. Beginning in the 1940s, psychiatrist Leo Kanner popularized a theory that autism in children was the result of emotionally distant parenting.[10] Since the 1960s, this theory has been rejected owing to research supporting genetic and environmental origins.[11]

Most cases of ASD are hypothesized to stem from multiple genetic and/or environmental factors that may be interdependent (e.g., gene–environment interactions).[12] Genetic factors associated with ASD include both inherited and *de novo* variants. A meta-analysis of monozygotic and dizygotic twin studies estimated the heritability of ASD to be between 64% and 91%.[13,14] Common single-nucleotide polymorphisms are estimated to collectively contribute 12–52% to ASD development.[15] Novel epigenetic changes, alternations to genetic material that affect how a gene is expressed without changing the DNA sequence, have been found in the early brain development period among children diagnosed with ASD.[16,17] Environmental exposures can lead to epigenetic changes that in turn affect neurodevelopment.[18]

While environmental exposures occur throughout the life course, those that occur during pregnancy may play an especially important role in ASD development.[19] Studies have explored the relationship between ASD and a variety of exposures that have the potential to impact neurodevelopment. Examples of prenatal exposures that may augment the likelihood of ASD include the use of sodium valproate[20] and selective serotonin reuptake inhibitors,[21] maternal health conditions, including obesity,[22] polycystic ovary syndrome,[23] fever,[24] autoimmune conditions,[25] folic acid deficiency,[26] older parental age,[27] shorter interpregnancy intervals,[28] and exposure to air pollutants[29] and pesticides.[30] Multiple cohort studies and meta-analyses have found no statistically significant relationship between maternal prenatal tobacco use and ASD diagnosis,[31–33] but one study found significantly more ASD traits among children whose mothers used prenatal tobacco.[34] Increasingly, thyroid disrupting compounds are being investigated as a possible environmental cause of ASD.[35,36]

Thyroid dysfunction during pregnancy

Hypothyroidism is estimated to affect 4% of pregnancies (3.5% subclinical hypothyroidism and 0.5% overt hypothyroidism), and hyperthyroidism is estimated to affect 2.4% of pregnancies (1.8% subclinical hyperthyroidism and 0.6% overt hyperthyroidism) in the United States.[37,38] Since the 1960s, overt maternal hypothyroidism during pregnancy has been linked to cretinism and other developmental disabilities.[39,40] More recent research has explored relationships between milder forms of thyroid dysfunction and differences in developmental outcomes. Findings from a meta-analysis suggest that maternal subclinical hypothyroidism and hypothyroxinemia may be associated with increased risk for intellectual disability in children.[41] Both high and low maternal free thyroxine (fT4) concentrations have been associated with a lower child intelligence quotient (IQ), lower gray matter, and cortex volume.[42]

Maternal thyroid autoimmunity during pregnancy has been associated with decreased cognitive and motor functioning in offspring compared with children born to mothers without thyroid autoimmunity, although study results are inconsistent.[43,44] In the maternal immune activation model proposed for ASD, maternal autoimmune diseases or other events triggering an immune response during pregnancy are suggested to alter neurodevelopment toward ASD through inflammatory pathways.[45] Thyroid autoimmunity is common during pregnancy, with prevalence of thyroid peroxidase antibody (TPO-Ab) positivity and thyroglobulin antibody (Tg-Ab) positivity estimated to be 5–14% and 3–18%, respectively.[43]

This narrative review focuses on the relationship between maternal thyroid dysfunction during pregnancy and ASD in the child. We aim to: (1) review existing literature on associations between maternal thyroid dysfunction during pregnancy and ASD in the child, (2) evaluate the strengths and limitations of existing literature, and (3) develop strategies for future research to effectively address knowledge gaps.

Review

Scope

The literature search focused on original human research studies that examined the relationship between maternal thyroid dysfunction during pregnancy and child ASD outcomes. ASD outcomes included a clinical ASD diagnosis (as reported in medical records, registry, or research study evaluation) or results from a nondiagnostic ASD assessment (screening tests that may be suggestive of an autism diagnosis or measures of autism traits). We did not consider studies that only assessed maternal thyroid dysfunction outside of pregnancy, only measured thyroid function in the child, did not report thyroid-specific results (e.g., any autoimmune or endocrine diseases), or were not published in scientific journals. In this review, all studies used a significance level of 5% and associations were deemed statistically significant when confidence intervals (CIs) did not include the null value.

