

## ORIGINAL ARTICLE

# Thyroid hormone replacement therapy in pregnancy and motor function, communication skills, and behavior of preschool children: The Norwegian Mother, Father, and Child Cohort Study

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## Abstract

**Purpose:** Limited research has focused on the association between prenatal thyroid hormone replacement therapy (THRT) and motor function, communication skills, and behavior in preschool children. Here, we estimated the association between THRT during pregnancy and the first trimester and these developmental outcomes.

**Methods:** This study was based on the Norwegian Mother, Father, and Child Cohort Study (MoBa) and other national registries. We included mother–child pairs exposed to THRT during pregnancy ( $n = 663$ ), after delivery ( $n = 728$ ), or unexposed ( $n = 28\,040$ ). Exposure to THRT was defined according to filled prescriptions. Child outcomes, presented as  $T$ -score differences, were parent-reported using the Ages and Stages Questionnaire, Strengths and Difficulties Questionnaire, and Child Behavior Checklist.

**Results:** Of 29 431 mother–child pairs, 2.3% were prenatally exposed to THRT. We found no difference between prenatally exposed and unexposed children in regards to gross motor function ( $\beta$ : 0.17, 95% CI  $-1.19, 1.54$ ), fine motor function ( $\beta$ :  $-0.17$ , 95% CI  $-1.14, 0.80$ ), communication ( $\beta$ :  $-0.31$ , 95% CI  $-1.58, 0.96$ ), externalizing ( $\beta$ :  $-0.03$ , 95% CI  $-1.07, 1.01$ ), internalizing ( $\beta$ : 0.89, 95% CI  $-0.20, 1.97$ ), or social behaviors ( $\beta$ :  $-0.04$ , 95% CI  $-0.92, 0.84$ ). Somatic complaints were higher in THRT-exposed children ( $\beta$ : 0.98, 95% CI 0.08, 1.87), and children whose mothers were exposed after delivery had more sleep problems than unexposed children ( $\beta$ : 0.99, 95% CI 0.24, 1.74).

**Conclusions:** Children prenatally exposed to THRT have developmental outcomes as positive as unexposed children on motor function, communication, and behavior. The association with somatic complaints and sleep were not clinically relevant.

## KEYWORDS

behavior, communication, hypothyroidism, MoBa, motor function, pregnancy

## 1 | INTRODUCTION

The prevalence of overt hypothyroidism is approximately 0.5%, and 2–4% for subclinical hypothyroidism (SCH) in women of reproductive age.<sup>1</sup> Pregnancy changes the production and demand of hormones and nutrients.<sup>2</sup> As a result, the prevalence of SCH during pregnancy is up to 7%.<sup>3</sup>

Thyroid hormones play an important role during child development. Children start to produce considerable amounts of thyroid hormone in week 18–20 of gestation.<sup>4</sup> Consequently, the child is dependent on the thyroid hormone supply from the mother in the first weeks of pregnancy.<sup>4</sup> Therefore, low maternal thyroid hormone levels could impact child growth<sup>5</sup> and brain development.<sup>6</sup>

As argued by Hjorth et al.,<sup>7</sup> establishing neurodevelopmental safety includes assessing a wide variety of outcomes important for the child's daily functioning, including motor skills, communication, cognition, and behavior. Most prior research has focused on the link between hypothyroidism and cognitive outcomes. However, limited attention has been given to behavioral development, and no study has focused on communication skills. Ghassabian et al.<sup>8</sup> found that elevated maternal thyroid peroxidase antibody (TPOAb) levels are associated with externalizing problems, but other studies could not replicate this association.<sup>9–11</sup>

Studies focusing on motor function have produced conflicting results. On the one hand, several studies have suggested that child motor function may be impaired if thyroid hormone levels are inadequate during pregnancy.<sup>12,13</sup> On the other hand, some studies did not find this association,<sup>14–17</sup> and two studies found no difference in fine motor function between children of treated, untreated, and euthyroid mothers.<sup>11,14</sup>

Due to the importance of thyroid hormones and adverse associations between hypothyroidism and child development, treatment with thyroid hormone replacement therapy (THRT) during pregnancy is recommended. Approximately 2.2% of women use THRT during pregnancy.<sup>18</sup> However, limited studies have investigated the effect of THRT during pregnancy on developmental outcomes. This study aims to estimate the association between THRT during pregnancy, specifically in the first trimester, and motor function, communication skills, and behavior at 3 years of age in a large population-based cohort.

## 2 | METHODS

### 2.1 | Data

In the present study, multiple data sources were combined. Data from the Norwegian Mother, Father, and Child Cohort Study (MoBa), the Norwegian Prescription Database (NorPD), the Norwegian Medical Birth Registry (MBRN), Norwegian Environmental Biobank, and the Norwegian Patient Registry (NPR) were linked using the personal identification number allocated to every citizen in Norway.

MoBa is a population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health. Participants were recruited from all over Norway from 1999 to 2008. Women consented to

### Key Points

- Thyroid hormones play an important role during child development.
- Establishing the neurodevelopmental safety of THRT treatment includes assessing a wide variety of outcomes important to the child's daily functioning, including motor function, communication skills, and behavior.
- Using thyroid hormone levels in the analysis to adjust for the severity of the hypothyroidism reduces the risk of confounding by severity.
- Children exposed to THRT in pregnancy, and specifically the first trimester, have developmental outcomes as positive as children not exposed to THRT during pregnancy in terms of motor function, communication, and behavior.
- These findings underline the importance of adequate THRT treatment in pregnancy

participation in 41% of pregnancies. The cohort now includes 114 500 children, 95 200 mothers, and 75 200 fathers.<sup>19,20</sup> The current study is based on version 10 of the quality-assured data files released for research purposes. Women filled out the first questionnaire (Q1) after inclusion around week 17 of the pregnancy. During follow-up, several other questionnaires were sent in week 22 (Q2) and week 30 (Q3) of gestation, and when the child was 6 months, 18 months, 36 months (Q6), 5 years, 7 years, and 8 years old.<sup>21</sup>

The MBRN is a national health registry containing information about all births in Norway. This registry includes confirmed medical records related to maternal health before and during pregnancy.<sup>22</sup> Records retrieved from the MBRN included hyperthyroid diagnosis (International Classification of Diseases, 10th Revision [ICD-10] code 'e05') and other thyroid diagnosis (ICD-10 code 'e0-other').

