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ORIGINAL REPORT

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Thyroid hormone replacement therapy patterns in pregnant women and perinatal outcomes in the offspring

Anna S. Frank[1] | Angela Lupattelli[1] | David S. Matteson[2,3] | Helle Margrete Meltzer[4] | Hedvig Nordeng[1,5]

[1] Pharmacoepidemiology and Drug Safety Research Group, Department of Pharmacy, University of Oslo, Oslo, Norway

[2] Department of Statistical Science, Cornell University, Ithaca, NY, USA

[3] Department of Biological Statistics and Computational Biology, Cornell University, Ithaca, NY, USA

[4] Division of Infectious Diseases and Environmental Health, Norwegian Institute of Public Health, Oslo, Norway

[5] Department of Child Health and Development, Norwegian Institute of Public Health, Oslo, Norway

Correspondence
A. S. Frank, Department of Pharmacy, University of Oslo, Norway, PO Box 1068 Blindern, Oslo 0316, Norway.
Email: asfrank88@gmail.com

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Abstract

Purpose: It remains unknown to what degree thyroid hormone replacement therapy (THRT) during and initiation after pregnancy determines pregnancy outcomes. The present study primarily aimed to quantify the impact of THRT patterns (including trajectories) on gestational age, birth weight, and head circumference of infants. The secondary aim was to compare results of trajectory with traditional analysis.

Methods: We combined data from the Norwegian Mother, Father and Child Cohort Study (MoBa) to other Norwegian registry data and the Norwegian Environmental Biobank. The study population included 54 020 women enrolled in MoBa in 2005 to 2008. On the basis of prescription records, we classified women into nonhypothyroid (n = 51 390; reference group), THRT after delivery (n = 1397), or medicated (n = 1233) groups. Applying Group-Based-Trajectory Models (GBTMs), we determined THRT trajectories among women in the medicated group. Propensity score weighting linked multiple treatment groups to pregnancy outcomes.

Results: Patterns were identified among women using medication during (Decreasing-Low, Increasing-Medium, Constant-Medium, and Constant-High) and after pregnancy. Women in the Increasing-Medium (adjusted Odds Ratio [aOR] = 1.69; 95% Confidence Interval [CI], 1.06-2.73) and the THRT after delivery (aOR = 1.19; 95% CI, 1.01-1.42) groups had increased risk of giving birth to an LGA infant. In the traditional analysis, only women in the THRT after delivery group showed increased risk for an LGA infant (aOR = 1.19; 95% CI, 1.00-1.42). We found no other differential effect among the five THRT patterns on the other outcomes.

Conclusions: Women with THRT after delivery or late onset THRT treatment showed increased risk of LGA infants.

KEYWORDS

birth weight, head circumference, inverse probability of treatment weighting, (large-for-) gestational-age, MoBa, pharmacoepidemiology, trajectory modeling

1 | INTRODUCTION

Approximately 3% of women of reproductive age experience overt or subclinical hypothyroidism.[1] In addition, during pregnancy, women are more vulnerable to developing hypothyroidism because of the increased demand for thyroid hormone production.[2] Inadequate treatment of hypothyroidism during gestation has been associated with adverse pregnancy outcomes, like preterm delivery.[3] Therefore, thyroid hormone replacement therapy (THRT) is recommended.[4] The literature has reported conflicting results on the beneficial effect of THRT on pregnancy outcomes.[5,6] However, there is evidence that the effectiveness of THRT depends on timing (first trimester) and dosage to match severity of the condition.[3] A number of previous studies failed to include first trimester exposure information or lacked information on dosage and severity levels, eg, thyroid hormone blood levels.[6,7] Exposure groups reflecting variations in THRT use with respect to timing, duration, and dosage during gestation may be biologically more appropriate than simply grouping women into users and nonusers when assessing the impact of THRT on pregnancy outcomes.[8]

The current study builds on our prior work showing that Group-Based Trajectory Models (GBTMs) could be used to identify women with distinct patterns of THRT use in pregnancy.[8] Our primary aim is to analyze the association between THRT patterns during pregnancy (using GBTM) and immediate pregnancy outcomes, such as infant birth weight, gestational age at birth, and head circumference. To address confounding by maternal underlying disease, we also compared women initiating THRT after delivery with the nonhypothyroid group. After analyzing these associations for all women with a prescription of THRT during pregnancy, a secondary aim is to compare the analysis of this joint group with the one that splits THRT users during pregnancy into disjoint trajectories. This helps illustrate the relevance of clustering techniques in studies of medication safety in pregnancy. An important advantage of this study over prior observational studies is the use of data on maternal thyroid hormone blood levels in pregnancy to account for severity levels of hypothyroidism.