Summary

Description of the literature

Articles were published between 2013 and 2022 (Table 1).[46,47] Study designs included case–control,[48–51] cohort, [46,47,52–55] nested case–control,[56] case-cohort,[57] meta-analysis of cohorts,[58] or randomized control trial.[59] One study, a pilot study surveying parents about pregnancy risk factors for ASD diagnosis, used a cross-sectional design (Table 1).[60]

Table 1. Summary of Studies Examining Thyroid Dysfunction During Pregnancy and Autism Spectrum Disorder Outcomes

First author (year)[Ref.]	*Study design*	*Sample size and description*	*ASD outcome and ascertainment*	*Child age at assessment*	*Time of thyroid condition evaluation*	*Thyroid conditions and ascertainment*	*Effect estimates with CIs and reference group*
Román (2013)[54]	Population-based birth cohort	4039 Children, included mothers treated for thyroid dysfunction (Gen R, Netherlands)	Parent report of autistic traits ($n=80$)	Until 6 years	13.4 weeks (SD 1.9, range 5.9–17.9)	Hypothyroxinemia, autoimmunity (Laboratory)	Hypothyroxinemia: OR 3.98 [CI 1.83–8.20] (Ref.: no hypothyroxinemia) TPO-Ab positivity: OR 0.78 [CI 0.28–2.16] (Ref.: TPO-Ab negative)
Lyall (2014)[51]	Case–control	560 ASD cases, 168 DD cases, 391 TD controls, included mothers treated for thyroid dysfunction (CHARGE, California)	Clinician diagnosis (ADOS and ADI-R)	Before 36 months	3 Months before pregnancy through breastfeeding	Maternal thyroid autoimmune disease (Self-report)	OR 0.99 [CI 0.61–1.60] (Ref.: no autoimmune disease reported)
Andersen (2014)[52]	Population-based birth cohort	857,014 Children, included mothers treated for thyroid dysfunction (Danish nationwide cohort study)	Diagnosis in nationwide registries ($n=5311$)	3 Years	Before, during, and after pregnancy	Hypo- and hyperthyroidism, (ICD-8/10 codes from registry)	Hypothyroidism: HR 1.30 [CI 1.11–1.53] Hyperthyroidism: HR 1.18 [CI 0.96–1.45] (Ref.: no hypo- or hyperthyroidism diagnosis)
George (2014)[49]	Unmatched case–control	143 ASD cases, 200 children without ASD, did not report if treated mothers were included (Kerala, India)	Clinician diagnosis	2–6 Years	Antenatal	Hypothyroidism (Self-report)	OR 4.25 [CI 1.38–13.07] (Ref.: no report of hypothyroidism)
Yau (2015)[50]	Case–control	78 ASD cases, 45 DD cases, 149 general population, did not have data on treatment (EMA, California)	Diagnosis from medical record	3–4 Years	15–19 Weeks	TSH levels only (Laboratory)	Inverse relationship between child ASD diagnosis and log-transformed maternal TSH: OR 0.33 [CI 0.12–0.91] (Ref.: general population)

(*continued*)

TABLE 1. (CONTINUED)

First author (year)[Ref.]	*Study design*	*Sample size and description*	*ASD outcome and ascertainment*	*Child age at assessment*	*Time of thyroid condition evaluation*	*Thyroid conditions and ascertainment*	*Effect estimates with CIs and reference group*
Brown (2015)[56]	Nested case–control	967 Matched case–control pairs from the Finnish prenatal study of autism, did not report if treated mothers were included	Diagnosis from hospital and outpatient registry	2+ Years, median of 4 years	Case mean 11.1 weeks (SD 3.1); control mean 10.9 weeks (SD 3.5)	Autoimmunity, hypo- and hyperthyroidism, (Laboratory)	TPO-Ab positivity: OR 1.78 [CI 1.16–2.75] (Ref.: TPO-Ab negative) Hypothyroidism: clinical, OR 0.67 [CI 0.27–1.63]; subclinical: OR 1.17 [CI 0.72–1.90] Hyperthyroidism: clinical: OR 1.06 [CI 0.54–2.10]; subclinical, OR 1.10 [CI 0.67–1.83] (Ref.: euthyroid)
Getahun (2018)[53]	Retrospective cohort	397,201 Children, included mothers treated for thyroid dysfunction (Kaiser Permanente members, California)	Diagnosis from medical records ($n = 6475$)	2–17 Years	Included women at any point in pregnancy	Hypothyroidism (ICD-9 codes from medical record)	Before pregnancy: HR 1.30 [CI 1.07–1.58], during pregnancy: HR 1.33 [CI 1.05–1.69] (Ref.: no hypothyroidism)
Andersen (2018)[57]	Case–cohort	7624 Children from subcohort random sample, 302 children with ASD, included mothers treated for thyroid dysfunction (Danish National Birth Cohort)	Diagnosis from medical record	Median age of 5.3 years	9 Weeks of pregnancy (range 5–19 weeks)	Hypo- and hyperthyroidism, Isolated low free thyroxine (Laboratory)	Hypothyroidism: overt, HR 2.03 [CI 0.71–5.77]; subclinical, HR 1.70 [CI 1.04–2.75] Hyperthyroidism: overt, HR 2.18 [CI 1.08–4.39]; subclinical, HR 0.37 [CI 0.09–1.52] Hypothyroxinemia: Girls: HR 4.92 [CI 2.03–11.9]; Boys: HR 0.92 [CI 0.39–2.15] (Ref.: euthyroid)