The Norwegian Environmental Biobank is a sub-cohort within the MoBa cohort (MoBa eTox) that comprises 2999 women from whom biological data are collected, including thyroid stimulating hormone (TSH), free triiodothyronine (FT3), FT4, and TPOAb at 17–18 weeks gestation.<sup>23,24</sup> Blood samples were obtained from both parents during pregnancy and from mothers and children (umbilical cord) at birth.

The NorPD, established in 2004, contains data on all prescription drugs dispensed to individuals in ambulatory care. The NorPD uses the Anatomical Therapeutic Chemical (ATC) classification system.<sup>25</sup> The NPR has records of individual patient diagnoses according to the ICD-10. Since 2008, all government-owned and government-financed hospitals and outpatient clinics have mandatorily reported this information to receive financial reimbursement.<sup>26</sup> Records retrieved from the NPR included hyperthyroid diagnosis (International Classification of Diseases, 10th Revision [ICD-10] code 'e05') and other thyroid diagnosis (ICD-10 code 'e0-other'). An overview is shown in Supplementary Figure 1.

## 2.2 | Ethics

The establishment of and data collection in MoBa were originally based on a license from the Norwegian Data Protection Agency (01/4325) and approval from The Regional Committee for Medical Research Ethics (S-97045, S-95113) and are now based on regulations related to the Norwegian Health Registry Act. All participants provided written informed consent prior to participation. The current study was approved by The Regional Committee for Medical Research Ethics (2015/1241, REK Sør-Øst B). All data were handled and stored at the Service for Sensitive Data (TSD), which is University of Oslo's platform for storing, computing, and analyzing research-sensitive data in compliance with General Data Protection Regulation (GDPR) regulations regarding individuals' privacy.

## 2.3 | Study population

We included singleton, live-born children entering MoBa after the establishment of the NorPD in 2004 (Figure 1). Women who did not complete questionnaires Q1, Q3, and Q6, women who had other thyroid disorders, and those who had conflicting information on diagnosis or medication use were excluded from the study.

## 2.4 | Exposure

THRT exposure was defined based on prescription records from the NorPD (ATC code H03AA). We previously showed that THRT

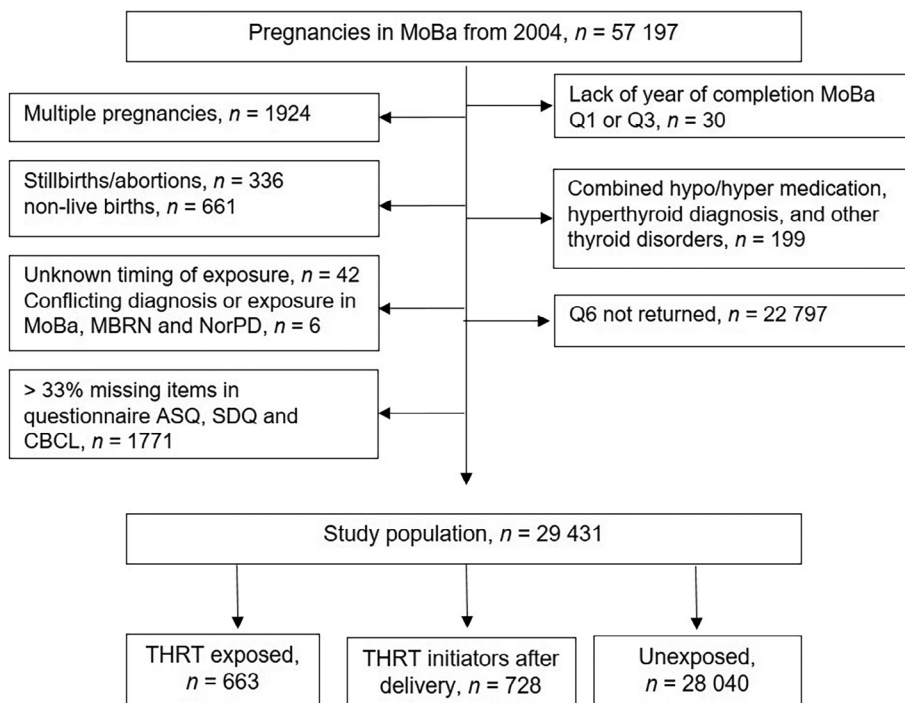
exposure based on filled prescriptions is more complete than self-reported medication use in MoBa.<sup>27</sup>

Exposure was categorized into three groups: THRT-exposed, THRT initiators after delivery, and unexposed. Women who filled at least one THRT prescription from the date of last menstrual period (LMP) until delivery were classified as THRT-exposed. Women who did not fill any THRT prescription during pregnancy, but retrieved a THRT prescription within 1 year after delivery, were categorized as THRT initiators after delivery. Unexposed women were defined as women who were not exposed to THRT during, before, or within 1 year after pregnancy.

In the secondary analyses, the time window for exposure was restricted to the first trimester. Women who filled a prescription in the first trimester were classified as exposed irrespective of exposure status later in pregnancy. Women who did not fill a prescription on THRT in the first trimester were classified as non-exposed in this time period, irrespective of exposure status later in pregnancy.