Key points

- This study extends existing literature on the association between THRT and immediate perinatal outcomes by including thyroid hormone blood levels.
- Pregestational and first trimester THRT use is important for infant health.
- Underlying or undiagnosed hypothyroid condition during pregnancy increases the risk of LGA infants.
- Compared with analyses grouping women into users or nonusers of medication, GBTM enables a more biologically tailored investigation of the association between THRT and immediate pregnancy outcomes.
- Clustering approaches might be useful in future studies on drug safety in pregnancy, when timing, duration, and dose of exposure are important for fetal safety.

2 | METHODS

2.1 | Data sources

The following data sources were linked using the unique 11-digit person identification number given to all legal residents in Norway.

The Norwegian Mother, Father and Child Cohort Study (MoBa) is a prospective, population-based cohort study of pregnancies in Norway that was initiated in 1999 by the Norwegian Institute of Public Health.[9] From 1999 to 2008, all women in Norway were invited to participate through a postal invitation in relation to the routine ultrasound examination around gestational week 17 by filling MoBa questionnaire 1 (MoBa Q1). Of the invited women, 41% consented to participate. During gestation, women were then prospectively followed-up via a series of questionnaires, which were filled in at gestational week 22 (MoBa Q2) and gestational week 30 (MoBa Q3). During the study period, the cohort included 114 500 children, 95 200 mothers, and 75 200 fathers.[10] The current study was based on Version 10 of the quality-assured data that was released for research purposes in 2017.

The recently established Norwegian Environmental Biobank (Biobank), a nonrandom subcohort within the MoBa, comprised 2999 women and collected biological data on plasma levels of thyroid hormones (free triiodothyronine [FT3], free thyroxine [FT4], thyroid stimulating hormone [TSH]) and thyroid peroxidase antibodies (TPOAb) in gestational week 18.[11] The method of selecting participants for the Biobank subgroup is described by Caspersen et al.[12]

The Medical Birth Registry of Norway (MBRN) is a nationwide health registry of information about all births in Norway.[13] The registry includes confirmed medical records related to maternal health before and during pregnancy.[13] The Norwegian Prescription Database (NorPD) is a nationwide prescription registry that was established in January 2004. Since then, all pharmacies in Norway were mandated to send data electronically to the Norwegian Institute of Public Health on all prescribed drugs dispensed to individuals in ambulatory care.[14]

Starting in 2008, all government-owned and government-financed hospitals and outpatient clinics were required to report individual-level International Classification of Diseases, 10th Revision diagnoses (ICD-10 codes) to the Norwegian Patient Registry (NPR) to receive financial reimbursement.[15,16]

2.2 | Study population

We restricted the study population to singleton and life births in MoBa between 2005 and 2009 from mothers who completed MoBa Q1 and MoBa Q3 and who were successfully linked to NorPD (Figure 1). We excluded pregnant women with prescriptions for other thyroid disorders (Anatomical Therapeutic Chemical [ATC] code

