

## ORIGINAL ARTICLE

# Maternal cognitive function during pregnancy in relation to hypo- and hyperthyroxinemia

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## Abstract

**Objective:** To assess a possible relationship between maternal cognitive dysfunction during pregnancy and hypothyroxinemia, adjusted for major confounders.

**Background:** Thyroid dysfunction in general is associated with cognitive dysfunction. Cognitive dysfunction is common during pregnancy.

**Design:** Prospective follow-up study from 12 to 32 weeks of pregnancy.

**Participants:** 2082 healthy pregnant women.

**Measurements:** Cognitive function, depression and sleeping problems were assessed by self-report questionnaires at 12, 22 and 32 weeks of gestation, higher scores reflecting more symptoms. FT4, TSH and TPO-Ab were assessed at 12 weeks of gestation.

**Definitions:** healthy (euthyroxinemia) control group: FT4 within 10-90th percentiles, without elevated TPO-Ab titres and TSH within first trimester-specific reference range (0.23-4.0 mU/L). Hypothyroxinemia: FT4 <2.5th percentile with TSH within first trimester-specific reference range. Poor cognitive function: a score >1 SD > mean on the cognitive function scale.

**Results:** A total of 54 women showed hypothyroxinemia and 1476 women had euthyroxinemia. At 12 weeks, multiple logistic regression showed that poor cognitive function was independently related to hypothyroxinemia: OR: 2.9 (95% CI: 1.6-5.4), adjusted for depression (OR: 3.1; 95% CI: 2.7-4.6) and sleeping problems (OR: 2.8, 95% CI: 1.9-3.9). TPO-Ab + women with hypothyroxinemia had the highest levels of cognitive dysfunction. Other cut-offs of hypothyroxinemia (<5th or <10th percentile with normal TSH) showed similar results. GLM-ANOVA showed that throughout pregnancy women with hypothyroxinemia at 12 weeks had significantly higher cognitive dysfunction scores compared with the healthy controls:  $F = 12.1$ ,  $P = .001$ .

**Conclusions:** Women with hypothyroxinemia during early gestation are at risk for poor cognitive function throughout gestation, adjusted for depression and sleeping problems.

## KEYWORDS

cognitive function, hypothyroxinemia, pregnancy, thyroid

## 1 | INTRODUCTION

About 50%-80% of pregnant women perceive memory deficits often called 'pregnancy brain'.<sup>1,2</sup> Decline of verbal memory, associate learning, reaction time and verbal recall have been reported.<sup>3</sup> The exact mechanism is largely unknown but is likely to be multifactorial.<sup>4</sup> Pregnancy is also associated with sleeping difficulties that in turn can have detrimental effect on health-related quality of life and contribute to worse cognitive functioning.<sup>5</sup> Cognitive dysfunction and sleeping problems are also common symptoms of depressive disorders and depression occurs in 10%-15% of pregnant women.<sup>6,7</sup>

Thyroid hormones (THs) are critical for normal brain functioning.<sup>8,9</sup> Poor cognitive functioning is one of the most prominent and persistent symptoms reported by patients with Hashimoto thyroiditis who are biochemically euthyroid after long-term levothyroxine (T4) replacement.<sup>10</sup>

In most studies, thyroid status in pregnant women is categorized using the classical biochemical criteria of trimester-specific fT4 and TSH reference ranges irrespectively of TPO-Ab status: overt hypo- and hyperthyroidism as well as subclinical hypo- and hyperthyroidism.<sup>11</sup> These conditions have been associated with poor obstetric and infant outcome.<sup>12</sup> However, even 5%-7% of pregnant women who are biochemically euthyroid have elevated TPO-Ab titres. These women are also at risk for unfavourable obstetric outcome.<sup>12</sup> Two decades ago another subgroup with suboptimal thyroid function was defined: those with fT4 concentration in the lower percentile cut-offs ranges (<2.5th, <5th or 10th percentile) with TSH concentration within the reference range.<sup>11,13,14</sup> The logical 'counterpart' of this concept, that is hyperthyroxinemia, referring to women with fT4 concentration in the highest 90th, 95th or 97.5th percentile ranges with TSH concentration within the reference limits, has hardly been documented. Despite numerous reports of the association between gestational hypothyroxinemia and impaired neurodevelopment of the offspring, others doubt the relevance of the concept of hypothyroxinemia.<sup>11</sup> But a very recent report of over 45 000 pregnant women underlines the importance of this concept showing that hypothyroxinemia is independently related to (very) preterm birth.<sup>15</sup> The exact origin of gestational hypothyroxinemia in iodine sufficient areas is unknown but is thought to be explained by the 'massive foetal consumption' of trans-placental transported T4 during gestation and the substantial de-iodination of T4 by the placenta.<sup>16</sup>

If this concept is relevant, it is obvious that defining women into (sub)clinical hypo- and hyperthyroidism versus a control euthyroid group will implicate that in the latter a substantial number of women will have hypo- and hyperthyroxinemia eventually resulting in possible false interpretation of the results. For example, we recently reported that at 12 weeks of gestation, there were no differences in thyroid dysfunction symptoms between women with (sub)clinical thyroid dysfunction when compared to euthyroid women.<sup>17</sup> However, we did not correct for hypo- and hyperthyroxinemia in the 'euthyroid' group nor for TPO-Ab status. Many other studies (summarized elsewhere) did also not correct for hypothyroxinemia in the 'euthyroid' control group.<sup>12</sup>

Cognitive functioning *during pregnancy* in relation to *thyroid function* has hardly been investigated. Therefore, the current study focuses on a possible association of cognitive function with gestational hypo- and hyperthyroxinemia. Primary hypothesis is that women with hypothyroxinemia will have more cognitive dysfunction compared with the reference group. Secondary hypothesis is that women with hyperthyroxinemia will have even better cognitive function compared with the reference group. Possible associations are adjusted for two important determinants of cognitive function in general: sleeping problems and depression. A third hypothesis is that if women with hypothyroxinemia present poor cognitive function, it will be most prominent in those with elevated TPO-Ab titres.