## 2.5 | Child developmental outcome

Child motor function, communication skills, and behavior were parent-reported at 3 years of age using the Child Behavior Checklist (CBCL), the Ages and Stages Questionnaire (ASQ), and the Strengths and Difficulties Questionnaire (SDQ). These questionnaires are internationally widely used to recognize and validate screening measures of child development.<sup>28-30</sup> In each questionnaire, a mean score per domain was calculated when no more than one-third of the items in that particular questionnaire were missing. Each score was standardized using the population of MoBa Q6, giving a mean *T*-score of



**FIGURE 1** Flow chart of the study population. Abbreviations: MoBa=Norwegian Mother, Father and Child Cohort Study, MoBa Q1=MoBa questionnaire 1, MoBa 3=MoBa questionnaire 3, MBRN=Medical Birth Registry of Norway, NorPD=Norwegian Prescription Database, Q6=MoBa questionnaire 6, ASQ=Ages and Stages Questionnaire, SDQ=Strengths and Difficulties Questionnaire, CBCL=Child Behavior Checklist, THRT=thyroid hormone replacement therapy

**TABLE 1** Study population characteristics

	THRT exposed during pregnancy (n = 663)	THRT initiators after delivery (n = 728)	Unexposed (n = 28 040)	Total (n = 29 431)
<i>Maternal hypothyroid diagnosis<sup>a</sup></i>				
No	207 (31.2)	719 (98.8)	28 024 (99.9)	28 950 (98.4)
Yes	456 (68.8)	9 (1.2)	16 (0.1)	481 (1.6)
<i>Maternal age, years</i>				
≤24	29 (4.4)	58 (8.0)	2313 (8.2)	2400 (8.2)
25–29	176 (26.5)	225 (30.9)	9107 (32.5)	9509 (32.3)
30–34	268 (40.4)	292 (40.1)	11 339 (40.4)	11 899 (40.4)
≥35	190 (28.7)	153 (21.0)	5281 (18.8)	5624 (19.1)
<i>Paternal age, years</i>				
≤24	13 (2.0)	29 (4.0)	935 (3.3)	977 (3.3)
25–29	115 (17.3)	148 (20.3)	6137 (21.9)	6400 (21.7)
30–34	231 (34.8)	279 (38.3)	11 112 (39.6)	11 622 (39.5)
≥35	300 (45.2)	269 (37.0)	9781 (34.9)	10 350 (35.2)
Missing	4 (0.6)	3 (0.4)	75 (0.3)	82 (0.3)
<i>Married/cohabiting</i>				
No	28 (4.2)	36 (4.9)	1019 (3.6)	1083 (3.7)
Yes	635 (95.8)	692 (95.1)	27 021 (96.4)	28 348 (96.3)
<i>Parity</i>				
Multiparity	306 (46.2)	358 (49.2)	14 192 (50.6)	14 856 (50.5)
Primiparity	357 (53.8)	370 (50.8)	13 848 (49.4)	14 575 (49.5)
<i>Maternal education, years</i>				
<9	7 (1.1)	6 (0.8)	256 (0.9)	269 (0.9)
9–12	144 (21.7)	195 (26.8)	5907 (21.1)	6246 (21.2)
13–16	297 (44.8)	282 (38.7)	12 289 (43.8)	12 868 (43.7)
>16	205 (30.9)	231 (31.7)	9115 (32.5)	9551 (32.5)
Missing	10 (1.5)	14 (1.9)	473 (1.7)	497 (1.7)
<i>BMI, kg/m<sup>2</sup></i>				
≤18	14 (2.1)	16 (2.2)	826 (2.9)	856 (2.9)
19–24	348 (52.5)	423 (58.1)	17 681 (63.1)	18 452 (62.7)
25–29	178 (26.8)	181 (24.9)	6559 (23.4)	6918 (23.5)
≥30	109 (16.4)	92 (12.6)	2479 (8.8)	2680 (9.1)
Missing	14 (2.1)	16 (2.2)	495 (1.8)	525 (1.8)
<i>Total score depressive and anxiety symptoms</i>				
Mean (SD)	6.36 (2.09)	6.45 (2.10)	6.14 (1.85)	6.16 (1.86)
Median (min–max)	6.0 (5.0–20.0)	6.0 (5.0–20.0)	5.0 (5.0–27.0)	5.0 (5.0–27.0)
Missing (%)	14 (2.1)	18 (2.5)	721 (2.6)	753 (2.6)
<i>Maternal income, (USD/year)<sup>b</sup></i>				
Low (<16 000)	135 (20.4)	170 (23.4)	5765 (20.6)	6070 (20.6)
Average (16 000–54 400)	385 (58.1)	444 (61.0)	17 205 (61.4)	18 034 (61.3)
High (>54 400)	122 (18.4)	93 (12.8)	4375 (15.6)	4590 (15.6)
Missing	21 (3.2)	21 (2.9)	695 (2.5)	737 (2.5)
<i>Gender child</i>				
Boy	348 (52.5)	373 (51.2)	14 294 (51.0)	15 015 (51.0)
Girl	315 (47.5)	355 (48.8)	13 746 (49.0)	14 416 (49.0)
<i>Supplement use<sup>c</sup></i>				
No	152 (22.9)	188 (25.8)	8043 (28.7)	8383 (28.5)
Yes	511 (77.1)	540 (74.2)	19 997 (71.3)	21 048 (71.5)

(Continues)