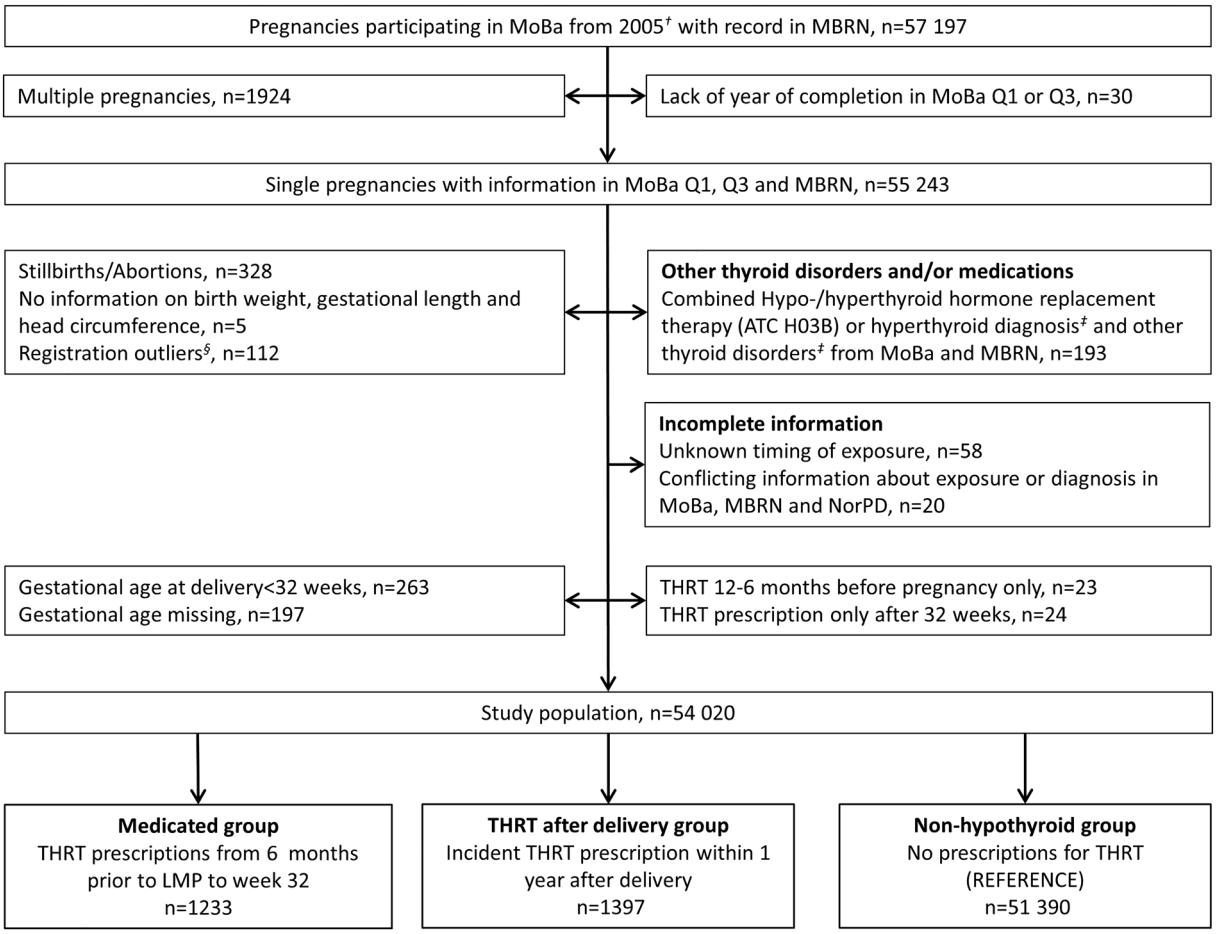

FIGURE 1 Flow chart of study population. †NorPD was established in 2004, thus required restriction of the MoBa population to pregnancies recruited from 2005. ‡Hyperthyroid diagnosis (ICD-10 code "e05"), other thyroid diagnosis (ICD-10 code "e0-other") from MBRN. §Gestational age > 313 days, birth weight < 1290 g, head circumference > 42 cm, and head circumference < 28 cm. These outliers are considered implausible for live-born infants. Abbreviations: ATC code, Anatomical Therapeutic Chemical Classification System code; cm, centimeter; g, gram; LMP, Last Menstrual Period; MBRN, Medical Birth Registry of Norway; MoBa Norwegian Mother, Father and Child Cohort Study; MoBa Q1, MoBa questionnaire 1; MoBa Q3, MoBa questionnaire 3; NorPD, Norwegian Prescription Database; THRT, thyroid hormone replacement therapy

H03B, a combination of ATC H03AA and H03B, and ICD-10 code "e0-other") or a diagnosis of hyperthyroidism (ICD-code "e05") in the MBRN. Diagnosis information from the NPR was not considered a selection criterion for the study population, because the NPR was established in 2008.

From the original cohort of participants (n = 55 243), we excluded around 2.2% of women because of incomplete or inconsistent information on THRT use, missing information, and registration outliers on pregnancy outcomes.[17,18] We restricted the study sample to the first 32 gestational weeks, in order to make sure that all women have equal time available in relation to the exposure (see Supporting Information).