(*continued*)

Table 1. (Continued)

First author (year)[Ref.]	*Study design*	*Sample size and description*	*ASD outcome and ascertainment*	*Child age at assessment*	*Time of thyroid condition evaluation*	*Thyroid conditions and ascertainment*	*Effect estimates with CIs and reference group*
Levie (2018)[58]	Meta-analysis of population-based cohorts	9036 Mother–child pairs (Gen R, Netherlands; INMA, Spain; ALSPAC, United Kingdom) Excluded mothers with history of thyroid disease, did not report if any mothers received treatment during study	Parent report of autism traits ($n = 339$)	Gen R: median 5.9 years, INMA: median 4.6 years, ALSPAC: median 7.6 years	INMA: 13.1 (SD 1.3 weeks); Gen R: 13.4 (SD 2.0) weeks; ALSPAC: 11 (SD 3.2) weeks	Hypo- and hyperthyroidism, hypothyroxinemia (Laboratory)	Subclinical hypothyroidism: OR 1.2 [CI 0.8–1.9] Subclinical hyperthyroidism: OR 1.3 [CI 0.7–2.6] Hypothyroxinemia: OR 1.8 [CI 1.1–2.8] (Ref.: euthyroid)
Hales (2020)[59]	Follow-up to CATS randomized clinical trial	475 Mother–child pairs (CATS participants, United Kingdom) Excluded mothers with a history of thyroid disease, treated and untreated mothers	Parent report of possible ASD ($n = 19$)	Mean 9.5 years (SD 0.8)	Median 12 weeks and 3 days of pregnancy	Suboptimal gestational thyroid function (Laboratory)	No association (Ref.: normal thyroid function)
Rotem (2020)[55]	Retrospective cohort	437,222 Children, included mothers treated for thyroid dysfunction (Maccabi Health Services, Israel)	Diagnosis from medical record ($n = 4022$)	Children followed until at least 8 years	Before and after delivery (medical records) First trimester (TSH)	Hypo- and, hyperthyroidism, autoimmunity (ICD-9 codes, dispensing record from medical record) TSH levels (subset of sample)	Hypothyroidism: before delivery: OR 1.28 [CI 1.11–1.49] after delivery: OR 1.23 [CI 1.02–148], ever: OR 1.26 [CI 1.12–1.42] Hyperthyroidism: before delivery: OR 1.39 [CI 0.88–2.18] after deliver OR 1.45 [CI 0.95–2.21] (Ref.: no diagnosis of thyroid dysfunction)
Magdalena (2020)[60]	Cross-sectional survey	221 Children, did not report if treated mothers were included (Poland)	Clinician diagnosis (ADOS-2; $n = 121$)	Ages 3–12 years	Not specified—preconception thyroid disease	Thyroid disease (Parent and physician report)	RR 1.56 [CI 1.23–1.98] (Ref.: no report of thyroid disease)

(*continued*)

Table 1. (Continued)

First author (year)[Ref.]	*Study design*	*Sample size and description*	*ASD outcome and ascertainment*	*Child age at assessment*	*Time of thyroid condition evaluation*	*Thyroid conditions and ascertainment*	*Effect estimates with CIs and reference group*
Chen (2020)[48]	Matched case–control	330 Mothers with hyperthyroidism and their children, 1320 matched control pairs, included mothers treated for thyroid dysfunction (Taiwan Longitudinal Health Insurance Research Database)	Diagnosis from medical record ($n=5$)	Cases: 7.8 years (SD 2.7) Controls: 7.9 years (SD 2.7)	Not specified—diagnosis before birth of child	Hyperthyroidism (ICD codes from medical record)	OR 6.62 [CI 1.08–40.47] (Ref.: no history of thyroid disease)
Ge (2022)[46]	Population-based cohort	422,156 Mother–child pairs (Hong Kong Clinical Data Analysis and Reporting System) Excludes mothers with history of thyroid medication, included mothers who received treatment during study	Diagnosis from medical record ($n=10,892$)	Mean follow-up, exposed: 10.6 years (SD 4.2); control: 10.8 years (SD 4.0)	Started levothyroxine at median of 18 gestational weeks	Levothyroxine use during pregnancy (dispensing records)	HR 1.00 [CI 0.78–1.29] (Ref.: no history of thyroid dysfunction)
Teng (2022)[47]	Retrospective cohort	2455 Mother–child pairs (Ma'anshan Birth Cohort study, China). Excludes mothers with history of thyroid disease, did not report if any mothers received treatment during study	Parent report of possible ASD ($n=142$)	1.5–5 Years	First trimester: mean 10 weeks; second trimester: mean 25 weeks; third trimester: mean 34 weeks	TPO-Ab and Tg-Ab (Laboratory)	TPO-Ab positive and Tg-Ab negative: Boys, first trimester: RR 2.01 [CI 1.24–3.27]; second trimester: RR 2.15 [CI 1.08–4.26]; third trimester: RR 2.13 [CI 1.20–3.79] Girls, first trimester: RR 0.92 [CI 0.45–1.87]; second trimester: RR 1.21 [CI 0.53–2.79]; third trimester: RR 1.08 [CI 0.46–2.52] (Ref.: TPO-Ab and Tg-Ab negative)