## 2 | MATERIALS AND METHODS

The current report is part of the longitudinal prospective HAPPY project (Holistic Approach to Pregnancy and the first Postpartum Year), of which the details have been described elsewhere.<sup>17,18</sup>

### 2.1 | Participants and procedure

From January 2013 to September 2014, pregnant women who had their first antenatal visit at one of the 17 participating community midwife offices in the south-east of the Netherlands were invited to participate in the HAPPY. During the 18 months of women recruitment period, approximately 4150 women visited the participating midwife offices. Only Dutch-speaking women (N = 3475) were invited to participate. Exclusion criteria in this study were gemelli or higher-order pregnancy, an endocrine disorder currently or in the past (diabetes type I, thyroid disorder or use of thyroid medication), a known current diagnosis of depression, a known severe psychiatric disease (borderline, personality disorder), a known drug or alcohol addiction, HIV or any other disease resulting in treatment with drugs that are potentially adverse for the foetus and need careful follow-up during pregnancy. The participants within the HAPPY study were nonpsychiatric, healthy pregnant women. A total of 3159 women were eligible, of whom 2275 (response rate = 72%) signed a written informed consent.<sup>18</sup> The study was approved by the Psychology Ethics Committee of Tilburg University (protocol number EC-2012.25) and additionally evaluated by the Medical Ethical Committee of the Máxima Medical Center in Veldhoven.

### 2.2 | Assessments

This study is reported in line with the STROBE guidelines.<sup>19</sup> At 12 weeks of gestation, women completed a set of questionnaires that evaluated demographic and obstetric features and lifestyle habits. Moreover, at 12, 22 and 32 weeks of gestation, a 50-item questionnaire with a wide variety of somatic, mental and cognitive items was administered. The items of this questionnaire were derived from in-depth interviews with focus groups of pregnant women, women who recently confined and community midwives.

In the total sample, two at random selected subsamples of 1000 women were defined for the construct validation analysis of this 50-item symptom scale. In the first sample, principal component factor analysis with varimax rotation showed poor factor loadings of 20 items, which were omitted, resulting in a 30-item symptom scale. This 30-item questionnaire was further explored in the second sample by factor analysis showing an instrument with five dimensions: a 2-item cognitive function symptom subscale (Cronbach's alpha: .71); a 2-item sleeping problems symptom subscale (Cronbach's alpha 0.70); a 3-item nauseous symptom subscale (Cronbach's alpha: 0.69); a 9-item 'muscle/skeletal symptom subscale' (Cronbach's alpha 0.71); and a 13-item 'psychosomatic' symptom subscale (Cronbach's alpha 0.72). The total 30-item scale had a Cronbach's alpha of 0.82 and is shown in Table S1. For the current study, the 2-item cognitive function symptom and the 2-item sleeping problem subscale were used.

### 2.2.1 | Cognitive function

Women were asked: 'Did you experience during the previous weeks of pregnancy symptoms of: 'difficulties concentrating?' or 'memory difficulties?' Responses were recorded on a 5-point Likert type scale with possible scores ranging from 'never (0)' to 'very often/ nearly always (4)'. This 2-item cognitive symptoms scale (CSS) showed appropriate reliability during the study with the Cronbach's coefficient alpha of 0.71, 0.76, 0.78 at 12, 22 and 32 weeks of gestation, respectively. Higher scores of the CSS reflect poorer perceived cognitive functioning.

### 2.2.2 | Sleeping problems

Women were also asked: 'Did you experience during the previous weeks of pregnancy symptoms of: 'troubles to fall asleep?' or 'troubles to sleep through the night?' with a similar 5-point Likert scale answer category as described above. This 2-item sleeping problem questionnaire showed appropriate reliability during the study with Cronbach's alpha of 0.70, 0.72 and 0.74 at 12, 22 and 32 weeks of gestation, respectively. Higher scores were indicative of greater sleep difficulties.

### 2.2.3 | Depression symptoms

Depression symptoms over the past seven days were assessed at 12, 22 and 32 weeks of pregnancy using the Dutch version of the 10-item Edinburgh (Postnatal) Depression Scale (E(P)DS). The EPDS was originally developed by Cox for assessing depressive symptoms during the postpartum period (Cox & Sakowsky 1987) and in non-postnatal women resulting in the nomenclature of EDS (Cox et al 1996).<sup>20,21</sup> It was validated postnatally and during pregnancy in the Netherlands.<sup>22,23</sup> The total score ranges from 0 to 30, with higher scores indicating higher levels of depressive symptoms. In the current study, the Cronbach's alphas of the EDS at 12, 22 and 32 weeks of pregnancy were 0.82, 0.84 and 0.83, respectively.

### 2.2.4 | Thyroid function assessment

At 12th week of gestation, TSH, fT4 and TPO-Abs concentrations were determined in lithium heparin plasma using the electrochemiluminescence assays (Cobas\_e 601; Roche Diagnostics). The nonpregnant reference range of TSH is 0.40-4.0 mIU/L, of fT4 10.0-24.0 pmol/L and of TPO-Abs <35 kIU/L. The reference ranges of TSH and fT4 during pregnancy were defined in TPO-Ab-negative women of the current study at 12th gestational week using the 2.5th and 97.5th percentiles to define the lower and upper limit of normal thyroid function. The following subgroups of thyroid (dys)function were defined: (a) euthyroid (TSH and FT4 within the reference limit); (b) overt thyroid dysfunction (TSH and FT4 outside the reference limits); (c) subclinical thyroid dysfunction (TSH outside the reference limit with normal FT4); (d) hypothyroxinemia (FT4 <2.5th, <5th or <10th percentile with normal TSH); and finally (e) hyperthyroxinemia (FT4 >90th, >95th or >97.5th percentile with normal TSH concentration). We used different percentile cut-offs to define hypothyroxinemia because we demonstrated earlier—looking at a possible association between