2.3 | Exposure definitions

Women with hypothyroidism were identified based on dispensed THRT prescriptions before and during pregnancy or first time within 1 year after delivery.

Therefore, women were assigned to the medicated group (n = 1233), when they received at least one THRT prescription during the period starting 6 months prior to the pregnancy and ending at 32 gestational weeks. The THRT after delivery group (n = 1397) included women that received THRT prescriptions within 1 year after delivery and served as a proxy for a disease-comparator group. This group is important to study, as women might develop postpartum hypothyroidism because of postpartum thyroiditis.[19] Hence, these women might have thyroid antibodies present during pregnancy, which has previously been connected to adverse immediate pregnancy outcomes.[20,21]

The nonhypothyroid group (n = 51 390) was defined as the reference group and included women that did not receive a THRT prescription before, during, or after pregnancy.

THRT was classified based on the ATC Classification System and included thyroid hormones (ATC code H03AA).[22]

GBTMs are finite mixture models, which split a population into a finite, disjointed number of groups based on the latent mixture probability of group membership.[23] First, we split the exposure period, starting from 6 months prior to pregnancy and ending with gestational

week 32, into months (in total 14 months). To classify women in the medicated hypothyroid group into trajectories, we then applied the GBTM approach to each woman's dispensing of prescription over the 14 months (ie, exposed/unexposed), similar to Frank et al[8], who used GBTM to define long-term THRT adherence patterns before, during, and after pregnancy.

2.4 | Outcome definitions

We retrieved data on child outcomes from the MBRN, including birth weight (g), gestational age (days), and head circumference (cm), all modelled as continuous. In the Norwegian population, the average birth weight is 3,489 g, with a standard deviation (SD) of 591 g; the average gestational age is 275.1 days with SD of 13.3 days; the average head circumference is 35.30 cm with SD of 0.04 cm.[24,25] The large-for-gestational age (LGA) infant outcome was analyzed and dichotomized at the 90th percentile in the MoBa population. Other potential outcomes, such as small-for-gestational age, low birth weight, premature (gestational weeks <37) birth, and small or large head circumference, could not be analyzed because of the low number of cases ($\leq$5) within the trajectory groups.

2.5 | Confounder variables

Confounders were identified based on the literature and causal diagrams.[26] Information about sociodemographic characteristics was retrieved from the MoBa Q1 and MoBa Q3, including maternal education, income, body mass index (BMI) at conception, smoking habits, and alcohol consumption. Maternal age, marital status, gender of the infant, and parity were retrieved from the MBRN. The MoBa Q1 and MoBa Q3 provided data on the perinatal use of recommended nutritional supplements, including vitamin D, folic acid, and additional supplements (eg, iodine and omega-3 fatty acids). Fiber intake, retrieved from the Food Frequency Questionnaire (MoBa Q2), was classified, based on whether maternal intake was above or below the median intake of the study population and is used as proxy for a healthy lifestyle. Somatic comorbidity was classified as medicated or nonmedicated depending on whether the woman had a registered diagnosis in the MBRN and whether she reported in the MoBa Q1 treatment for epilepsy (ATC code N03A), arthritis (L04A, M01, N02), diabetes mellitus (A10A, A10B, A10X), anemia (B03A, B03B, B03X), or cardiovascular disorders (C01-C10). Mental comorbidities (depression and/or anxiety) were determined from the MoBa Q1 and MoBa Q3, and they were categorized as medicated or nonmedicated, depending on whether the woman reported psychotropic drug use (ATC codes N05 and N06). Thyroid hormone blood levels, TSH, FT4, FT3, and TPOAb levels, were retrieved from the Biobank subsample.[27]

We considered the sufficient set of confounders to be maternal age, BMI, parity, marital status, comorbidities, fiber intake, educational level, income, supplement use, smoking and alcohol habits, gender of child, FT3, FT4, TSH severity, and the TPOAb category.

Thyroid diagnoses were retrieved from MBRN and NPR (ICD-10 code "e03"—hypothyroidism and "e05"—hyperthyroidism).[15,16]

2.6 | Ethical approval

The establishment and data collection in MoBa were previously based on a license from the Norwegian Data Protection Agency, with approval from The Regional Committee for Medical Research Ethics. Currently, it is based on regulations related to the Norwegian Health Registry Act.