**TABLE 1** (Continued)

	THRT exposed during pregnancy (n = 663)	THRT initiators after delivery (n = 728)	Unexposed (n = 28 040)	Total (n = 29 431)
<i>Smoking</i>				
No	556 (83.9)	579 (79.5)	23 316 (83.2)	24 451 (83.1)
Yes	22 (3.3)	50 (6.9)	1385 (4.9)	1457 (5.0)
Stopped in pregnancy	37 (5.6)	51 (7.0)	1774 (6.3)	1862 (6.3)
Missing	48 (7.2)	48 (6.6)	1565 (6.5)	1661 (5.6)
<i>Alcohol use<sup>d</sup></i>				
No	541 (77.5)	515 (70.7)	20 083 (71.6)	21 112 (71.7)
Yes	125 (18.9)	159 (21.8)	6426 (22.9)	6708 (22.8)
Missing	24 (3.6)	54 (7.4)	1533 (5.5)	1611 (5.5)
<i>Mental comorbidities<sup>e</sup></i>				
No	565 (85.2)	599 (82.3)	24 943 (89.0)	26 107 (88.7)
Medicated	31 (4.7)	27 (3.7)	597 (2.1)	655 (2.2)
Non-medicated	67 (10.1)	102 (14.0)	2500 (8.9)	2669 (9.1)
<i>Somatic comorbidities<sup>f</sup></i>				
No	491 (74.1)	628 (86.3)	25 060 (89.4)	26 179 (89.0)
Medicated	96 (14.5)	39 (5.4)	1067 (3.8)	1202 (4.1)
Non-medicated	76 (11.5)	61 (8.4)	1913 (6.8)	2050 (7.0)
<i>Fiber intake</i>				
<29.8 g/day	337 (50.8)	397 (54.5)	14 561 (51.9)	15 295 (52.0)
≥29.8 g/day	326 (49.2)	331 (45.5)	13 479 (45.5)	14 136 (48.0)

Note: Data are presented as n (%) unless otherwise noted. Education, BMI, depressive and anxiety symptoms, income of the mother, supplement use, smoking and drinking habits were obtained from Q1. Fiber consumption was obtained from Q2.

Abbreviations: max, maximum; min, minimum; SD, standard deviation; THRT, thyroid hormone replacement.

<sup>a</sup>Thyroid diagnoses are available only for a sub-sample of the study population because reporting thyroid diagnoses is not mandatory in the MBRN and information in the NPR is incomplete if women were diagnosed before 2008.

<sup>b</sup>(USD/year): 1.00 NOK ≈ 0.13 USD.

<sup>c</sup>Supplements include folate, vitamins (B1, B2, B6, B12, C, D, niacin, pantothenic acid, biotin), omega-3 fatty acids, and minerals (calcium, copper, chromium, iodine, iron, magnesium, selenium, and zinc).

<sup>d</sup>Alcohol consumption, No stands for 'less than once a month' and Yes for 'once or more a month'.

<sup>e</sup>Mental comorbidities include anxiety and depression.

<sup>f</sup>Somatic comorbidities include epilepsy, arthritis, anemia, diabetes mellitus (including gestational diabetes mellitus), and cardiovascular disorders.

50 and a standard deviation of 10. Higher *T*-scores indicated greater developmental difficulties (e.g., more problems externalizing).

The CBCL measures the behavior of children in three domains: internalizing, externalizing, and sleep behavior (Supplementary Table 1). Motor function and communication skills were measured by four and six items, respectively, on the ASQ (Supplementary Table 2).<sup>30</sup> The SDQ is designed to address emotional and behavioral problems in children.<sup>28</sup> In MoBa, the SDQ measures children's social behavior (Supplementary Table 3). In this study, the Cronbach's alpha for the ASQ, SDQ, and CBCL was 0.71, 0.77, and 0.76, respectively.

## 2.6 | Missing data

A total of 86.6% of the study sample had complete data for all covariates used in the adjusted analysis, except thyroid hormone levels. Missing values for the covariates and thyroid hormone levels

were imputed using multiple imputation by chained equations (10 imputations).<sup>31</sup> The imputation procedure included covariates, and additional variables with predictive value (Supplementary Information). The implementation of multiple imputation and its analysis were adapted from Frank et al.<sup>32-34</sup>

## 2.7 | Statistical analysis

The characteristics of the parents and children were described using descriptive statistics. To estimate associations between THRT in pregnancy and child outcomes, we fit crude and adjusted generalized linear regression models, with robust standard errors to take the skewed data into account. Possible confounders were explored using directed acyclic graphs and subject knowledge.<sup>35</sup> A sufficient set of confounders included maternal age, maternal body mass index (BMI), education, income, comorbidity, fiber consumption, severity of hypothyroidism,

**TABLE 2** Crude and adjusted mean T-score differences in child developmental outcomes in the three-group comparison ( $n = 27\ 866$ )

