MECHANISMS IN ENDOCRINOLOGY

Maternal thyroid dysfunction during pregnancy and behavioural and psychiatric disorders of children: a systematic review

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Abstract

Background: Maternal thyroid dysfunction during pregnancy may lead to persistent neurodevelopmental disorders in the offspring appearing in later life. This study aimed to review the available evidence concerning the relationship between maternal thyroid status during pregnancy and offspring behavioural and psychiatric disorders.

Methods: Systematic electronic database searches were conducted using PubMed, Embase, PsycNET, Scopus, Google Scholar and Cochrane library. Studies including gestational thyroid dysfunction as the exposure and offspring behavioural and psychiatric disorders as the outcome were included. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was followed and, after thorough screening by two independent reviewers, 13 articles remained eligible for inclusion in this study.

Results: Indicators of maternal thyroid dysfunction, including low and high thyroid hormone level and autoimmune thyroiditis, during early pregnancy, were found to be associated with several offspring behavioural and psychiatric disorders such as attention deficit hyperactivity disorder (ADHD), autism, pervasive developmental problems, externalising behaviour, in addition to epilepsy and seizure. The majority of associations were found with low maternal thyroid hormone level.

Conclusion: Maternal thyroid function during pregnancy, particularly hypothyroidism, is associated with behavioural and psychiatric disorders in children. Further studies are needed with a capacity to adjust for a fuller range of confounding factors.

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Introduction

A developing foetus is entirely dependent on maternal thyroid hormone in the first trimester of pregnancy, and although foetal production of thyroid hormone begins during the second trimester, the developing foetus remains partially reliant on maternally supplied thyroid hormone for the remainder of the pregnancy (1). Thyroid hormone disorders are contributors to the majority of maternal pregnancy-related complications and adverse

pregnancy outcomes (2). Maternal hypothyroidism is strongly associated with preterm birth, low birth weight, reduced head circumference growth in infants and young children, placental abruption, cognitive delay and many other abnormal neurobehavioural problems of exposed offspring (3, 4, 5, 6, 7, 8). On the other hand, maternal hyperthyroidism is also found to be robustly associated with maternal and foetal adverse events, such

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as pre-eclampsia, miscarriage, stillbirth, preterm birth and intrauterine growth restriction (4).

Evidence suggest that disorders in maternal thyroid hormone during pregnancy may lead to offspring neurodevelopmental disorders, which become apparent later in life. In turn, the aforementioned adverse events during pregnancy can disrupt the function of the developing nervous system resulting in poor offspring neurodevelopment (9). Both animal and human studies have established that important phases of neocortex development can be altered by early maternal thyroid dysfunction and result in persistent negative consequences in offspring (10, 11, 12, 13). One of the mechanism by which thyroid hormones may influence brain development is via the regulation of the expression of brain-derived neurotrophic factor and *Reln* gene; *Reln* produces Reelin, essential for the proper migration and the establishment of neocortical layers (14).

A research finding reported that approximately one-fourth of youth experience mental health disorder for the last 1 year and one-third experience a lifetime disorder (15). Although no single factor during intrauterine development leads to psychiatric disorders in children, maternal thyroid hormone plays a major role in foetal brain development and is therefore implicated in the development of a range of offspring behavioural and psychiatric problems (16). This is supported by several research findings suggesting associations between early pregnancy thyroid disorders and cognitive development of offspring (6, 17, 18, 19, 20, 21, 22, 23, 24). There are however fewer studies investigating the potential relationship between maternal thyroid disorders during pregnancy and behavioural and psychiatric disorders in offspring at different ages, and no systematic reviews on the subject. The aims of this review were to summarise and identify the impact of maternal thyroid status during pregnancy on offspring behavioural and mental health outcomes.

Methods

Searching strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was followed for this systematic review (25). A systematic literature search of PubMed, EMBASE, Cochrane, PsycINFO, Scopus and Google Scholar were conducted using keywords (Fig. 1). We also searched references and citations from resulting studies to identify potential additional papers.

The search was limited to studies published in the English language since 1996. The following search terms were used in different combinations and Boolean operators: thyroid*, thyroid, 'maternal thyroid function', 'maternal thyroid dysfunction', 'maternal thyroid hormone', hypothyroidism, hyperthyroidism, hypothyroxinemia, hyperthyroxinemia, pregnan*, gestation*, 'behavioral development', 'behavioural development', behavio*, neurological, neurodevelopment, mental disorder, mental illness, attention deficit, depression, anxiety, cogniti*, IQ, psychopathology, child, child*, adolescent and offspring. Duplicates were removed. Titles, abstracts and the content of the articles were screened to determine the suitability for inclusion.