The overall MoBa study was approved by the Norwegian Data Inspectorate (01/4325) and The Regional Committee for Medical Research Ethics (S-97045, S-95113). 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.

Blood samples were obtained from both parents during pregnancy and from mothers and infants (umbilical cord) at birth.

2.7 | Statistical analysis

To take into account differences in characteristics across women in the various treatment groups, we performed propensity score analysis, with inverse probability of treatment weighting (IPTW), after multiple imputation.[28,29] The subsample of thyroid hormone blood levels from the Biobank was multiple imputed together with other missing covariate information.[30] By exploring the patterns of missing data, we assumed that data are missing at random (MAR), as also done in prior MoBa studies.[31] Though MAR is untestable, by including a wide variety of predictors in the imputation model, the assumption is likely to be plausible (see also Supporting Information).[32,33] The optimal number of THRT trajectories was selected by the highest (least negative) BIC value and estimated group proportions greater than 5.0%.[8] Boosted logistic regression models were applied to determine the conditional probability of six group comparisons, where the THRT trajectories from the medicated and the THRT after delivery group were compared with the nonhypothyroid group.[28] The propensity scores were calculated conditioned on the sufficient set of confounders. We did not adjust for gestational age when analyzing birth weight, head circumference, or LGA infant, as gestational age can introduce collider bias.[34] Weights were truncated at the 99th percentile. For balance assessment, the Maximal Averaged Standardized Difference (MASD) was applied. The MASD is a balance diagnostic for the generalized propensity score after multiple imputations (see Supporting Information). In the final weighted regression model, we took repeated pregnancy participation in MoBa into account. A summary of the analytical procedure can be found in Algorithm S1.

2.8 | Sensitivity analyses

We compared the trajectory analysis to a more traditional approach. With "traditional analysis," we specifically refer to the analysis where

the medicated (previously split into disjoint trajectories) and THRT after delivery groups are compared with the nonhypothyroid group. Furthermore, the trajectory analysis was done without inclusion of blood levels. Finally, we performed a complete case analysis.

A priori power calculations are presented in detail in the Supporting Information.

GBTMs were built with the "traj" Stata plugin (Stata version 15.1).[35] The remainders of the analyses were performed in R (version 3.4.4). For multiple imputation, we used the "mice" R package;[29] for the generalized propensity score, we used the "twang" R package and its "mnps" function for multiple treatments.[28] Regression analysis with IPTW was performed with the "survey" R package.[36]

3 | RESULTS

The final study population consisted of 54 020 pregnancies, including the medicated (n = 1233), THRT after delivery (n = 1397), and nonhypothyroid (n = 51 390) groups (Figure 1).

In the medicated group, we identified four disjointed trajectories (Figure 2). These trajectories exhibited the following patterns: Decreasing-Low (n = 81, 6.6%), Increasing-Medium (n = 140, 11.4%), Constant-Medium (n = 476, 38.6%), and Constant-High (n = 536, 43.4%).

Maternal characteristics are presented according to treatment groups in Table 1. Differences among groups were observed in socioeconomic characteristics, concomitant health, medication use, and lifestyle factors. The frequency of thyroid diagnoses also varied between groups (Table 1). Drug utilization for each THRT trajectory and the medicated hypothyroid group are shown in Table S1. Individual covariates had missing information ranging from 1.8% to 11.7%. In total, 29.0% had missing data in one or several variables. Table S2 presents the data on thyroid hormone blood levels before and after multiple imputation.

3.1 | Trajectory analysis

The results of the trajectory analysis are shown in Table 2. There were no significant or clinical differences in gestational age, birth weight, or head circumference in any of the THRT trajectory and THRT after delivery groups compared with the nonhypothyroid group. Infants born to women in the Increasing-Medium (adjusted Odds Ratio [aOR] = 1.69; 95% Confidence Interval [CI], 1.06-2.73) and in the THRT after delivery (aOR = 1.19; 95% CI, 1.01-1.42) groups were more likely to be LGA infants than their nonhypothyroid counterparts (Figure 3d).

3.2 | Traditional and other sensitivity analyses

In the traditional analysis (Table S4), only the THRT after delivery group showed a significant difference in the risk of LGA infants (aOR = 1.19; 95% CI, 1.00-1.42) compared with the nonhypothyroid group. Only small, insignificant deviations in the traditional analysis without blood levels were observed compared with the analysis including these data as confounders (Table S5).