ADI-R, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule; ALSPAC, Avon Longitudinal Study of Parents and Children; ASD, Autism Spectrum Disorder; CATS, Controlled Antenatal Thyroid Screening; CHARGE, CHildhood Autism Risk from Genetics and the Environment; CI, confidence interval; DD, developmental disability; EMA, Early Markers for Autism; Gen R, Generation R; HR, hazard ratio; INMA, Infancia Y Medio Ambiente; OR, odds ratio; RR, relative risk; SD, standard deviation; TD, typically developing; Tg-Ab, thyroglobulin antibody; TPO-Ab, thyroid peroxidase antibody; TSH, thyrotropin.

Hypothyroidism was the most frequently investigated type of thyroid dysfunction, compared with hyperthyroidism and hypothyroxinemia. Studies also examined thyroid autoimmunity, continuous measures of thyroid hormones, or levothyroxine use in relation to ASD outcomes. Most studies ascertained maternal thyroid conditions through medical records or laboratory analysis of thyroid hormone concentrations, instead of relying on maternal self-reports. ASD outcomes included probable autism based on screening tests or measures of autism traits[47,54,58,59] and ASD diagnosis. Among studies using an ASD diagnosis as an outcome, less than half specified that gold standard measures, ADOS and/or ADI-R, were used in the ASD diagnostic process (Table 1).[51,53,56,60]

All but two studies [49,60] described the confounders considered for regression models. Most studies controlled for multiple characteristics that may be associated (either directly or as a proxy) with ASD and maternal thyroid function, including maternal age,[27,61] smoking,[34,62] income or socioeconomic status,[63] ethnicity,[5,61] and parity.[28,61] When participants were not matched by sex of the child, regression models were adjusted for sex[48,52–55,57–59] and/or stratified by sex.[46,47,53,56,57]

Discussion of the relationship between maternal thyroid dysfunction and ASD

Across all studies, there was evidence supporting an association between maternal thyroid dysfunction during pregnancy and ASD in children, but much remains unknown. Of the 15 studies, 12 found statistically significant associations between a maternal thyroid abnormality and ASD outcomes, and three studies[46,51,59] reported no significant associations. Of the studies that did not report any associations, Hales et al. and Ge et al. primarily investigated levothyroxine treatment and Lyall et al. examined thyroid autoimmunity. A more detailed summary of findings by each type of thyroid problem follows.

Hypothyroidism and ASD outcomes. Five out of the seven studies examining hypothyroidism found that maternal hypothyroidism during pregnancy significantly increased the likelihood of ASD outcomes. This includes four population-based studies,[52,53,55,57] and a smaller unmatched case–control study (George et al.),[49] all of which used ASD diagnosis as an outcome. Two of these analyzed participants from the Danish National birth registry during similar time periods and for this reason, these studies may not each represent novel findings.[52,57]

In the unmatched case–control study, mothers who reported hypothyroidism during pregnancy had more than four times the odds of having a child diagnosed with ASD compared with mothers who reported not having hypothyroidism[49] (Table 1). However, the sample size was relatively small and CIs were wide. The likelihood of ASD increased by less than twofold in all four population-based studies, but effect estimates from these studies had narrower CIs indicating less uncertainty (Table 1).

Two studies distinguished between subclinical and overt thyroid dysfunction,[56,57] and there were no clear patterns related to the severity of thyroid dysfunction and ASD outcomes. Brown et al. found that the direction of effect differed depending on whether the hypothyroidism was subclinical (increased odds of ASD) or overt (decreased odds of ASD), although none of the relationships between thyroid dysfunction and ASD was statistically significant.[56] Andersen et al. found that subclinical hypothyroidism was significantly associated with ASD, while overt hypothyroidism was not.[57] For each study, after stratifying by hypothyroidism severity, the number of women in each group was small.