Study selection

Studies were assessed for eligibility according to the inclusion criteria. These criteria included studies with paired study participants of mothers and their offspring, maternal thyroid status determined during all stages of pregnancy, child behavioural and/or psychiatric disorders measured, and both retrospective and prospective cohort studies. Appropriateness of statistical analysis was also assessed, studies with only descriptive analysis being excluded. Animal studies, conference papers and studies that did not fulfil the inclusion criteria were excluded. A total of 13 articles were eligible (Fig. 1).

Data extraction

The title and abstracts of articles yielded from the electronic search were carefully screened. Two authors (D F and K B) extracted information independently from each study using the data extraction form and discrepancies were resolved by consensus. Information extracted included characteristics of participants, sample size, study design, study country, maternal thyroid status, child outcomes with behavioural and psychiatric disorders measured and outcome ascertainment, presence of statistical associations and potential confounders included in each study.

Study analysis

We undertook a narrative analysis of the included studies. Meta-analysis was not conducted due to heterogeneity of the exposure and outcome variables. Methodological quality of each study was assessed with points attributed for representative sampling, validated exposure and

Figure 1

Flow diagram showing the number of articles sourced at each stage of the systematic review.

outcome measures, appropriate control of potential confounders and overall quality.

Results

After removing duplicates, 5305 records were identified by the electronic database searches. Based on the title screening, 850 records were eligible for abstract screening, of which 60 articles met the criteria for full article review. Following thorough review of the articles, 13 (26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38) remained eligible (Fig. 1). All eligible studies were conducted in European countries with the exception of two studies from the USA. All studies were based on (a) population-based prospective birth cohort studies and (b) national register-based retrospective studies. Sample sizes ranged from 287 to 1 699 693, with the large samples derived from registry studies. One study was based on very few participants (16 cases, 11 controls). Exposure variables included hypothyroidism, subclinical hypothyroidism, mild and severe hypothyroxinaemia, subclinical hyperthyroidism, hyperthyroidism, thyroid-stimulating hormone (TSH), free thyroxine (fT4) and thyroperoxidase antibodies positive (TPO-Abs+) or autoimmune thyroiditis. Study outcomes included ADHD, autism, internalising and externalising behaviours, schizophrenia, oppositional defiant problems, as well as epilepsy and seizure disorders.

As shown in (Table 1), maternal thyroid status was measured during the first trimester and early second

trimester in six studies (26, 27, 28, 29, 34, 35, 38); in one study it was measured during late second trimester (32) and in four studies timing was not reported (30, 31, 33, 36). Offspring outcomes were measured between 3 and 8 years of age in most studies (26, 27, 29, 31, 32, 33, 34, 35), except for some studies where outcomes were measured in young adulthood (28, 36) and from age 15 through to 31 years (30).

Overall, the included studies reported associations between maternal hypothyroxinaemia during early pregnancy and several behavioural and psychiatric disorders. Both high and low levels of maternal thyroid hormones were associated with ADHD, schizophrenia, epilepsy and seizure. Maternal TPO-Abs+ and high TSH concentration were found to be associated with externalising behaviour of children aged 3 whereas none of the studies found an association with internalising behaviour. These associations are described in more detail in the following sub-sections.

Attention deficit hyperactivity disorder

Of 13 studies included in this review, seven studies investigated the association between maternal thyroid dysfunction and offspring ADHD or ADHD symptoms. Andersen *et al.* (31) found a correlation between maternal hyperthyroidism and offspring ADHD at age 3 using a large register-based cohort, adjusted for covariates. The study sampled 857 014 mother-child pairs, singletons only.

Table 1 Characteristics of studies with maternal thyroid dysfunction exposure and offspring's behavioural and psychiatric disorders.