**TABLE 1** Characteristics of 2082 women with thyroid and cognitive function assessment at 12 wk of gestation

	Mean (SD)	N (%)
Demographic features		
Age (in years)	30.5 (3.5)	
Educational level		
Low		589 (28.3)
Medium		117 (5.6)
High <sup>a</sup>		1376 (66.1)
Marital status		
With partner		1970 (94.6)
Single		112 (5.4)
Obstetric features		
Primiparous		1022 (49.1)
Previous miscarriage		518 (24.9)
Lifestyle habits during pregnancy		
Smoking		129 (6.2)
Any alcohol intake		75 (3.6)
Prepregnancy BMI	23.8 (3.7)	
Thyroid parameters		
TSH mIU/L	1.76 (2.93)	
fT4 pmol/L	14.5 (2.48)	
TPO-Ab > 35 IU/L		179 (8.6)
TPO between 35-50		28 (1.3)
TPO-Ab between 50-100		51 (2.4)
TPO-Ab between 100-250		61 (2.9)
TPO-Ab > 250		41 (2.0)

Abbreviation: BMI, body mass index.

<sup>a</sup>Bachelor or Master's degree

gestational hypothyroxinemia and offspring's neurodevelopmental outcome—that up to the 10th percentile cut-off of FT4 showed significant differences.<sup>24</sup>

Power calculation showed that at 95% confidence level and with 5% margin of error the sample size drawn of 3000 eligible women should be at least 341.

### 2.3 | Statistics

Statistical analysis was performed using the IBM SPSS Statistics for Windows v 24.0 (IBM Corp.). Descriptive statistics were used to analyse the prevalence of abnormal thyroid dysfunction. The total sum scores on the cognitive scale between different subgroups of women as a function thyroid dysfunction were compared using the *t* test (two-tailed). Because the cut-off of TSH and fT4 for diagnosing thyroid disorders during pregnancy are rather arbitrarily, we defined a *healthy control group as women with fT4 and TSH between the 10th and 90th percentile and without elevated TPO-Ab titres*. Cognitive dysfunction between the different groups of women stratified by thyroid dysfunction in relation to the reference control group of euthyroid women was compared by using *t* test, the chi-square and logistic regression statistics.

Single and multiple logistic regression analyses were performed at 12 weeks of gestation to evaluate the possible independent effect of hypothyroxinemia on cognitive function (dependent variable). We adjusted for several possible predefined confounders (depressive symptoms, sleeping problems, parity, education, foetal sex, BMI, smoking/ alcohol habits and age). Finally, we

examined the possible relationship between hypo- and hyperthyroxinemia and cognitive function over the course of pregnancy (12, 22 and 32 weeks of pregnancy) using the generalized linear model (GLM) repeated-measures ANOVA.

## 3 | RESULTS

Of the 2,275 participants, blood assessments were not available in 78 women. Of the 2197 remaining women, there were missing item(s) on the questionnaires at 12 weeks of gestation in 115 (5.2%) women. These women did not differ from the remaining women with regard to parity, education, age, lifestyle habits and thyroid parameters. Due to this low number of missing data, we did not perform imputation of the missing data and these women were excluded; hence data analysis refers to 2082 women (Table 1). The number of women with an elevated TPO-Ab titre was 179 (8.6%), and 151 of these women showed a titre >50 kU/L. The correlation between logTSH and logTPO was  $r: 0.16$  ( $P < .001$ ).

### 3.1 | Independent variable: thyroid function

As summarized in the recent guidelines, the reference ranges (2.5<sup>th</sup>-97.5<sup>th</sup> percentile) of FT4 and TSH were defined in the current study in TPO-Ab-negative women. This was for TSH: 0.23-4.0 mU/L and for fT4: 11.5-18 pmol/L.<sup>11</sup> Based on these cut-offs, various thyroid dysfunction subgroups at 12 weeks are shown in Table 2A which have been discussed in detail elsewhere.<sup>17</sup>

**TABLE 2** Different subgroups of thyroid (dys)function at first trimester in 2082 healthy pregnant women

	N (%)	logTSH (IU/L)		fT4 (pmol/L)	N (%) TPO-Ab + (> 35 kU/L)
		Median	range	Mn (SD)	
<b>A. different subgroups with euthyroid function and with (sub)clinical thyroid dysfunction</b>					
Euthyroid women	1952 (93.8)	0.15	-0.64 to 0.66	14.4 (1.7)	145 (7.4)
Overt hypothyroidism	9 (0.6)	0.82	0.67 to 1.44	10.3 (1.2)	8 (89)
Overt hyperthyroidism	17 (0.8)	- 1.30	-2.0 to - 0.77	22.0 (5.8)	1 (5.9)
Subclinical hypothyroidism	70 (3.3)	0.70	0.60 to 1.11	13.9 (1.4)	24 (34.3)
Subclinical hyperthyroidism	32 (1.5)	- 0.88	-2.0 to -0.68	15.8 (1.6)	3 (9.4)
<b>B. subgroups with hypothyroxinemia (normal TSH)</b>					
		Median logTSH		Mn TPO	
fT4 < 2.5th percentile: <11.5 pmol/L, N = 54 (2.6%)		0.27		41	
fT4 < 5th percentile: <12.0 pmol/L, N = 88 (4.2%)		0.26		35	
fT4 < 10th percentile: < 12.5 pmol/L, N = 209 (10%)		0.25		33	
<b>C. subgroups with hyperthyroxinemia (normal TSH)</b>					
fT4 > 97.5th percentile:>18.0 pmol/L, N = 32 (1.5%)		0.21		31	
fT4 > 95th percentile:>17.3 pmol/L, N = 99 (4.8%)		0.22		29	
fT4 > 90th percentile:>17.0 pmol/L, N = 170 (8.2%)		0.23		19	
Control group: euthyroxinemia: fT4: 10th - 90th percentile with normal TSH and normal TPO-Ab titre, N = 1467					
		Median (range) logTSH mU/L: 0.15 (-0.64-0.60)		Mn (SD) FT4: 14.5 (1.0) Mn (SD) TPO: 10.4 (4.7)	

Note: Reference range for TSH: 0.23 - 4.0 IU/L for FT4: 11.5 - 18 pmol/L, 2.5th and 97.5th percentile in TPO-Ab (< 35 kU/L)-negative women. Euthyroid: normal TSH and FT4. Overt thyroid dysfunction: TSH and FT4 outside reference range. Subclinical thyroid dysfunction: normal FT4 with TSH outside reference range.