Three studies tested interaction terms between child sex and hypothyroidism, but no interactions were statistically significant (reported p-values ranged from 0.30 to 0.38).[53,55,57] However, one of these studies (Getahun et al.) observed differences in ASD risk between male and female children depending on when the mother was diagnosed with hypothyroidism. In analyses stratified by child sex, the risk of ASD for female children was greatest when their mother was diagnosed with hypothyroidism before pregnancy (adjusted hazard ratio [HR] = 1.61 [CI: 1.09–2.40]), compared with during pregnancy when the associations were not significant for any trimester (adjusted HR ranging from 0.85 [CI: 0.21–3.38] in the third trimester to 1.60 [CI: 0.51–4.96] in the second trimester).

The risk of ASD for male children remained relatively constant and not significant regardless of whether maternal hypothyroidism was diagnosed before or during pregnancy (adjusted HR ranging from 1.24 [CI: 0.68–2.23] in the second trimester to 1.41 [CI: 0.80–2.48] in the third trimester).[53]

Hyperthyroidism and ASD outcomes. There was less evidence supporting an association between hyperthyroidism during pregnancy and ASD outcomes in the child. Of the six studies that examined hyperthyroidism, two found statistically significant associations. Andersen et al. reported that overt, but not subclinical, hyperthyroidism was significantly associated with ASD diagnosis.[57] Chen et al. reported that hyperthyroidism was significantly associated with ASD diagnosis, but did not differentiate between subclinical and overt cases.[48] Both studies found that ASD likelihood or odds more than doubled among children of affected mothers, but CIs were wide in Chen et al. (odds ratio [OR] 6.62 [CI 1.08–40.47]) (Table 1). The remaining four studies found a positive, but not statistically significant, relationship between maternal hyperthyroidism during pregnancy and child ASD. Given that ASD is a relatively rare condition among the general population,[63] it is possible that effect estimates for hyperthyroidism were underpowered in some studies.

For example, Chen et al. only had three ASD cases with maternal hyperthyroidism[48] and Andersen et al. had nine ASD cases with overt maternal hyperthyroidism and two ASD cases with subclinical maternal hyperthyroidism.[57] However, because the reviewed studies did not provide power calculations, it cannot be confirmed that studies were underpowered.

Hypothyroxinemia and ASD outcomes. Three studies examined hypothyroxinemia. Román et al. reported that maternal hypothyroxinemia (normal thyrotropin [TSH] with fT4 in the lower fifth percentile) increased the odds of probable autism in children nearly fourfold. Using the same definition of hypothyroxinemia, Levie et al. found that maternal hypothyroxinemia nearly doubled the odds of autism

traits (Table 1). Román et al. also tested a broader cutoff point for fT4 and found no association with ''mild'' hypothyroxinemia (normal TSH and fT4 in the lower 10th percentile).[54] Andersen et al. found a significant positive association between maternal hypothyroxinemia and ASD diagnosis, but only in girls (Table 1).[57] Román et al. found no difference by child sex,[54] and sex differences for maternal hypothyroxinemia and ASD outcomes were not examined by Levie et al.[58]

Thyroid hormones as continuous exposure measures and ASD outcomes. Only one study, Yau et al., found a significant association between continuous thyroid hormone measures and ASD outcomes. In this study, log-transformed maternal TSH and child ASD diagnosis were inversely related (Table 1).[50] Two studies found no significant association between fT4 or TSH, treated as continuous variables, and ASD outcomes.[57,58] Brown et al. reported no significant association between continuous measures of fT4 or TSH and ASD but did not state whether a nonlinear relationship was tested.[56]

Thyroid autoimmunity and ASD outcomes. Evidence regarding a relationship between thyroid autoimmunity and autism outcomes was discordant. Teng et al.[47] and Brown et al.[56] found a significant positive association with ASD outcomes, while Lyall et al.[51] and Román et al.[54] found no significant association. Teng et al. stratified children by sex and found that boys whose mothers were TPO-Ab positive and Tg-Ab negative had about double the likelihood of probable ASD compared with boys born to mothers who were negative for both antibodies (Table 1). This association was not found among girls or boys born to Tg-Ab-positive mothers.[47]

Brown et al. found that the odds of having a child diagnosed with ASD were increased by 80% in TPO-Ab-positive mothers compared with TPO-Ab-negative mothers (Table 1). When treated as a continuous measure, TPO-Ab titers were associated with ASD, but the strength of the association was weakened.[56] Brown et al. found no significant interaction between TPO-Ab and child sex.[56]

Challenges and limitations

Several themes emerged surrounding the challenges of this research topic and the limitations of studies included in this review. First, achieving an adequate sample size may have been challenging. Thyroid conditions during pregnancy (especially hyperthyroidism) and ASD are relatively rare among the general population.[37,63] The challenges and impacts of misclassification, selection (including survival), and publication bias warrant further consideration for strengthening the evidence in future studies, as summarized in Table 2.