Outcome	Mean T-score	Crude Estimate (95% CI)	Adjusted Estimate (95% CI)	Crude Estimate (95% CI)	Adjusted Estimate (95% CI)
<b>Communication (ASQ)</b>					
THRT exposed	49.96	-0.01 (-0.78, 0.75)	-0.31 (-1.58, 0.96)	0.01 (-1.03, 1.06)	-0.05 (-1.22, 1.31)
THRT initiators after delivery	49.94	-0.03 (-0.76, 0.70)	0.26 (-1.12, 0.60)	Ref	Ref
Unexposed	49.97	Ref	Ref	0.03 (-0.70, 0.76)	0.26 (-0.60, 1.12)
<b>Motor function (ASQ)</b>					
<i>Fine motor function</i>					
THRT exposed	50.12	0.14 (-0.63, 0.91)	-0.17 (-1.14, 0.80)	-0.18 (-1.23, 0.87)	-0.57 (-1.73, 0.59)
THRT initiators after delivery	50.30	0.32 (-0.42, 1.05)	0.40 (-0.38, 1.19)	Ref	Ref
Unexposed	49.99	Ref	Ref	-0.32 (-1.05, 0.42)	-0.40 (-1.19, 0.38)
<i>Gross motor function</i>					
THRT exposed	50.27	0.28 (-0.49, 1.05)	0.17 (-1.19, 1.54)	0.56 (-0.49, 1.61)	0.22 (-1.22, 1.67)
THRT initiators after delivery	49.72	-0.28 (-1.01, 0.46)	-0.05 (-0.83, 0.73)	Ref	Ref
Unexposed	49.99	Ref	Ref	0.28 (-0.46, 1.01)	0.05 (-0.73, 0.83)
<b>Social behavior (SDQ)</b>					
THRT exposed	50.07	0.02 (-0.75, 0.79)	-0.04 (-0.92, 0.84)	0.12 (-0.94, 1.17)	-0.02 (-1.13, 1.10)
THRT initiators after delivery	49.96	-0.10 (-0.83, 0.64)	0.02 (-0.80, 0.75)	Ref	Ref
Unexposed	50.06	Ref	Ref	0.10 (-0.64, 0.83)	0.02 (-0.75, 0.80)
<b>Behavior (CBCL)</b>					
<i>Internalizing<sup>a</sup></i>					
THRT exposed	50.66	0.68 (-0.09, 1.46)	0.89 (-0.20, 1.97)	0.11 (-0.94, 1.17)	0.54 (-0.65, 1.73)
THRT initiators after delivery	50.55	0.57 (-0.17, 1.31)	0.35 (-0.46, 1.15)	Ref	Ref
Unexposed	49.98	Ref	Ref	-0.57 (-1.31, 0.17)	-0.35 (-1.15, 0.46)
<i>Anxiety/depression</i>					
THRT exposed	50.53	0.55 (-0.22, 1.32)	0.67 (-0.40, 1.74)	0.22 (-0.83, 1.27)	0.49 (-0.70, 1.68)
THRT initiators after delivery	50.31	0.33 (-0.41, 1.06)	0.18 (-0.61, 0.97)	Ref	Ref
Unexposed	49.98	Ref	Ref	-0.33 (-1.06, 0.41)	-0.18 (-0.97, 0.61)
<i>Somatic complaints</i>					
THRT exposed	50.97	1.01 (0.23, 1.78)	0.98 (0.08, 1.87)	0.29 (-0.77, 1.34)	0.55 (-0.57, 1.67)
THRT initiators after delivery	50.68	0.72 (-0.02, 1.46)	0.42 (-0.34, 1.19)	Ref	Ref
Unexposed	49.96	Ref	Ref	-0.72 (-1.46, 0.02)	-0.42 (-1.19, 0.34)
<i>Emotional reactivity</i>					
THRT exposed	49.68	-0.32 (-1.09, 0.45)	0.16 (-1.03, 1.36)	-0.44 (-1.50, 0.61)	0.08 (-1.13, 1.28)
THRT initiators after delivery	50.12	0.12 (-0.62, 0.85)	0.08 (-0.80, 0.97)	Ref	Ref
Unexposed	50.00	Ref	Ref	-0.12 (-0.85, 0.62)	-0.08 (-0.97, 0.80)
<i>Externalizing<sup>b</sup></i>					
THRT exposed	49.92	-0.05 (-0.82, 0.73)	-0.03 (-1.07, 1.01)	-0.59 (-1.65, 0.47)	-0.38 (-1.58, 0.83)
THRT initiators after delivery	50.51	0.54 (-0.20, 1.29)	0.35 (-0.50, 1.20)	Ref	Ref
Unexposed	49.96	Ref	Ref	-0.54 (-1.29, 0.20)	-0.35 (-1.20, 0.50)
<i>Attention</i>					
THRT exposed	49.67	-0.32 (-1.09, 0.45)	-0.07 (-0.98, 0.83)	-1.28 (-2.34, -0.23)	-0.72 (-1.87, 0.44)
THRT initiators after delivery	50.95	0.97 (0.23, 1.70)	0.64 (-0.13, 1.42)	Ref	Ref
Unexposed	49.99	Ref	Ref	-0.97 (-1.70, -0.23)	-0.64 (-1.42, 0.13)
<i>Aggression</i>					
THRT exposed	50.04	0.09 (-0.69, 0.86)	-0.002 (-1.05, 1.05)	-0.10 (-1.16, 0.96)	-0.10 (-1.29, 1.09)
THRT initiators after delivery	50.14	0.18 (-0.55, 0.92)	0.10 (-0.77, 0.96)	Ref	Ref
Unexposed	49.95	Ref	Ref	-0.18 (-0.92, 0.55)	-0.10 (-0.96, 0.77)

(Continues)

**TABLE 2** (Continued)

Outcome	Mean T-score	Crude Estimate (95% CI)	Adjusted Estimate (95% CI)	Crude Estimate (95% CI)	Adjusted Estimate (95% CI)
<i>Sleep</i>					
THRT exposed	50.16	0.24 (−0.53, 1.00)	0.27 (−0.70, 0.47)	−0.82 (−1.87, 0.22)	−0.72 (−1.91, 0.47)
THRT initiators after delivery	50.98	1.06 (0.33, 1.79)	0.99 (0.24, 1.74)	Ref	Ref
Unexposed	49.92	Ref	Ref	−1.06 (−1.79, −0.33)	−0.99 (−1.74, −0.24)

Note: Each score was standardized using the population of MoBa Q6, giving a mean T-score of 50 and a standard deviation of 10. Higher T-scores indicated greater developmental difficulties (e.g., more problems externalizing). A difference of 10 from the mean equals a difference of one standard deviation.