Table 2B shows that in the category of women with hypothyroxinemia, up to 12%-13% showed elevated TPO-Ab titres irrespective of the cut-off used while in the subgroups with hyperthyroxinemia (Table 2C) the number of women with TPO-Ab decreased with decreasing upper limit fT4 percentile cut-offs. In parallel, the median TSH concentration and mean TPO-Ab titre remained high in the hypothyroxinemia subgroups (however within reference range) but decreased with increasing FT4 cut-off.

### 3.2 | Dependent variable: cognitive function

At 12th week of gestation, the mean score of cognitive function in the total group was 1.83 (SD: 1.47) and range: 0-8. Cognitive function scores were not correlated with logTSH ( $r = -.003$ ,  $P = .86$ ) or logTPO titres ( $r = -.014$ ,  $P = .53$ ). In Table 3, mean cognitive function scores are shown in relation to different fT4 percentile cut-offs of hypo- and hyperthyroxinemia and compared with the euthyroxinemic group (controls, fT4 between 10<sup>th</sup>-90th percentiles with normal TSH and TPO-Ab titre).

**TABLE 3** Mean cognition dysfunction scores at 12 weeks of gestation according to different subgroups of women with hypo-, eu (10th - 90th percentile)- and hyperthyroxinemia (normal TSH, Table 3A), and in relation to TPO-Ab status (Table 3B)

A. According to different fT4 cut-off's		Mean cognitive symptoms (SD) (higher scores reflecting poorer functioning)
1. 2.5th and 97th percentiles <sup>*</sup>		
Hypothyroxinemia: fT4 < 2.5th percentile: N = 54		2.52 (1.73)
Euthyroxinemia: fT4 between 10th and 90th percentiles: N = 1467		1.81 (1.48)
Hyperthyroxinemia: fT4 > 97.5th percentile, N = 32		1.75 (1.70)
2. 5th and 95th percentiles <sup>**</sup>		
Hypothyroxinemia: fT4 < 5th percentile: N = 88		2.44 (1.68)
Euthyroxinemia: fT4 between 10th and 90th percentiles: N = 1467		1.81 (1.48)
Hyperthyroxinemia: fT4 > 95th percentile, N = 99		1.74 (1.37)
3. 10th and 90th percentiles <sup>***</sup>		
Hypothyroxinemia: fT4 < 10th percentile: N = 209		2.15 (1.56)
Euthyroxinemia: fT4 between 10th and 90th percentiles: N = 1467		1.81 (1.48)
Hyperthyroxinemia: fT4 > 90th percentile, N = 170		1.85 (1.34)
B. Hypothyroxinemia and TPO-Ab status		TSH median mIU/L
1. <2.5th percentile, N = 54		
TPO-Ab negative, N = 47	2.49 (1.75)	1.75
TPO-Ab positive, N = 7	2.74 (2.70)	1.98
2. <5th percentile, N = 88		
TPO-Ab negative, N = 76	2.41 (1.51)	1.74
TPO-Ab positive, N = 12	2.67 (2.60)	2.52
3. <10th percentiles N = 209		
TPO-Ab negative, N = 184	2.11 (1.48)	1.67
TPO-Ab positive, N = 25	2.48 (2.10)	2.60
Euthyroxinemia: fT4 between 10th and 90th percentiles and normal TSH: N = 1467		1.40

\*ANOVA: F (1662): 6.1,  $P = .002$ .

\*\*ANOVA: F (1762): 8.1,  $P < .001$ .

\*\*\*ANOVA: F (1955): 5.2,  $P = .005$ .

Table 3A shows that women with fT4 concentration at >97.5th percentile had the lowest mean scores of cognition dysfunction (ie better perceived cognitive functioning) while hypothyroxinemic women consistently showed the poorest cognitive function. Post hoc analysis (Sheffé) showed that these differences were mainly explained by the high (poor) scores in the hypothyroxinemic groups.

Table 3B shows that within the subgroups of women with hypothyroxinemia, those with elevated TPO-Ab titres showed the poorest cognitive function. In all three subgroups with hypothyroxinemia, the TPO-Ab-positive women showed the highest median of TSH compared to the TPO-Ab-negative women with hypothyroxinemia.

A commonly used cut-off to define a high score of depression self-rating scales is a score of >1 SD above the mean if there is a normal distribution of the scores.<sup>25</sup> Cognitive dysfunction scores showed a normal distribution, and we defined poor cognitive function (high symptom level) as a score on the CSS of >1 SD > mean (>3.30). In the total sample of 2082 women, there were 254 (12.5%) women with poor cognitive function. We subsequently compared prevalence rates of poor cognitive function in 1467 TPO-Ab-negative women

with definite sufficient fT4 hormone (fT4 between 10-90th percentiles with normal TSH = controls) vs different subgroups of percentiles cut-offs of hypo- and hyperthyroxinemia (Figure 1).

Figure 1 shows that women with fT4 concentration in the lowest percentiles had the highest prevalence rate of cognitive dysfunction. Similarly, women with hyperthyroxinemia had the lowest cognitive dysfunction prevalence rate compared with controls.

### 3.3 | Confounders of cognitive function: depression and sleeping problems

#### 3.3.1 | Depression

At 12 weeks of gestation, the mean EDS score in the total group was 4.45 (SD:4.22) and range: 0–25. There were 200 (10.2%) women who had an EDS score above the trimester-specific cut-off (>10). There were no significant differences in depression frequency according to different cut-offs of hypo- and hyperthyroxinemia compared with controls (data not shown).