Misclassification of exposure. In regions without a universal thyroid screening during pregnancy, women with subclinical cases may have been misclassified as euthyroid in medical records. The four studies that used medical records to identify thyroid dysfunction[48,52,53,55] were conducted in countries that do not have universal screening for thyroid dysfunction during pregnancy (Denmark,[64,65] Israel,[66] the United States,[67,68] and Taiwan[48]). Misclassification of the exposure could result in a bias toward the null, although there is not enough research on the relationship between subclinical thyroid outcomes and ASD outcomes to assess the extent to which this would occur. Prospective studies evaluating women using thyroid laboratory tests are critical to learning more about whether the nature or strength of the relationship between thyroid dysfunction and ASD outcomes differs based on thyroid dysfunction severity.

Findings on thyroid autoimmune diseases could have been affected by misclassification bias. In this review, self-reported thyroid autoimmune diseases had no significant association with ASD diagnosis,[51] but TPO-Ab positivity was associated with a significantly increased likelihood of ASD.[47,56] By using self-reported thyroid autoimmunity, mothers with thyroid autoimmunity who were not aware of

Table 2. Considerations for Examining Associations Between Maternal Thyroid Dysfunction During Pregnancy and Autism Spectrum Disorder Outcomes

Study design	Consider nested designs
Sample size	Adequate power to detect differences for specific types of thyroid dysfunction and autism phenotypes
	Sample size should allow for stratification by child sex
Sample description	Women with well-characterized medical history, including history of thyroid problems, treatment for thyroid problems, and use of thyroid-interfering medications
Thyroid conditions and ascertainment	Hypothyroidism (subclinical and overt), hyperthyroidism (subclinical and overt), hypothyroxinemia, thyroid autoimmunity
	Measure thyroid hormone concentrations across sample and classify thyroid dysfunction using pregnancy-specific reference ranges
	Assess nonlinearity when examining continuous thyroid hormone concentrations
Time of thyroid condition evaluation	Early in pregnancy, when the fetus is most likely to be affected by maternal thyroid levels ($\sim$8–14 weeks of gestation)
ASD outcome and ascertainment	Clinician assesses all children in the study for ASD diagnosis or ASD traits
Child age at assessment	Follow until the age when most children are diagnosed for their country of residence
Additional variables to examine	Maternal iodine, maternal exposure to thyroid disrupting compounds hypothesized to increase likelihood of ASD in offspring
	Variables that affect fetal survival and ASD development

their status might have been misclassified as not having a thyroid autoimmune condition and findings may have been biased toward the null.

Misclassification of outcome. Child age at ASD assessment ranged from <36 months in a case–control study[51] to 2–17 years in a retrospective cohort study (Table 1).[53] When children were assessed for ASD at too young an age, misclassification could have arisen. A study conducted through a university health center was able to achieve ASD diagnostic stability by age 14 months (as determined by the 36-month reassessment),[69] but some children with less severe symptoms could be missed,[70,71] and in practice, children are usually diagnosed at a later age. In the United States, the median age of ASD diagnosis is estimated to be 51 months.[72] Globally, the average age of diagnosis among children 10 years or younger is estimated to be 43.2 months (range 30.9–74.7 months).[73] ASD can be diagnosed during adulthood, but this is rare.[74]

Because many of the studies to date relied on clinical diagnosis from medical records or registries rather than research-grade assessments of all enrolled children, ASD would be less likely to be reported for younger children in these studies.

Both Brown et al. and Yau et al. stated that some children may have been misclassified as typically developing controls because the age at classification overlapped with the age at which ASD is most commonly diagnosed.[50,56] If this misclassification was nondifferential with respect to maternal thyroid dysfunction, it could result in a bias toward the null. Despite this, both studies found associations between a thyroid measure and ASD diagnosis, although the strength of the association could have been affected by misclassification bias.

Survival bias. Survival bias is present in pregnancy studies because developmental outcomes such as ASD are only known for children who are conceived and survive.[75] Maternal thyroid dysfunction can reduce the likelihood of conception and survival to the age of ASD diagnosis by decreasing fertility or increasing pregnancy loss. Thyroid dysfunction can cause hormonal disruptions that affect fertility. Women with overt hyperthyroidism or hypothyroidism may have impaired fertility compared with euthyroid women, although this is better documented in hypothyroid women than hyperthyroid women.[76] A meta-analysis found that TPO-Ab- or Tg-Ab-positive women had 1.5 times the odds [CI: 1.1–2.0] of unexplained subfertility compared with antibody-negative women, however, these findings may be confounded by co-occurring autoimmune diseases that affect fertility.[76,77]