Abbreviations: ASQ, Ages and Stages Questionnaire; CBCL, Child Behavior Checklist; CI, confidence interval; SDQ, Strength and Difficulties Questionnaire; THRT, thyroid hormone replacement.

<sup>a</sup>Internalizing comprises the domains anxiety/depression, emotional reactivity, and somatic complaints.

<sup>b</sup>Externalizing comprises the domains attention and aggression.

substance use, anxiety and depressive symptoms, and supplement use (Supplementary Information and Supplementary Figure 2). To adjust for the severity of hypothyroidism, we included blood thyroid hormone levels in the analysis. To assess the importance of the timing of exposure, a second adjusted generalized linear regression model was fit. The exposure group consisted of women who had filled at least one prescription in the first trimester of pregnancy, which was compared to women unexposed in that time window.

Statistical analyses were performed in R (version 3.4.4). Multiple imputation was performed using the ‘mice’ package,<sup>31</sup> and regression analysis using the ‘mice’ and ‘mitools’ packages.<sup>36</sup> Significance was set to a two-sided *P*-value of 0.05.

## 2.8 | Sensitivity analysis

Several pre-planned sensitivity analyses were performed to test the robustness of the results. First, we included maternal depressive and anxiety symptoms in the models when filling in the Q6 questionnaire to account for the distortion bias (differential rating due to mental health status). Next, we restricted the analysis to women who participated in MoBa with only one pregnancy (93.5% of the total population). Lastly, we restricted the analysis to only women with a diagnosis of hypothyroidism.

## 3 | RESULTS

The study population consisted of 29 431 pregnancy-child pairs, of which 663 (2.2%) were THRT-exposed during pregnancy, 728 (2.5%) THRT initiators after delivery, and the remaining 28 040 (95.3%) unexposed (Figure 1). Children prenatally exposed to THRT were born to mothers and fathers with an older age than the other two exposure groups (Table 1). Furthermore, THRT-exposed women had a higher BMI at baseline and more mental and somatic comorbidities than unexposed women.

The descriptive data on thyroid hormone levels according to THRT exposure group are given in Supplementary Table 1. In this study

population, MoBa eTox data were available for 28 (4.2%) THRT-exposed women, 41 (5.6%) THRT initiators after delivery, and 1483 (5.3%) unexposed women. The large portion of missing values in the eTox data was due to the fact that only a subsample of the MoBa was included in the MoBa eTox substudy. THRT-exposed women had higher TPOAb, TSH, and FT4 levels compared to the other exposure groups.

Table 2 shows the results of the crude and adjusted analyses. The crude analysis showed that children of THRT-exposed women had more somatic complaints compared to unexposed ( $\beta = 1.01$ , 95% CI: 0.23, 1.78). Children of THRT-exposed women had fewer attention problems compared to women initiating THRT after delivery ( $\beta = -1.28$ , 95% CI  $-2.34, -0.23$ ), and children of women initiating THRT after delivery had more attention ( $\beta = 0.97$ , 95% CI 0.23, 1.70) and sleep problems ( $\beta = 1.06$ , 95% CI 0.33, 1.79) than unexposed women. After adjusting for the necessary confounders, the difference in somatic complaints between unexposed and THRT-exposed ( $\beta = 0.98$ , 95% CI 0.08, 1.87) and the difference in sleep problems between children of women initiating THRT after delivery and unexposed ( $\beta = 0.99$ , 95% CI 0.24, 1.74) remained significant, albeit of small effect size.

Table 3 shows the results for the first trimester exposure analysis. The observed point estimates did not deviate from those relating to the THRT in pregnancy exposure window, including child sleep ( $\beta = 0.99$ , 95%CI  $-0.24, 1.74$ ) and somatic complaints ( $\beta = 1.05$ , 95% CI 0.11, 1.99).

## 3.1 | Sensitivity analyses

The results of the adjusted complete-case analysis were similar to those found in the imputed adjusted analysis. After adjusting for maternal anxiety and depressive symptoms at child age 3 years, the results changed slightly (Supplementary Table 2). The difference in sleep problems in children from women initiating THRT after delivery compared to unexposed women lost its significance ( $\beta = 0.73$ , 95% CI  $-0.02, 1.48$ ). However, the difference in somatic problems between THRT-exposed and unexposed children remained significant ( $\beta = 0.97$ , 95% CI 0.08, 1.87).

**TABLE 3** Adjusted mean T-score differences in child developmental outcomes in first trimester exposure analysis (n = 27 866)