#### 3.3.2 | Sleeping problems

At 12 weeks of gestation, the mean score on the sleeping subscale questionnaire was 1.8 (SD: 1.7, range 0-8) for the whole group with a normal distribution. We defined women with a score of >1 SD of the mean as women with significant sleeping problems: >3.5, N = 313 (15%). Sleeping problems were not related to hypo- and hyperthyroxinemia (data not shown). However, of the 200 women with depression at 12 weeks, 63 (31%) reported sleeping problems, compared with 137 of the 1754 (7.8%) without depression ( $\chi^2(1): 39, P < .001$ ).

### 3.4 | Relation between hypothyroxinemia and cognitive dysfunction after adjustment for confounding factors

In Table 4A, single logistic regressions are shown with cognitive dysfunction at 12 weeks as dependent variable. The TPO-Ab-negative

control group of women was compared with women with hypothyroxinemia and hyperthyroxinemia using the 2.5th and 97.5th percentile cut-offs. Moreover, the possible relation between poor cognitive function and confounders as depression and sleeping problems as well as and other variables that are known to possibly interfere with cognitive function: age, parity, alcohol intake, smoking, foetal sex and education was investigated.

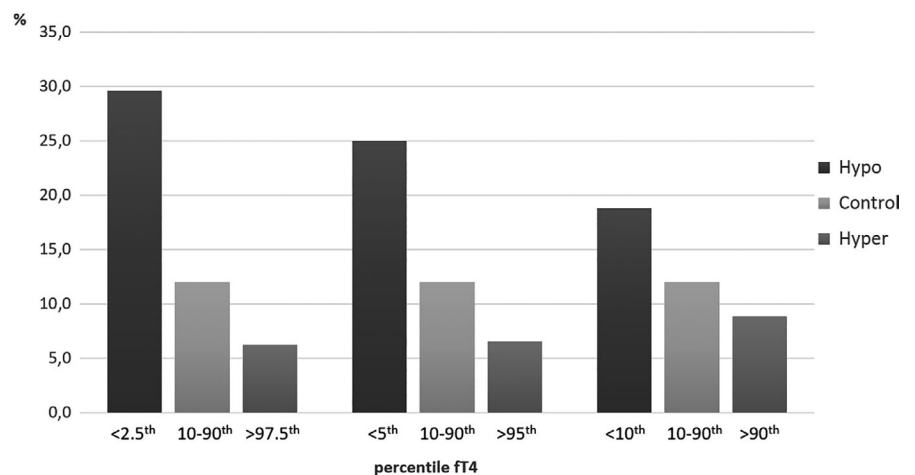
Table 4A shows that hyperthyroxinemia was not (negatively) associated with cognitive dysfunction but hypothyroxinemia, smoking, sleeping problems and depression were all significantly related to cognitive dysfunction. These variables were subsequently entered into a multiple logistic regression model (Table 4B). Hypothyroxinemia was independently related to cognitive dysfunction at 12 weeks of gestation: OR: 2.9 (95% CI: 1.6-5.4). When we repeated the multiple logistic regression analyses using FT4 cut-offs at 5th and 10th percentiles, similar independent associations were found between hypothyroxinemia and cognitive dysfunction: OR: 2.3 (95% CI: 1.4-4.0) and OR: 1.6 (95% CI: 1.1-2.4), respectively.

### 3.5 | Prospective follow-up of cognitive function throughout gestation

Throughout pregnancy, cognitive function scores were available in 1935 women. In these women, the mean scores of cognitive dysfunction increased from 1.83 (SD: 1.47) at 12 weeks to 2.33 (SD: 1.66) at 22 weeks and to 2.46 (SD: 1.70) at 32 weeks of gestation, reflecting significant increase in cognitive decline with advancing pregnancy (paired t test:  $T = 17.7, P < .001$ , large effect size).

In Figure 2, GLM repeated measurements ANOVA showed that women with hypothyroxinemia (fT4 < 2.5th percentile with normal TSH) had significantly worse cognitive dysfunction throughout gestation compared with the TPO-Ab-negative control group (fT4 between 10th and 90th percentiles with normal TSH, N = 1467,  $F = 12.1, P = .001$ ). In the hypothyroxinemic group, cognitive dysfunction scores increased from 12 to 22 weeks followed by a small decrease towards the end of gestation but they remained significantly higher throughout the gestation compared with the reference group.

**FIGURE 1** Percentage of women with cognitive dysfunction in women with hypothyroxinemia (with fT4 cut-offs at the 2.5th, 5th, 10th percentiles), hyperthyroxinemia (with fT4 cut-offs at 90th, 95th and 97.5th percentiles) and TPO-Ab-negative controls (fT4 between 10 and 90th percentiles). Cognitive dysfunction: score of > 1 SD (1.47) > mean (1.83) of the total group = 3.30 (range 0-8)





**TABLE 4** Logistic regression analysis in 1553 women, dependent variable: cognitive dysfunction symptom scores at 12 weeks of gestation above the cut-off of 1 SD > mean