Study year, reference	Country	Study design	Participants	Maternal thyroid status	Child Outcome	Child outcomes ascertainment	Association between maternal thyroid status and child outcome
2015, (26)	Netherlands	Population-based birth cohort	<ul style="list-style-type: none"> 3873 mother-child pairs, GA (mean (s.d.)) = 13.6 (1.9) of 6.6–17.9 weeks Children age = 8 years 	<ul style="list-style-type: none"> Hypothyroxinaemia SCH Hypothyroxinaemia 	ADHD	Conners' Parent Rating Scale-Revised Short Form (CPRS-R:S) reported by mothers	$\beta = -0.07$ (0.03, 0.14), $P = 0.04$ $\beta = -0.01$ (–0.07, 0.05), $P = 0.80$ $\beta = 0.02$ (–0.04, 0.08), $P = 0.49$
2015, (27)	Finland	Nested case-control design (Birth cohort)	<ul style="list-style-type: none"> Maternal sera of 1010 case-control pairs for fT4 (GA in WK = mean (s.d.): 11 (4)). 948 case-control pairs for TSH (GA in WK = mean (s.d.): 10.8 (4.1)) Up to 26 years old child included 	<ul style="list-style-type: none"> Hypothyroxinaemia Hypothyroidism SCH Hyperthyroidism Subclinical hyperthyroidism 	Oppositional Scale	Diagnosis from psychiatric hospital admissions and psychiatric outpatient treatment based on ICD-10 F20 and ICD-10 F25	$OR = 1.7$ (1.13, 2.55), $P = 0.010$ $OR = 0.86$ (0.23, 3.24), $P = 0.827$ $OR = 0.80$ (0.47, 1.37), $P = 0.424$ $OR = 0.87$ (0.41, 1.82), $P = 0.706$ $OR = 1.91$ (1.14, 3.20), $P = 0.014$
2015, (28)	Finland	Nested case-control design (Birth cohort)	<ul style="list-style-type: none"> 960 case-control pairs for TPO-Ab 954 case-control pairs for TSH 958 case-control pairs for fT4 Up to 20 years old child included 	<ul style="list-style-type: none"> TPO-Ab+ Hypothyroidism SCH Hyperthyroidism Subclinical hyperthyroidism 	Autism	Diagnosis from psychiatric hospital admissions and outpatient visits of childhood autism (ICD-10F84.0)	$OR = 1.78$ (1.16, 2.75), $P = 0.009$ $OR = 0.67$ (0.27, 1.63), $P = 0.37$ $OR = 1.17$ (0.72, 1.90), $P = 0.54$ $OR = 1.06$ (0.54, 2.10), $P = 0.86$ $OR = 1.10$ (0.67, 1.83), $P = 0.71$
2014, (29)	Finland	Population-based birth cohort	<ul style="list-style-type: none"> 5131 mother-child pairs, GA in WK = mean (s.d.): 10.7 (2.8) Children age = 8 years 	<ul style="list-style-type: none"> Hypothyroxinaemia High TSH 	<ul style="list-style-type: none"> Inattention (boys) Inattention (girls) Hyperactivity (boys) Hyperactivity (girls) Combined ADHD (boys) Combined ADHD (girls) 	Teachers evaluated the children's ADHD symptoms at 8 years using the Rutter B2 scale	$OR = 0.75$ (0.33, 1.69) $OR = 0.66$ (0.15, 2.83) $OR = 0.69$ (0.31, 1.56) $OR = 1.07$ (0.31, 3.65) $OR = 0.61$ (0.18, 2.03) NA $OR = 0.76$ (0.51, 1.12) $OR = 1.14$ (0.66, 1.97) $OR = 1.07$ (0.75, 1.52) $OR = 1.20$ (0.70, 2.03) $OR = 0.89$ (0.52, 1.50) $OR = 1.69$ (0.79, 3.56)

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2014 ^a , (30)	Denmark	Cohort (register) study	- 542 100 adolescents and their mothers included	Hypothyroidism (1977–1995 group)	Anxiolytics	Drug prescription registers and psychiatric diagnoses based on ICD-8: 295.0–301.9 and ICD-10: F20.0–F48.9	HR=1.23(1.03, 1.48)
			- Offspring's age=15–31 years	Hypothyroidism (1996–2005 group)	Antipsychotics Antidepressants Anxiolytics		HR=1.22(1.03, 1.44) HR=1.07 (0.98, 1.17) HR=0.96 (0.84, 1.10)
2014 ^b , (31)	Denmark	Cohort (register) study	- 857 014 mother–child pairs, singletons only	Hypothyroidism	Antipsychotics Antidepressants ADHD	Diagnosed at hospital based on F90 (ICD–10)	HR=1.04 (0.92, 1.17) HR=1.00 (0.95, 1.06) HR=1.10 (0.98, 1.25)
			- Children age=3 years	Hyperthyroidism Hypothyroidism	Autism spectrum disorder (ASD)	Diagnosed at hospital based on F84 (ICD–10)	HR=1.18 (1.03, 1.36) HR=1.30 (1.11, 1.53)
2013, (33)	Denmark	Cohort (register) study	- 1 699 693 mother–live born singletons	Hyperthyroidism	Epilepsy	Registers diagnosed based on ICD-8 and ICD-10	HR=1.18 (0.96, 1.45) HR=1.22 (1.06, 1.40), P=0.005
			- Child median age=1.4 years for febrile seizure and 5.3 years for epilepsy	Hyperthyroidism Hypothyroidism Hyperthyroidism	Seizure		HR=1.20 (1.09, 1.32), P<0.001 HR=1.20 (1.11, 1.30), P<0.001 HR=1.08 (1.02, 1.15), P=0.009
2013, (32)	Netherlands	Cohort study	- 4039 mother–child pairs, GA in WK = mean (s.d.): 13.4 (1.9)	Mild hypothyroxinaemia	Neonatal seizure		HR=1.78 (1.30, 2.44), P<0.001
			- Children age=6 years	Severe hypothyroxinaemia TPO-Abs+ Mild hypothyroxinaemia Severe hypothyroxinaemia TPO-Abs+	Febrile seizure AUTISTIC SYMPTOMS Pervasive developmental problems (PDP)	Parent-reported using 2 instruments: the PDP subscale of the CBCL for toddlers (CBCL 1.5–5) and the SRS	HR=1.22 (0.92, 1.62), P=0.161 HR=1.21 (1.10, 1.32), P<0.001 HR=1.03 (0.95, 1.11), P=0.464 OR=1.41 (0.78, 2.57), P=0.26
2012, (34)	Netherlands	Cohort study	- 3139 mother–child pairs, GA in WK = mean (s.d.): 13.5 (1.8)	TPO-Abs+ Mild hypothyroxinaemia Severe hypothyroxinaemia TPO-Abs+	Social responsiveness scale (SRS)		OR=2.60 (1.30, 5.18), P=0.01
			- Children age=3 years	TPO-Abs+ Mild hypothyroxinaemia Severe hypothyroxinaemia TPO-Abs+	Internalising problems Affective problems Anxiety problems	CBCL 1.5–5 reported by parents	OR=0.78 (0.28, 2.16), P=0.63 $\beta=0.02$ (–0.01, 0.04), P=0.33 $\beta=0.05$ (0.01, 0.10), P=0.01 $\beta=0.03$ (–0.01, 0.06), P=0.11 OR=1.21 (0.84, 1.74), P=0.31
					Externalising problems ADHD problems Oppositional deviant problems		OR=1.02 (0.63, 1.65), P=0.95 OR=1.27 (0.81, 2.00), P=0.29 OR=1.64(1.17, 2.29), P=0.004 OR=1.77(1.15, 2.72), P=0.01 OR=1.39 (0.95, 2.03), P=0.09