Outcome	Mean T score	Crude Estimate (95% CI)	Adjusted Estimate (95% CI)	Crude Estimate (95% CI)	Adjusted Estimate (95% CI)
<b>Communication (ASQ)</b>					
THRT exposed in 1. trimester	49.89	-0.31 (-1.58, 0.96)	-0.47 (-1.79, 0.84)	-0.05 (-1.22, 1.31)	-0.20 (-1.43, 1.02)
THRT initiators after delivery	49.94	0.26 (-1.12, 0.60)	-0.27 (-1.12, 0.59)	Ref	Ref
Unexposed	50.20	Ref	Ref	0.26 (-0.60, 1.12)	0.27 (-0.59, 1.12)
<b>Motor function (ASQ)</b>					
<i>Fine motor function</i>					
THRT exposed in 1. trimester	49.73	-0.17 (-1.14, 0.80)	-0.29 (-1.31, 0.73)	-0.57 (-1.73, 0.59)	-0.69 (-1.90, 0.51)
THRT initiators after delivery	50.30	0.40 (-0.38, 1.19)	0.40 (-0.38, 1.18)	Ref	Ref
Unexposed	49.90	Ref	Ref	-0.40 (-1.19, 0.38)	-0.40 (-1.18, 0.38)
<i>Gross motor function</i>					
THRT exposed in 1. trimester	49.94	0.17 (-1.19, 1.54)	0.40 (-1.04, 1.83)	0.22 (-1.22, 1.67)	0.44 (-1.06, 1.95)
THRT initiators after delivery	49.72	-0.05 (-0.83, 0.73)	-0.05 (-0.83, 0.74)	Ref	Ref
Unexposed	49.77	Ref	Ref	0.05 (-0.73, 0.83)	0.05 (-0.74, 0.83)
<b>Social behavior (SDQ)</b>					
THRT exposed in 1. trimester	49.94	-0.04 (-0.92, 0.84)	-0.41 (-1.34, 0.53)	-0.02 (-1.13, 1.10)	-0.37 (-1.52, 0.78)
THRT initiators after delivery	49.96	0.02 (-0.80, 0.75)	-0.03 (-0.81, 0.74)	Ref	Ref
Unexposed	49.98	Ref	Ref	0.02 (-0.75, 0.80)	0.03 (-0.74, 0.81)
<b>Behavior (CBCL)</b>					
<i>Internalizing<sup>a</sup></i>					
THRT exposed in 1. trimester	51.09	0.89 (-0.20, 1.97)	1.05 (-0.08, 2.19)	0.54 (-0.65, 1.73)	0.71 (-0.53, 1.94)
THRT initiators after delivery	50.55	0.35 (-0.46, 1.15)	0.35 (-0.46, 1.15)	Ref	Ref
Unexposed	50.20	Ref	Ref	-0.35 (-1.15, 0.46)	-0.35 (-1.15, 0.46)
<i>Anxiety/depression</i>					
THRT exposed in 1. trimester	50.80	0.67 (-0.40, 1.74)	0.75 (-0.37, 1.88)	0.49 (-0.70, 1.68)	0.57 (-0.66, 1.81)
THRT initiators after delivery	50.31	0.18 (-0.61, 0.97)	0.18 (-0.61, 0.97)	Ref	Ref
Unexposed	50.13	Ref	Ref	-0.18 (-0.97, 0.61)	-0.18 (-0.97, 0.61)
<i>Somatic complaints</i>					
THRT exposed in 1. trimester	51.23	0.98 (0.08, 1.87)	1.05 (0.11, 1.99)	0.55 (-0.57, 1.67)	0.63 (-0.53, 1.79)
THRT initiators after delivery	50.68	0.42 (-0.34, 1.19)	0.42 (-0.34, 1.19)	Ref	Ref
Unexposed	50.26	Ref	Ref	-0.42 (-1.19, 0.34)	-0.42 (-1.19, 0.34)
<i>Emotional reactivity</i>					
THRT exposed in 1. trimester	50.20	0.16 (-1.03, 1.36)	0.38 (-0.86, 1.62)	0.08 (-1.13, 1.28)	0.29 (-0.96, 1.53)
THRT initiators after delivery	50.12	0.08 (-0.80, 0.97)	0.09 (-0.80, 0.98)	Ref	Ref
Unexposed	50.04	Ref	Ref	-0.08 (-0.97, 0.80)	-0.09 (-0.98, 0.80)
<i>Externalizing<sup>b</sup></i>					
THRT exposed in 1. trimester	50.13	-0.03 (-1.07, 1.01)	0.10 (-1.01, 1.16)	-0.38 (-1.58, 0.83)	-0.27 (-1.52, 0.97)
THRT initiators after delivery	50.51	0.35 (-0.50, 1.20)	0.35 (-0.50, 1.20)	Ref	Ref
Unexposed	50.16	Ref	Ref	-0.35 (-1.20, 0.50)	-0.35 (-1.20, 0.50)
<i>Aggression</i>					
THRT exposed in 1. trimester	50.04	-0.002 (-1.05, 1.05)	0.08 (-1.02, 1.17)	-0.10 (-1.29, 1.09)	-0.02 (-1.25, 1.21)
THRT initiators after delivery	50.14	0.10 (-0.77, 0.96)	0.10 (-0.77, 0.96)	Ref	Ref
Unexposed	50.04	Ref	Ref	-0.10 (-0.96, 0.77)	-0.10 (-0.96, 0.77)
<i>Attention</i>					
THRT exposed in 1. trimester	50.23	-0.07 (-0.98, 0.83)	0.04 (-0.91, 0.99)	-0.72 (-1.87, 0.44)	-0.60 (-1.79, 0.58)
THRT initiators after delivery	50.95	0.64 (-0.13, 1.42)	0.65 (-0.13, 1.42)	Ref	Ref
Unexposed	50.31	Ref	Ref	-0.64 (-1.42, 0.13)	-0.65 (-1.42, 0.13)

(Continues)



**TABLE 3** (Continued)

Outcome	Mean T score	Crude Estimate (95% CI)	Adjusted Estimate (95% CI)	Crude Estimate (95% CI)	Adjusted Estimate (95% CI)
<i>Sleep</i>					
THRT exposed in 1. trimester	50.26	0.27 (−0.70, 0.47)	0.37 (−0.67, 1.40)	−0.72 (−1.91, 0.47)	−0.62 (−1.86, 0.62)
THRT initiators after delivery	50.98	0.99 (0.24, 1.74)	0.99 (0.24, 1.74)	Ref	Ref
Unexposed	49.99	Ref	Ref	−0.99 (−1.74, −0.24)	−0.99 (−1.74, −0.24)

Note: Each score was standardized using the population of MoBa Q6, giving a mean T-score of 50 and a standard deviation of 10. Higher T-scores indicated greater developmental difficulties (e.g., more problems externalizing). A difference of 10 from the mean equals a difference of one standard deviation.