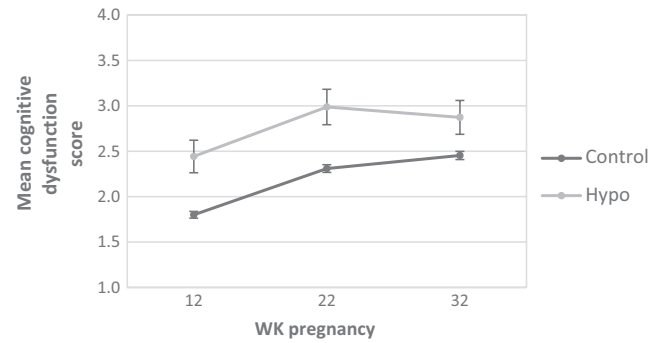
	OR	95% CI	P
A. Single logistic regressions			
logTSH	1.29	0.7-2.3	.37
Hypothyroxinemia (fT4 < 2.5th percentile, nl TSH)	3.0	1.7-5.6	<.001
Hyperthyroxinemia (fT4 > 97.5th percentile, nl TSH)	0.46	0.1-1.9	.29
TPO-Ab + (>35 IU/L)	0.97	0.6-1.7	.94
Male foetal sex	1.22	0.9-1.7	.20
Higher education	0.92	0.8-1.1	.25
Smoking	1.8	1.2-2.9	.011
Alcohol intake	1.1	0.9-1.9	.06
Depression (EDS > 10)	3.5	2.5-4.9	<.001
Sleeping problems	2.8	2.5-3.8	<.001
Multiparity	1.2	0.9-1.6	.087
Higher age	0.97	0.93-1.01	.095
BMI	1.01	0.97-1.05	.40
B. Multiple logistic regression*			
Hypothyroxinemia (<2.5th percentile)	3.0	1.6 - 5.8	.001
Smoking	1.7	1.1-2.7	.048
Depression (EDS > 10) at 12 weeks	3.0	2.0-4.5	<.001
Sleeping problems	2.8	2.0-4.0	<.001
Higher age	0.96	0.96-1.05	.11
Multiparity	1.28	0.92-1.78	.14
Alcohol intake	1.2	0.95-1.8	.07

\*only variables with a >90% significant OR at single level were entered into the multiple regression

## 4 | DISCUSSION

The current study shows that fT4 concentrations below the 2.5th, 5th or 10th percentiles and with TSH concentration within reference ranges are independently related to poor perceived cognitive functioning at first trimester of pregnancy and this association was independent from other psychosocial risk factors of cognitive impairment. Moreover, prospective follow-up showed that cognitive dysfunction remained significantly worse throughout the pregnancy in the hypothyroxinemia group compared to the TPO-Ab-negative control group with sufficient fT4 (between 10 and 90th percentiles). Women with hyperthyroxinemia showed less (but not significantly) cognitive dysfunction compared with the TPO-Ab-negative control group. Finally, within the hypothyroxinemic subgroups of women, those with elevated titres of TPO-Ab showed the poorest cognitive function.

Hypothyroidism is associated with cognitive impairment, suggesting that THs are critical for normal brain functioning and cognition.<sup>8,9</sup> Animal studies in rats showed that the cholinergic



**FIGURE 2** Repeated measurements GLM-ANOVA comparing mean cognitive dysfunction scores at each trimester in women with hypothyroxinemia (fT4 <2.5th percentile, normal TSH) at 12 weeks and TPO-Ab-negative controls (fT4 between 10th and 90th percentiles with normal TSH)

neurotransmitter system involved in learning and memory seems to be a mediator of the effects of THs on cognition activating different proteins and mitogen-activated protein kinases which have a role in neurotransmitter release.<sup>26,27</sup> Also, THs are involved in free radical production which has been associated with different forms of learning and memory.<sup>27</sup> There are also several human studies showing a relation between thyroid function and cognitive function in coronary artery disease patients and especially in patients with Hashimoto.<sup>10,28</sup> But a recent trial that examined thyroid hormone replacement therapy for subclinical hypothyroidism in individuals ≥65 years did not find beneficial effects across patient-reported outcomes, including executive cognitive function.<sup>29</sup> However, it might be questioned whether at this age, cognitive dysfunction is predominantly related to early dementia symptoms, commonly caused by cerebral-vascular problems or (early stages of) Alzheimer disease. Several RCTs showed no benefit of thyroid hormone replacement therapy in pregnant women using a subcategory of women with hypothyroxinemia similar to criteria as in the current study.<sup>30,31</sup> However, primary outcome was obstetric complications and neurodevelopment of the offspring with no data on the effect of such intervention for women cognitive functioning.

Several clinical and sociodemographic characteristics of women included in the current study are similar to that of the Dutch national perinatal obstetric data, including age, parity and previous abortion as discussed elsewhere.<sup>17</sup> Also, the thyroid parameters are similar to that of another large population pregnant sample of the Generation R study, as discussed in detail elsewhere.<sup>17</sup> The current sample was higher educated compared with the national standard and almost all women were Caucasian, compared with the national figure of 80%. Therefore, the results of the current study cannot be generalizable to the whole country. Recently, it was demonstrated that TSH levels already increase at TPO-Ab cut-offs below the normally used cut-off of <35 kU/L.<sup>32</sup> Inversely, higher TSH is associated with higher TPO-Ab titres. In women with hypothyroxinemia, TSH levels are higher (but still below the upper limit of 97.5th percentile) compared with euthyroid or euthyroxinemic controls. The lower the FT4 cut-off, the higher the TSH which was also the case in the current study.

This explains why women with hypothyroxinemia have (persistently) higher numbers of TPO-Ab + women.

The finding of the poorest cognitive function in TPO-Ab-positive hypothyroxinemic women is intriguing. It should be noticed in Table 2 that the prevalence of 13% is almost twice as high compared with euthyroid women (without subclinical and clinical thyroid dysfunction). It is obvious that these women already have their (previously unknown) elevated TPO-Ab titres concentration for several years reflecting an autoimmune process within the thyroid, although they are still biochemically euthyroid. Brain perfusion studies in patients with autoimmune thyroiditis who are biochemically euthyroid suggest that cerebral vasculitis can be an important component of the autoimmune thyroid syndrome which can explain the persisting of cognitive dysfunction in biochemically euthyroid Hashimoto patients.<sup>33</sup>

This study has several strengths and limitations. First strength is the relatively large sample size and the repeated measurements of cognitive function at each trimester. This enabled to look at different cut-offs of hypothyroxinemia in relation to cognitive function not only at a cross-sectional level but also throughout gestation. Another important strength is the adjustment of the possible association between THs and cognition for sleeping problems and depression. It is obvious that sleeping problems will result in cognitive dysfunction during the day. Cognitive dysfunction and sleeping problems are important aspects of depression.<sup>6</sup> The 10-item E(P)DS do not contain sleeping and cognition items.<sup>19</sup> Thus, the independent effect of high EDS scores on cognitive dysfunction during pregnancy may not to be explained by identical items in both questionnaires (EDS and the cognitive symptom scale) but rather suggests that key symptoms of depression such as depressed mood and anhedonia really interferes with concentration and memory capabilities.