(Continued)

Table 1 Continued.

Study year, reference	Country	Study design	Participants	Maternal thyroid status	Child Outcome	Child outcomes ascertainment	Association between maternal thyroid status and child outcome
2011, (35)	Netherlands	Cohort study	<ul style="list-style-type: none"> 3736 children and their mothers (GA in WK=mean (s.d.): 13.3 (1.7)) Children age=1.5 and 3 years 	Hypothyroxinaemia TSH fT4 Total T4	Internalising Externalising Externalising ADHD Oppositional defiant Internalising Externalising Externalising ADHD	CBCL 1.5–5 reported by parents	$\beta = -0.19$ (–0.75, 0.37), $P = 0.51$ $\beta = -0.17$ (–0.53, 0.87), $P = 0.64$ $\beta = 0.10$ (–0.01, 0.21), $P = 0.07$ $\beta = 0.22$ (0.04, 0.40), $P = 0.02$ $\beta = 0.08$ (0.01, 0.15), $P = 0.05$ $\beta = 0.08$ (0.02, 0.14), $P = 0.01$ $\beta = 0.01$ (–0.13, 0.15), $P = 0.91$ $\beta = -0.02$ (–0.16, 0.20), $P = 0.80$ $\beta = 0.09$ (–0.04, 0.22), $P = 0.19$ $\beta = 0.12$ (–0.06, 0.30), $P = 0.19$ $\beta = -0.65$ (–1.26, –0.04) $\beta = -0.10$ (–2.03, 1.82) $\beta = 0.00$ (–0.28, 0.27)
2011, (36)	USA	Cohort study	<ul style="list-style-type: none"> 287 mother–child pairs, GA in WK=mean (s.d.): 26.9 (3.4)) Children age=5 years 	TSH fT4 Total T4		CBCL 1.5–5 reported by mothers	
2004, (38)	Italy	Prospective follow-up	<ul style="list-style-type: none"> 16 children born to 16 healthy mothers living in the moderately iodine-deficient area and 11 controls born to 11 age-matched women from sufficient iodine intake area 	Hypothyroxinaemia	ADHD	(DSM-IV-TR)	χ^2 , 2.34; $P = 0.001$
1999, (37)	USA	Cohort study	<ul style="list-style-type: none"> 62 mother–child pairs, 124 matched control women–child pairs Children age = 7–9 years 	Hypothyroidism	Attention (Children of women with hypothyroidism) Attention (Children of treated women with hypothyroidism)	<ul style="list-style-type: none"> WISC-III freedom from distractibility score Conners' Continuous Performance Test by certified psychologists WISC-III freedom from distractibility score Conners' Continuous Performance Test by certified psychologists 	$P = 0.08$ $P = 0.01$ $P = 0.80$ $P = 0.01$ $P = 0.03$ $P = 0.04$

fT4, free thyroxine; GA, gestational age; ICD, International Classification of Diseases; SCH, subclinical hypothyroidism; TSH, thyroid-stimulating hormone; TPO-Abst, thyroperoxidase antibodies positive; CBCL, Child behaviour checklist; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition. Text Revision.