Multiple types of thyroid dysfunction are associated with increased likelihood of pregnancy loss. Women with overt or subclinical hypothyroidism are at increased risk of pregnancy loss compared with euthyroid women[78–80] and untreated hypothyroidism may be associated with early pregnancy loss.[37,81] TPO-Ab positivity is also associated with increased likelihood of miscarriage.[43,82,83]

Survival bias can affect results differently depending on the true nature of the relationship between the exposure and outcome and whether models are conditioned on conception or fetal survival. Liew et al. used the relationship between prenatal per-and polyfluoroalkyl substance (PFAS) exposure and child attention-deficit/hyperactivity disorder (ADHD) to demonstrate possible implications of survival bias on ORs.[75] When this relationship was modeled as null and conditioned on fetal survival through 6–12 weeks, PFAS appeared to be protective against ADHD, contradicting biological models. When the relationship between the exposure and outcome was modeled as casual and conditioned on fetal survival to 6–12 weeks, it could result in a bias toward the null.[75] If maternal thyroid dysfunction is a cause of ASD, the full magnitude of this relationship may be masked by survival bias, and studies might report a weaker relationship than is true.

Although survival bias cannot be eliminated from a study, the impact can be mitigated by adjusting for variables that affect both the study outcome and fetal survival.[75] Most studies to date adjusted for maternal body mass index (BMI) or body weight[47,50,55,57,58] and/or maternal mental illness,[46,48,52,54,56,57] two factors that are associated with increased ASD likelihood and reduced fertility and/or fetal loss.[84,85] However, adjustment for additional factors associated with both ASD outcomes and fetal survival such as the interpregnancy interval,[86] polycystic ovarian syndrome,[87] and pesticide exposure, could reduce live birth bias further.

Publication bias. In most areas of medical research, null results are more likely to remain unpublished compared with results showing an association.[88] As a result of publication bias, this review may underrepresent research that found no association between maternal thyroid dysfunction during pregnancy and child ASD outcomes. However, among the articles reviewed, null findings were not uncommon. Most studies examined multiple maternal thyroid conditions or multiple child development outcomes and published a combination of null and statistically significant findings in a single article.

Future directions: knowledge gaps and suggestions for further research

Effect of levothyroxine treatment. Multiple studies examining hypothyroidism stated that their sample included women who were receiving treatment for thyroid dysfunction.[52,53,55,57] Theoretically, if abnormal thyroid hormone levels during pregnancy increased the likelihood of ASD outcomes, treatment to normalize hormone levels would reduce ASD likelihood. This hypothesis was supported by Andersen et al. who found that an association between maternal hypothyroidism and child ASD was present among mothers diagnosed and treated with levothyroxine after birth, but not among mothers diagnosed and treated before birth.[52] However, Rotem et al. found that the odds of ASD were similarly elevated regardless of whether mothers were diagnosed and treated for hypothyroidism before or after giving birth, indicating that levothyroxine treatment may not influence ASD outcomes.[55] Among a subset of the sample who had TSH levels available, mothers treated for hypothyroidism before conception with normal TSH levels during pregnancy still had increased odds of having a child with ASD.[55]

Hales et al. performed a secondary analysis of a randomized clinical trial to examine the effects of levothyroxine treatment during pregnancy and found that treated mothers

were more than twice as likely as controls to have children with a positive ASD screen using the Social Communication Questionnaire.[59] However, the mean test scores did not vary significantly between the treated, untreated, and normal thyroid function groups and about a third of the treatment group was likely overtreated with levothyroxine.[59] Ge et al. found no increased likelihood of child ASD among mothers who used levothyroxine during pregnancy compared with euthyroid mothers, but this study did not include mothers with thyroid dysfunction not using levothyroxine as a comparison group.[46]

The relationship between levothyroxine treatment for hypothyroidism and ASD outcomes was challenging to elucidate for multiple reasons. First, both the adequacy and timing of levothyroxine might affect ASD outcomes. Fetal neurodevelopment is hypothesized to be most strongly affected by maternal thyroid function between 8 and 14 weeks of gestation.[89] Not all studies reported the gestational age at which thyroid function was measured, and many studies focused on the late first and early second trimester.[54,56–59] Also, studies did not describe how treatment for hypothyroidism would have likely affected maternal thyroid hormone levels during this proposed critical period of ASD development. Second, the three studies that examined treatment[52,55,59] had different approaches to measuring thyroid dysfunction (clinical diagnosis of hypothyroidism, suboptimal gestational thyroid function) and ASD (clinical diagnosis, nondiagnostic assessments), which make it difficult to generalize their results.