An important limitation of the current study is the way of assessing cognitive function by means of self-rating questionnaires rather than objective cognitive tests. However, especially in menopausal studies, there are several reports showing high correlations between self-reported cognitive dysfunction symptoms vs objective cognitive function tests, such as the California Verbal Learning Test, the Digit Span Test or the Wechsler Memory Scale.<sup>34</sup> Other studies also found a high correlation between objective cognitive functions tests and self-report symptoms of forgetfulness and concentrations problems.<sup>35</sup> Iodine status was not assessed in the current study. However, in a recent review, the reliability of a few urine (even 24 hours) iodine assessments (for example each trimester) has been questioned whether it reflects the general iodine intake during pregnancy.<sup>36</sup> In addition, food questionnaires assessed at midterm seem to reflect iodine intake but they are not user-friendly (including 225 items).<sup>36</sup> An alternative could be to assess thyroglobulin as a reflection of long-term iodine intake but TG is susceptible to physiological changes during pregnancy and the presence of Tg-Ab.<sup>37</sup>

How to explain the relatively large number of women with hypothyroxinemia during early pregnancy? The most prominent cause of hypothyroxinemia is low iodine intake. But the area where the current study was performed is iodine sufficient: in a recent

study in the same area (2008), the number of neonatal TSH heel results >5 mIU/L was 3% which is below the 5% indicating iodine deficiency during pregnancy.<sup>17</sup> This suggests that hypothyroxinemia is probably related to the 'massive foetal consumption' of transplacental transported T4 during gestation.<sup>12</sup> But poor iron status is also related to poor thyroid hormone status.<sup>38,39</sup> TPO is a haem enzyme that becomes active only after binding haem.<sup>35</sup> During pregnancy, many women have low iron status mostly to be explained by blood dilution because of total plasma volume extension. Low iron status has been associated with lower TSH, total T4 status and hypothyroxinemia during pregnancy.<sup>35,36</sup> In the current study, the number of women with elevated TPO-Ab in women with hypothyroxinemia at different cut-off's (<2.5th, <5th and <10th percentile) remained almost twice as high compared to biochemically euthyroid women (Table 2) suggesting that thyroid autoimmunity might be an important cause of hypothyroxinemia, possibly mediated by poor iron status? Unfortunately, iron status and the presence of anaemia were not assessed in the current study.

What might be the clinical relevance of the current findings? It is beyond the scope to participate in the discussion whether all pregnant women should be screened on thyroid dysfunction during early pregnancy. The international guidelines promote case finding in women possibly at risk for thyroid dysfunction including those with symptoms 'typically related to thyroid dysfunction'.<sup>11</sup> The current study shows evidence that women with high levels of cognitive dysfunction symptoms are at risk for poor thyroid hormone status. Assessing cognitive function by simple questionnaires during early gestation might help to detect women at risk for thyroid dysfunction. It is remarkable that until now all randomized clinical trials in which women with suboptimal thyroid function (subclinical hypothyroidism or hypothyroxinemia) were supplemented with T4 only used obstetric and neurodevelopmental offspring's outcome as end-point. General well-being of the pregnant woman was not taken into account. It would be interesting to include in future RCT general well-being during gestation also as end-point, including cognitive function. Although cognitive dysfunction in the perinatal period is generally believed to be self-limiting, there might be subgroups of women (those with hypothyroxinemia and elevated TPO-Ab titres?) who will report persistently high cognitive dysfunction symptom scores, like Hashimoto-treated patients. Longitudinal follow-up studies—preferentially starting before conception and lasting up to 12 months postpartum—could possibly discriminate between self-limiting and persistent cognitive dysfunction. Is it possible that maternal cognitive dysfunction might affect offspring's cognitive development? So far, the only link would be by maternal depression. Cognitive dysfunction is highly related to depression (also in the current study), and the negative impact of maternal depression on infant outcome (including cognitive development) is well documented.<sup>40</sup>

In conclusion, apart from depression and sleeping problems, women with low levels of thyroid hormone during early gestation are at risk for poor cognitive function throughout gestation, possibly related to the presence of elevated TPO-Ab titres.



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## CONFLICT OF INTEREST

Nothing to declare.

## DATA AVAILABILITY STATEMENT

Data are available on request with the corresponding author.