The gestational age at which the thyroid function measured was not reported by authors.

Ghassabian *et al.* (35) also reported an association between maternal autoimmune thyroiditis, at mean gestational age of 13.5 (s.d.=1.8) weeks, and increased risk of offspring ADHD problems (OR=1.77 (1.15, 2.72)) at age 3 ($n=3139$ mother-child pairs). Another study by Ghassabian *et al.* (29), among similar age group of children, also found an association between high TSH concentration during pregnancy, at mean gestational age of 13.3 (s.d.=1.7) weeks, and offspring ADHD ($n=3736$ mother-child pairs). In both studies, the authors adjusted for some of the potential confounders.

In a population-based birth cohort study of 3873 mother-child pairs Modesto *et al.* found that offspring born from hypothyroxinaemic mothers, at mean gestational age of 13.6 (s.d.=1.9) weeks, were found to be at increased risk of ADHD at age 8 ($\beta=0.07$ (0.03, 0.14)). The study was adjusted for a large number of potential confounders including maternal and child socio-demographic characteristics and maternal mental health during pregnancy (27). Similarly, a study by Haddow *et al.* (37) found association between maternal hypothyroidism and offspring attention at age 7–9 with Conners' Continuous Performance Test (CCPT). However, the authors did not adjust for confounders that might play a role in the association. Vermiglio *et al.* (38) also demonstrated that ADHD prevalence was significantly higher in children aged 8–10 years born from hypothyroxinaemic mothers in iodine-deficient area. However, this study was unadjusted for confounders and a very low number of cases (16 ADHD cases from iodine-deficient area and 11 age-matched controls from iodine-sufficient area).

On contrary, a study also found that abnormal levels of thyroid hormone were positively associated with child outcomes. Chevrier *et al.* (32) found an association ($\beta=-0.65$ (–1.26, –0.04)) between increasing maternal TSH concentration at mean gestational age of 26.9 (s.d.=3.4) weeks, and reduced risk of ADHD at the age of 5 years in the offspring ($n=287$ mother-child pairs). This study also adjusted for potential confounders such as maternal age, income, delivery complications and a 5-minute Apgar score. A further study (34) found no overall association, but an increased risk of ADHD problems (OR=1.39 (1.07–1.80)) among only female offspring born from mothers with higher TSH concentrations.

Most of the studies exhibited strong methodologies and were sufficiently powered, with capacity to adjust for potential confounders ($n=3189$ to 857014). Across these

studies, ADHD was assessed using different instruments, including the Conners' Parent Rating Scale-Revised Short Form reported by mothers (27), teachers evaluation using Rutter Scale B2 (34), and Child Behaviour Checklist (CBCL) reported by parents (29, 32, 35), although one study used hospital diagnosis and dispensed prescriptions of medications as indicators of ADHD which is more reliable given that appropriate recording and data extraction are applied (31).

Autism

Three studies investigated the relationship between autism problems and maternal thyroid function with all reporting a statistically significant association. Using a cohort study of 4039 mother-child pairs, Roman *et al.* (26) found a positive association (OR=2.6 (1.30, 5.18)) between maternal severe hypothyroxinaemia, at mean gestational age of 13.4 (s.d.=1.9) weeks, and autism problems in offspring at age 6. The authors have adjusted the model for a wide range of potential confounders, including demographics, socio-economic position, lifestyle factors and mental health status, which were not comprehensively controlled in other studies (Table 2). In support of this, Andersen *et al.* (31) have also reported the increased risk of autism spectrum disorder of the offspring at age 3 with maternal hypothyroidism during pregnancy (HR=1.30 (1.11, 1.53)). Importantly, this study failed to adjust for some important confounding variables such as antenatal maternal psychopathology and birth weight. Further, Brown *et al.* (36) examined the relationship between maternal autoimmune thyroiditis during pregnancy and offspring autism among 960 case-control pairs, and they have confirmed a positive association (OR=1.78 (1.16, 2.75)). The authors did not adjust the model as no covariate was associated with the outcome in univariate analyses.

Both Brown *et al.* (36) and Anderson *et al.* (31) identified cases of autism based on hospital-based clinical diagnosis whereas Roman *et al.* (26) used validated parent-reported instruments of the CBCL for toddlers (CBCL 1.5–5) and the Social Responsiveness Scale (SRS) (39). In some of these studies, hyperthyroidism was not associated with offspring autism as reported by Brown *et al.* and Anderson *et al.* (31, 36). Further studies are warranted to give a conclusive statement on whether hyperfunctioning of thyroid gland is not linked with autism.