Prenatal exposure to thyroid-disrupting compounds. It is possible that there is an additional factor that underlies both maternal thyroid dysfunction and ASD. As suggested by Rotem et al., environmental exposures affecting both maternal thyroid function and child neurodevelopment could result in an association between maternal thyroid dysfunction and ASD that is independent of treatment.[55] If maternal hypothyroidism is the result of an environmental exposure that could also increase the likelihood of having a child with ASD, treating the mother with levothyroxine may not reduce the likelihood of child ASD because the environmental exposure could still drive ASD development. Prenatal exposures to many chemical compounds are hypothesized to disrupt thyroid function and increase the likelihood of child ASD. Perchlorate and nitrate interfere with thyroid function by inhibiting the sodium–iodide symporter (NIS) and have been known to increase the likelihood of ASD.[90,91]

Both bisphenol A[92–94] and PFAS[35] are suspected of disrupting thyroid function, and prenatal exposure to either of these is associated with ASD.[95] However, the physiological effects of these compounds are not limited to the thyroid, and prenatal exposure to these compounds may alter neurodevelopment through multiple pathways,[96,97] including pathways that are likely independent of levothyroxine use. For example, prenatal exposure to chlorpyrifos, an organophosphate pesticide, has been found to disrupt thyroid function[98,99] and increase the likelihood of ASD.[100] However, prenatal exposure to chlorpyrifos can also lead to breakage and rearrangement of DNA in the gene *KMT2A*, a gene associated with ASD development.[15] Such genetic damage could occur independent of maternal thyroid hormone concentrations. Additional research is needed to identify the pathways by which prenatal exposure to thyroid-disrupting compounds could lead to ASD and to clarify how abnormal thyroid hormone concentrations resulting from exposure might contribute to ASD development.

Iodine, thyroid dysfunction, and ASD. Iodine is necessary for thyroid hormone synthesis.[40] Inadequate maternal iodine intake during pregnancy has long been tied to developmental disabilities in children.[40] In the United States and Europe, population estimates of inadequate iodine intake during pregnancy have decreased greatly in the last century as a result of food fortification policies, but mild-to-moderate iodine deficiency presently still remains a concern in these regions and globally.[101] Iodine deficiency during pregnancy is common within multiple countries included in this review. A median urinary iodine concentration (UIC) falling below the World Health Organization's recommended adequate range for pregnancy (median UIC 150–499 μg/L) was found in a representative sample of pregnant women in the United States (median UIC 129 μg/L)[102] and in two-thirds of the European countries that have assessed pregnancy UIC.[103]

It is unclear how maternal iodine concentrations are related to ASD outcomes. Two studies have investigated this topic and found no statistically significant association between maternal iodine deficiency and ASD traits[104] or ASD diagnosis.[105] These studies assessed for iodine status before 14 weeks of gestation[104] and between 26 and 28 weeks of gestation,[105] respectively. However, both studies used a single UIC measurement per woman, which is not diagnostic of habitual iodine intakes.[104,105] Because urinary iodine measures fluctuate based on recent consumption of iodine-containing foods, and consumption patterns could change throughout pregnancy, multiple urinary iodine measures per person are needed to estimate individual iodine deficiency status.[106,107]

Conclusions

Of the 15 studies included in this review, 12 studies found statistically significant associations between a maternal thyroid abnormality during pregnancy and increased likelihood of ASD outcomes in the child. The most consistent evidence was for hypothyroidism. The rigor of this research would be enhanced if additional steps were taken to mitigate misclassification bias and survival bias. Research with null findings should be given comparable consideration to research with significant findings to reduce publication bias. This review has limitations. As a narrative review, it does not include summary estimates or systematic assessments of article quality.

Future research is needed to investigate the possibility that the relationship between thyroid dysfunction and ASD outcomes is driven by a third factor. Certain environmental chemical exposures are associated with both ASD and thyroid dysfunction.[90–94] These relationships could be clarified by examining maternal exposure to thyroid-disrupting compounds in relation to both maternal thyroid dysfunction and child ASD outcomes. In addition, it is unclear whether levothyroxine treatment for mothers with mild hypothyroidism or hypothyroxinemia is protective for ASD development. This question would be best investigated using studies that are adequately powered to examine multiple ASD outcomes among mothers with different types and severity of thyroid dysfunction.

Iodine deficiency is a modifiable risk factor for hypothyroidism. Given the possible positive associations between maternal hypothyroidism during pregnancy and ASD outcomes, it is important to investigate the proportion of maternal hypothyroidism cases that are attributable to iodine deficiency. Public health strategies to prevent maternal iodine deficiency should continue to be enacted because these strategies could reduce potential downstream effects of iodine deficiency on maternal thyroid function and child neurodevelopment.

Authors' Contributions

Z.B.K.: conceptualization and writing—original draft; E.N.P.: writing—review and editing and supervision; S.Y.L.: writing—review and editing and supervision; H.-M.S.: writing—review and edition and supervision; R.J.S.: writing—review and editing and supervision.

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