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## REFERENCES

- Janes C, CaseyP HuntsdaleC, Angus G. Memory in pregnancy. I: subjective experiences and objective assessment of implicit, explicit and working memory in primigravid and primiparous women. *J Psychosom Obstet Gynaecol*. 1999;20(2):80-87.
- CaseyP HuntsdaleC, Angus G, Janes C. Memory in pregnancy. II: implicit, incidental, explicit, semantic, short-term, working and prospective memory in primigravid, multigravid and postpartum women. *J Psychosom Obstet Gynaecol*. 1999;20(3):158-164.
- Glynn LM. Giving birth to a new brain: hormone exposures of pregnancy influence human memory. *Psychoneuroendocrinology*. 2010;35(8):1148-1155.
- Brett M, Baxendale S. Motherhood and memory: a review. *Psychoneuroendocrinology*. 2001;26(4):339-362.
- LagadecN SM, Kapassi A, Magnier AM, et al. Factors influencing the quality of life of pregnant women: a systematic review. *BMC Pregnancy Childbirth*. 2018;18(1):455.
- Diagnostic and Statistical Manual of Mental Disorders V (DSM-V) American Psychiatric Association; 2013.
- Bennett HA, Taddio A, Koren G, Einarson TR. Prevalence of depression during pregnancy: systematic review. *Obstet Gynecol*. 2004;103(4):698-709.
- Burmeister LA, Ganguli M, Dodge HH, Toczek T, DeKosky ST, Nebes RD. Hypothyroidism and cognition: preliminary evidence for a specific defect in memory. *Thyroid*. 2001;11:1177-1185.
- Smith JW, Evans AT, Costall B, Smythe JW. Thyroid hormones, brain function and cognition: A brief review. *Neurosci Biobehav Rev*. 2002;26:45-60.
- Djurovic M, Pereira AM, Smit J, et al. Cognitive functioning and quality of life in patients with Hashimotothyroiditis on long-term levothyroxine replacement. *Endocrine*. 2018;62(1):136-143.
- Alexander EK, Pearce EN, Brent GA, et al. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid*. 2017;27(3):315-389.
- Korevaar T, Medici M, Visser TJ, Peeters RP. Thyroid disease in pregnancy: new insights in diagnosis and clinical management. *Nat Rev Endocrinol*. 2017;13(10):610-622.
- Pop VJ, Brouwers EP, Vader HL. Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. *Clin Endocrinol (Oxf)*. 2003;59(3):282-288.
- Pop VJ, Vulsma T. Maternal hypothyroxinaemia during (early) gestation. *Lancet*. 2005;365(9471):1604-1606.
- Korevaar TI, Derakhshan A, Taylor P, et al. Association of thyroid function abnormalities and thyroid immunity with preterm birth. A systematic review and meta-analysis of individual participating data. *JAMA*. 2019;322(7):632-641.
- Williams GR. Neurodevelopmental and neurophysiological actions of thyroid hormone. *J Neuroendocrinol*. 2008;20(6):784-794.
- Pop VJ, Broeren MA, Wiersinga WM, Stagnaro-Green A. Thyroid disease symptoms during early pregnancy do not identify women with thyroid hypofunction that should be treated. *Clin Endocrinol*. 2017;87(6):838-843.
- Truijens SE, Meems M, Kuppens SM, et al. The HAPPY study (Holistic Approach to Pregnancy and the first Postpartum Year): design of a large prospective cohort study. *BMC Pregnancy Childbirth*. 2014;14:1-12.
- von Elm E, Altman DG, Egger M, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ*. 2007;335(7624):806-808.
- Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression development of the 10-item Edinburgh Postnatal Depression Scale. *Br J Psychiatry*. 1987;150:782-786.
- Cox JL, Chapman G, Murray D, Jones P. Validation of the Edinburgh Postnatal Depression Scale (EPDS) in non-postnatal women. *J Affect Disord*. 1996;39:185-189.
- Pop VJ, Komproe IH, van Son MJ. Characteristics of the Edinburgh post natal depression scale in The Netherlands. *J Affect Disord*. 1992;26:105-110.
- Bergink V, Kooistra L, Lambregtse-van den Berg MP, et al. Validation of the Edinburgh Depression Scale during pregnancy. *J Psychosom Res*. 2011;70:385-389.
- Pop VJ, Kuijpers JL, van Baar AL, et al. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. *Clin Endocrinol (Oxf)*. 1999;50(2):149-155.
- Kline P. *The handbook of psychological testing*, 2nd edn. London: Routledge; 2000.
- Vara H, Martínez B, Santos A, Colino A. Thyroid hormone regulates neurotransmitter release in neonatal rat hippocampus. *Neuroscience*. 2002;110:19-28.
- Kopf SR, Benton RS, Kalfin R, Giovannini MG, Pepeu G. NO synthesis inhibition decreases cortical ACh release and impairs retention of a conditioned response. *Brain Res*. 2001;894:141-144.
- Burkauskas J, Bunevicius A, Brozaitiene J, et al. Cognitive functioning in coronary artery disease patients: associations with thyroid hormones, N-terminal Pro-B-type natriuretic peptide and high-sensitivity C-reactive protein. *Arch Clin Neuropsychol*. 2017;32(2):245-251.
- Stott DJ, Rodondi N, Kearney PM, et al. Thyroid hormone therapy for older adults with subclinical hypothyroidism. *N Engl J Med*. 2017;376(26):2534-2544.
- Lazarus JH, Bestwick JP, Shannon S, et al. Antenatal thyroid screening and child cognitive function. *N Engl J Med*. 2012;366(6):493-501.
- Casey BM, Thom EA, Peaceman AM, et al. Treatment of subclinical hypothyroidism and hypothyroxinemia in pregnancy. *N Engl J Med*. 2017;376(9):815-825.
- Korevaar T, Pop VJ, Chaker L, et al. Dose dependency and a functional cutoff for TPO-antibody positivity during pregnancy. *J Clin Endocrinol Metab*. 2018;103(2):778-789.
- Leyhe T, Müssig K. Cognitive and affective dysfunctions in autoimmune thyroiditis. *Brain Behav Immun*. 2014;41:261-266.
- Drogos LL, Rubin LH, Geller SE, Banuvar S, Shulman LP, Maki PM. Objective cognitive performance is related to subjective memory complaints in midlife women with moderate to severe vasomotor symptoms. *Menopause*. 2013;20(12):1236-1242.

35. Weber MT, Mapstone M, Staskiewicz J, Maki PM. Reconciling subjective memory complaints with objective memory performance in the menopausal transition. *Menopause*. 2012;19(7):735-741.
36. Bath SC. The effect of iodine deficiency during pregnancy on child development. *Proc Nutr Soc*. 2019;78(2):150-160.
37. Zhao W, Li X, Xia X, Gao Z, Han C. Iodine nutrition during pregnancy: past, present, and future. *Biol Trace Elem Res*. 2019;188(1):196-207.
38. Zimmermann MB, Burgi H, Hurrell RF. Iron deficiency predicts poor maternal thyroid status during pregnancy. *J Clin Endocrinol Metab*. 2007;92(9):3436-3440.
39. Teng X, Shan Z, Li C, et al. Iron deficiency may predict greater risk for hypothyroxinemia: a retrospective cohort study of pregnant women in China. *Thyroid*. 2018;28(8):968-975.
40. Liu Y, Kaaya S, Chai J, et al. Maternal depressive symptoms and early childhood cognitive development: a meta-analysis. *Psychol Med*. 2017;47:680-689.

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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