Table 2 Confounders and covariates adjusted in the association between maternal thyroid function and offspring's behavioural and psychiatric disorder.

Study year, reference	Maternal										Offspring				
	Paternal age	Age	Psychopathology	Smoking	BMI	Marital status	Income	Educational level	Parity	Gender	GA	Apgar score	Birthweight	No. of siblings	
2015, (26)		✓	✓	✓	✓	✓	✓	✓	✓	✓					
2015, (27)			✓	✓											
2015, (28)															
2014, (29)		✓		✓				✓	✓	✓				✓	
2014 ^a , (30)		✓	✓			✓	✓			✓					
2014 ^b , (31)		✓				✓	✓		✓	✓					
2013, (33)		✓	✓			✓	✓		✓	✓			✓		
2013, (32)			✓	✓		✓		✓	✓	✓	✓				
2012, (34)	✓	✓		✓						✓					
2011, (35)		✓	✓					✓		✓					
2011, (36)		✓					✓			✓		✓		✓	
2004, (38)															
1999, (37)															

Internalising and externalising behaviour

Only two studies tested the relationship between offspring internalising and externalising behaviour and maternal thyroid dysfunction. In a study of 3139 mother-child pairs (35), the odds of offspring externalising behaviour at age 3 were higher among children exposed to maternal prenatal autoimmune thyroiditis (OR=1.64 (1.17, 2.29)) at mean gestational age of 13.5 (s.d.=1.8) weeks compared with those who were not. High maternal TSH concentration, at mean gestational age of 13.3 (s.d.=1.7) weeks ($\beta=0.22$ (0.04, 0.40)), were also associated with increased offspring externalising behaviour at ages 1.5 and 3 years, whereas no associations were found with internalising behaviour (29). In both studies, the CBCL was used to obtain a standardised rating of the child's problem behaviour by parents. Both studies also adjusted for potential confounders but maternal psychopathology and smoking status were not universally controlled for.

Oppositional defiant problems

Three studies investigated relationships between maternal thyroid hormone ascertained in the first trimester and early second trimester with offspring oppositional defiant disorder measured at ages 3 and 8. Of these three studies, only one found a positive association ($\beta=0.08$ (0.02, 0.14)) (29); the other two found no apparent associations between hypothyroxinaemia and autoimmune thyroiditis and offspring's oppositional defiant problems at ages 3 and 8, respectively (27, 35).

Offspring oppositional defiant problems were measured using parental reports from the CBCL (1.5–5) in two studies (29, 35) and maternal reports of the CPRS-R:S (27). Parental reports are somehow problematic when assessing child's behaviour. It has been argued that parents often score their children as less affected in the domains of social deficits and communication and more affected on restricted interests and stereotypies than clinicians. Hence, future research using both clinician observation and parent interview is warranted to increase the reliability and validity of the diagnosis (40).

Schizophrenia

There is scant evidence on the relationship between maternal thyroid dysfunction and mental health problems in offspring. Only one study investigated the association of maternal thyroid dysfunction and schizophrenia in the offspring, finding increased odds of schizophrenia in

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offspring of mothers who experienced hypothyroxinaemia (OR=1.7 (1.13, 2.55)) and subclinical hyperthyroidism (OR=1.91 (1.14, 3.20)) during pregnancy (28). The study comprised of 1010 case-control pairs for fT4 investigation at a mean gestational age of 11 (s.d.=4) weeks, and 948 case-control pairs for TSH investigation at a mean gestational age of 10.8 (s.d.=4.1) weeks. Offspring included in the assessment ranged from childhood up to 26 years. The association remained after adjustment for maternal psychiatric history and maternal smoking during pregnancy. Interestingly, preterm birth was found to be a mediator in this relationship reducing the risk by 28% (28), strengthening suggestions that associations may be mediated via adverse obstetric outcomes.

Other outcomes

A national register study by Andersen *et al.* (30) identified an association between maternal hypothyroidism and medical prescription of anxiolytics and antipsychotics in adolescents and young adults ranging from age 15 to 31, in which the authors indicate higher risk of offspring anxiety and psychosis might be due to maternal hypothyroidism during pregnancy ($n=542\,100$). In a second study using the same study population but larger sample size ($n=1\,699\,693$) (33), maternal hypothyroidism was also statistically associated with epilepsy, seizure, neonatal seizure and febrile seizure in the offspring ascertained from hospital records. Offspring febrile seizure and epilepsy were diagnosed at median age of 1.4 and 5.3 years respectively by ICD-8 and ICD-10. In addition to hypothyroidism, maternal hyperthyroidism was found to increase the risk of offspring epilepsy and seizure but not the risk to neonatal and febrile seizure. In both studies, the large sample size allowed for increased statistical power of the study. However, lifestyle factors such as smoking and alcohol use during pregnancy were not adjusted for, making it difficult to verify the independent effect of thyroid disease on child outcomes. Also, maternal thyroid diseases were hospital-based diagnosis that accounts for symptomatic cases only. As to asymptomatic cases, these would have been identified in prospective studies given the opportunity to screen for full thyroid parameter test.