Abbreviations: ASQ, Ages and Stages Questionnaire; CBCL, Child Behavior Checklist; CI, confidence interval; SDQ, Strength and Difficulties Questionnaire; THRT, thyroid hormone replacement.

<sup>a</sup>Internalizing comprises the domains anxiety/depression, emotional reactivity, and somatic complaints.

<sup>b</sup>Externalizing comprises the domains attention and aggression.

After excluding the women who participated in MoBa with more than one pregnancy from the study population (Supplementary Table 3), the association between sleep and THRT initiators after pregnancy was of a lower magnitude ( $\beta = 0.79$ , 95% CI 0.02, 1.57), as well as the association between THRT and somatic complaints ( $\beta = 0.97$ , 95% CI 0.05, 1.88).

After excluding the women who did not have a diagnosis of hypothyroidism from the THRT exposed group, the main results and conclusion did not change.

## 4 | DISCUSSION

This study used data from the MoBa pregnancy cohort to estimate the association between THRT in pregnancy and child motor function, communication skills, and behavior at 3 years of age. Our overall findings indicate that children born to women with hypothyroidism and medicated with THRT during pregnancy, or specifically during the first trimester, have developmental outcomes as positive as those of children born to unexposed mothers with no hypothyroidism in terms of motor function, communication, and behavior at preschool age. Our results are in line with multiple studies that did not find any effect of THRT or maternal hypothyroidism on child behavior and motor function.<sup>9-11,14-17</sup>

We found no difference in fine and gross motor function, communication skills, and behavior. This is important because some women discontinue their THRT upon recognition of pregnancy<sup>37,38</sup> and, among those who are medicated, adherence to THRT is not always optimal.<sup>39</sup> Juch et al<sup>39</sup> found that 17% of pregnant women with hypothyroidism exhibit low adherence during pregnancy. This means that these women and children are at risk of suboptimal hypothyroidism control during pregnancy, which could negatively impact maternal-child health.<sup>5,6,8,12,13</sup> As the most important determinant of low THRT adherence during pregnancy was the woman's belief that the risks of their medication outweigh the benefits, efforts have to be made to lower this elevated perception of risk.<sup>39</sup> Although this study could not compare child developmental risks according to THRT discontinuation during pregnancy, our findings suggest that adequate treatment of hypothyroidism during pregnancy leads to positive child outcomes similar to unexposed pregnancies.

Furthermore, our results show that children exposed to THRT have more somatic complaints than unexposed children. This can be explained by the fact that thyroid hormones affect almost every organ of the gastrointestinal tract, including the stomach and intestines.<sup>40</sup> It is possible that THRT during pregnancy disturbs a delicate balance during development, leading to more somatic complaints. However, it is also possible that the somatic complaints are influenced by the child's eating habits, which in turn are influenced by the parents' diet.<sup>41</sup>

Children born to women initiating THRT after delivery had more sleep problems than those born to women not exposed to THRT, albeit the observed effect size was negligible. Sleep problems may be influenced by psychosocial stressors, such as anxiety and altered mood in the child and might not be related to possible maternal hypothyroidism during pregnancy.<sup>42</sup> For both associations we cannot rule out the possibility of chance, residual or unmeasured confounding. However, both estimates of the effect on somatic and sleep problems were small and not clinically relevant.

A major strength of the study is the measurement of thyroid hormone levels in the blood. Using these measurements, the analysis could be adjusted for the severity of the hypothyroidism, reducing the risk of confounding by severity.<sup>43</sup> A second strength of the study was the large sample size and long follow-up of the children. In addition, robust statistical methods, including multiple imputation were used in the study. Finally, multiple sensitivity analyses were performed, which all had similar results.

This study also has some limitations that warrant consideration. First, the low response rate of 41% is a limitation of the MoBa cohort. Second, selection bias may have occurred due to loss to follow-up and to the fact that women entering MoBa are generally healthier than the general birthing population in Norway.<sup>44</sup> This selection bias could affect the validity and generalizability of our findings. However, the potential for bias due to self-selection in MoBa has been explored by comparing MoBa with the total Norwegian birthing population<sup>44</sup>; although some prevalence estimates could not necessarily be generalized, those relating to some maternal chronic disorders (e.g., epilepsy, chronic hypertension) did not differ in the two data sources. In addition, the measures of associations tested by Nilsen et al<sup>44</sup> were found to be valid in MoBa. Furthermore, our proportion of THRT-exposed

mother-child pairs was similar to that observed in Norway in an unselected population sample.<sup>45</sup> Another limitation is that thyroid hormone levels were measured only once during pregnancy. Therefore, the variability of the thyroid hormone levels over the course of the pregnancy could not be taken into account. Finally, based on the computational burden involved, we decided to generate 10 imputed datasets. However, a higher number of imputed sets might help in detecting small effect sizes.<sup>46</sup> With the available data, we were unable to rule out these cases, leading to possible misclassification and biased results.

It is essential that future studies elucidate the effect of non-medicated hypothyroidism during pregnancy. Furthermore, more studies are needed to confirm the safe use of THRT in pregnancy regarding more developmental outcomes in children.

## 5 | CONCLUSION

This study indicates that children exposed to THRT during pregnancy have similar developmental outcomes as unexposed children at the age of 3 years. The negligible associations between THRT and somatic complaints and THRT initiation after delivery and sleep are below the threshold of clinical relevance.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest. This paper is original and has never been presented or posted anywhere else.

## ETHICS STATEMENT

The current study was approved by The Regional Committee for Medical Research Ethics (2015/1241, REK Sør-Øst B). All participants provided written informed consent prior to participation. All data were handled and stored at the Service for Sensitive Data (TSD), which is University of Oslo's platform for storing, computing, and analyzing research-sensitive data in compliance with GDPR regulations regarding individuals' privacy.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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