Discussion

Evidence from a range of scientific disciplines suggests that perinatal and obstetric factors are determinants of offspring mental health in later life stages (1, 13, 41,

42, 43, 44, 45, 46, 47). In this review, which focused on behavioural and psychiatric disorders of offspring born from mothers with thyroid dysfunction during pregnancy, we found that maternal thyroid dysfunction was associated with offspring mental health problems not only in early childhood but also in late adolescence and adulthood. Further, both maternal hypothyroidism and hyperthyroidism were strongly linked with behavioural and psychiatric problems among offspring. These epidemiological findings are supported by numerous studies which have shown that both low and high maternal thyroxine levels impact foetal brain size and structure (12, 13).

ADHD is among the most common neurobehavioural disorders in children and can persist into adulthood (48), and was the most investigated outcome in our eligible studies. The combined evidence of these studies indicates that maternal thyroid dysfunction may be directly implicated in the development of ADHD. The majority found positive associations between early gestational thyroid malfunction and ADHD problems in offspring (27, 29, 31, 35, 37). All studies (27, 29, 35, 37) but the study by Andersen *et al.* (31) were prospective population-based cohort studies and also had sufficient sample size to achieve adequate power, with capacity to adjust for potential confounders showing strong methodologies. However, the study by Andersen *et al.* (31) is the only study that ascertained offspring ADHD based on F90 (ICD-10) clinical diagnosis. Of the remaining studies, Pakkila *et al.* (34) found only a weak association among girls born from mothers with increased concentrations of TSH in the first trimester. In this study, ADHD was diagnosed based on a teacher-evaluated questionnaire, whereas the majority of the other studies used clinically measured outcomes or parent-reported CBCL, perhaps accounting for the difference in findings. Finally, a counterintuitive relationship was found by Chevrier *et al.* (32), which showed an increased concentration of maternal TSH reduced the risk of offspring ADHD at age 5. However, in this study gestational thyroid hormone was analysed during late second trimester unlike the other studies, most of which were conducted during the first and early second trimester as recommended (49, 50). This discrepancy might indicate either a chance finding or alternatively that early and not late pregnancy is a sensitive period in which thyroid hormone level is a determinant of childhood ADHD problems. Variation in the ages at which the behavioural and psychiatric disorders were assessed in children may account for some variations in the findings. Our review did not show

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age-patterned differences. However, it is important to bear in mind that thyroid hormone insufficiency in early life may alter neuronal plasticity including permanent modifications of synaptic plasticity in adult life through epigenetic modifications of genes involved (51). The obvious heterogeneity among the relatively small number of studies, particularly concerning heterogeneity of the exposure, precluded a meta-analysis capable of producing an estimate of the hypothesised association. However, the evidence currently available indicated an increased risk of ADHD in offspring of mothers with abnormal thyroid levels during early pregnancy, and we encourage further research in this area.

Studies included also suggested that children born of mothers with low levels of thyroxine during pregnancy were at an increased risk of autism (26, 31). Similarly, an increased risk of autism was found in offspring of mothers who had autoimmune thyroiditis during pregnancy (36); however, it was not clear whether the effect took place after birth due to the already transferred placental antibodies or during intrauterine growth. Diagnosis of autism was made by using ICD-10 clinical diagnosis in both studies by Brown *et al.* (36) and Anderson *et al.* (31) while Roman *et al.* (26) used validated parent-reported instruments (CBCL 1.5–5 and SRS) (39). The additional strength of the study by Brown *et al.* (36) is the use of matched controls and the ability to examine a wide range of offspring up to age 20. A study by Roman *et al.* also suggested that low maternal T4 plus inactivation of brain deiodinases lowered tissue levels of triiodothyronine (T3) resulting in abnormal neuronal migration. This neuropathological anomaly was suggested to be mediated via reelin dysregulation that is known to occur in the brains of subjects with autism (52). Berbel *et al.* (53) have reported that some of the T3-regulated genes at the transcriptional level are involved in corticogenesis. Many of these genes have been found to be altered in ASD, ADHD, schizophrenia and anxiety cases. Therefore, thyroid hormone imbalance at critical periods might cause permanent neurodevelopmental changes leading to these neurologic disorders. Hyperthyroidism on the other hand showed no relationship with child autism problems and more studies are needed to investigate if there indeed is no relationship.

Maternal autoimmune thyroiditis (35) and high maternal TSH concentrations (29) were found to increase the odds of offspring externalising behaviour and oppositional defiant disorders but not internalising behaviour. Such findings are in line with expectations, as being a determinant element in foetal brain development

thyroid hormone deficiency may be more likely implicated in neurobehavioural disorders. Studies have found that thinner brain cortex is strongly related with externalising behaviours in children, suggesting prenatal thyroid hormone deficiency, known to negatively impact foetal brain development, may increase the risk of externalising behaviours via this mechanism (54, 55). The consistent finding in these studies may increase once inference that maternal thyroid dysfunction during pregnancy has impact on offspring externalising behaviour but not on internalising behaviour. However, both of these limited studies were from the same cohort study, used the same instrument to ascertain the cases (CBCL 1.5–5) and included similar offspring age groups. Hence, further researches are needed before we conclude on the specificity of prenatal thyroid regulation to externalising and not internalising behaviour problems among offspring.

The relationship between maternal thyroid dysfunction and schizophrenia was only investigated by one study, Gyllenberg *et al.* (28), which found almost double risk of schizophrenia in offspring born of mothers with hypothyroxinaemia and subclinical hyperthyroidism during pregnancy. This could be explained by the fact that reductions in circulating thyroid hormone concentrations mediate impaired neurological development. The authors also confirmed that the relationship between maternal hypothyroxinaemia and schizophrenia was mediated by preterm birth indicating that adverse birth outcomes could play a major role in the relationship. Though Gyllenberg *et al.* examined prospectively matched case–controls and included adults of up to age 26, further studies are needed.

A study by Andersen *et al.* revealed an association between hypothyroidism during pregnancy and anxiety, affective disorders, psychosis, epilepsy, seizure, neonatal seizure and febrile seizure among offspring (30, 33). These disorders may have resulted due to structural and functional abnormalities associated with altered prenatal maternal thyroid exposure (8). Animal studies have demonstrated that progeny exposed to altered prenatal thyroid showed aberrations in cell migration coupled with subtle changes in the cytoarchitectonic structure, increasing the risk of impaired brain function (10, 56). This is in agreement with the above study findings where lower concentrations of maternal thyroxine hormone were highly related with these neurological disorders in offspring. Further prospective cohort studies are still needed to identify the stages of pregnancy most predictive of offspring neurological disorders.

To the best of our knowledge, this is the first systematic review to examine the association between maternal gestational thyroid dysfunction and offspring's behavioural and psychiatric outcomes. Thyroid function assessment is challenging due to the dramatic variation occurring across the pregnancy, and the variance in assessment of thyroid functioning along with variations in outcomes made meta-analysis impossible.

Although most of the articles reviewed are of a good quality, none of the articles considered offspring's thyroid status at the time of behavioural and psychiatric outcomes measured. Offspring thyroid status may be an important confounder variable and also suggested that maternal thyroid hormone level is related with offspring's thyroid function (57). Studies accounting for both maternal and offspring thyroid functions are needed to confirm the independent effect of maternal thyroid hormone during pregnancy. In addition, maternal alcohol use, smoking and substance use during pregnancy were not universally included across the studies, which may have confounded the associations of interest. These factors have been found to increase the risk of thyroid hormone imbalance during pregnancy, consequently affecting the pregnancy outcome (58, 59, 60, 61). Evidence also suggests that exposure to maternal tobacco, cannabis and alcohol use during pregnancy may lead to detrimental neurologic effects on the offspring (62). Moreover, the majority of the studies did not adjust for pregnancy-related complications and birth outcomes such as hypertensive disorders of pregnancy, birth weight and gestational age at birth, nor explore the potential of these factors to play an intermediary role. In addition, there is no information, except for a handful of well-controlled studies, on the possible influence of maternal comorbidities, in the association between maternal thyroid dysfunction and offspring neurobehavioural disorders. Only two studies (26, 27) had the capacity to include a wide variety of confounders in their analysis as shown in Table 2. Lastly, maternal and offspring's iodine and zinc intake should be accounted for in any future research, as brain function may be impaired due to transient or long-term deficiencies of these elements and of course iodine is a precursor for thyroid hormone synthesis (60). Likewise, selenium is also important for thyroid health. It is essential in the metabolism of thyroid hormone which removes the thyroid-harming substances (63). Thus selenium deficiency alone or in combination with iodine deficiency in pregnant women may lead to impairments in the developing foetal nervous system. Hence, in addition to iodine supplementation, the need

for selenium supplementation during pregnancy should be explored more.

In conclusion, evidence presented in our review indicated that disorders in maternal thyroid hormone during pregnancy are risk factors for offspring ADHD and autism, and externalising behaviour problems and other related behavioural and psychiatric problems in childhood. Further studies are needed with the capacity to investigate the association with consideration of a fuller range of confounding factors.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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