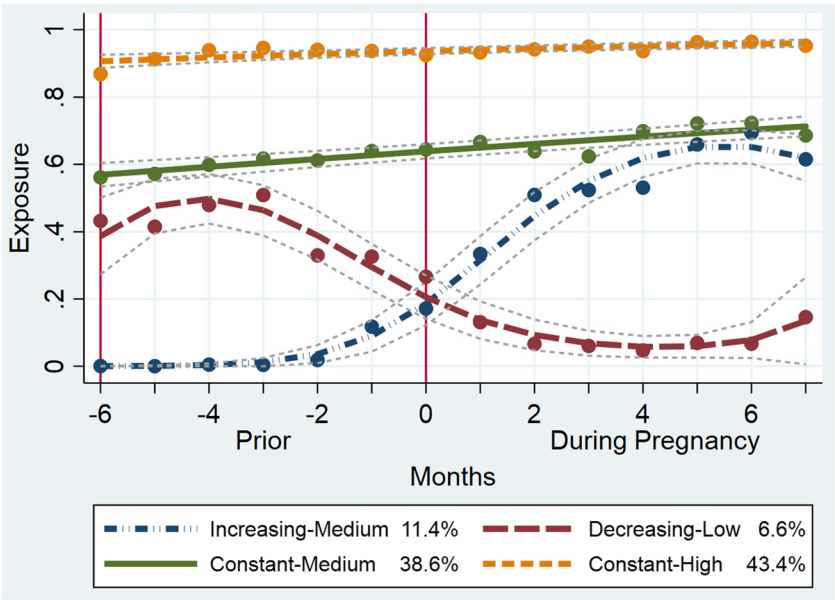

FIGURE 2 THRT trajectories from six months prior to pregnancy and up to gestational week 32. Legend: Estimated adherence trajectories (horizontal lines), observed group means at each month (dot symbols), and estimated percentages for each group: Decreasing-Low, Increasing-Medium, Constant-Medium, and Constant-High. Dashed thin lines are approximated 95% pointwise confidence intervals on the estimated trajectories. Vertical lines mark the start of the 6-month period prior to pregnancy (at month "−6"), the start of the pregnancy period (at month "0"). A month represents four gestational weeks. For example, month "0" stands for the gestational weeks 1 to 4. The Y-axis presents the group-average adherence rate to THRT per month. For example, women in the Constant-Medium group took THRT, on average, 60% of days in each month before and during gestation. On average, women in the Increasing-Medium trajectory took no THRT 4 months before gestation, but in pregnancy month 5, they took THRT in, on average, 60% of days. Abbreviations: THRT, thyroid hormone replacement therapy [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Maternal characteristics (n = 54 020)

Variables, n (%)	Decreasing-Low, n = 81	Increasing-Medium, n = 140	Constant-Medium, n = 476	Constant-High, n = 536	THRT after delivery, n = 1397	Nonhypothyroid group, n = 51 390
Maternal Age (y)						
≤24	7 (8.6)	17 (12.1)	31 (6.5)	13 (2.4)	138 (9.8)	5319 (10.4)
25-29	26 (32.1)	40 (28.6)	130 (27.3)	137 (25.6)	422 (30.2)	16 434 (31.9)
30-34	28 (34.6)	49 (35.0)	200 (42.0)	218 (40.7)	541 (38.7)	20 185 (39.2)
≥35	20 (24.7)	34 (24.3)	115 (24.2)	168 (31.3)	296 (21.2)	9452 (18.4)
BMI at conception (kg/m^2)						
≤18	2 (2.5)	6 (4.3)	9 (1.9)	9 (1.7)	32 (2.3)	1618 (3.1)
19-24	38 (46.9)	76 (54.3)	268 (56.3)	255 (47.6)	762 (54.5)	31 593 (60.8)
25-29	24 (29.6)	31 (22.1)	118 (24.8)	142 (26.5)	363 (25.9)	12 097 (23.3)
≥30	14 (17.3)	24 (17.1)	69 (14.5)	113 (21.1)	205 (14.7)	4862 (9.4)
Missing	3 (3.7)	3 (2.1)	12 (2.5)	17 (3.2)	35 (2.6)	1220 (2.4)
Married/cohabiting						
Yes	75 (92.6)	132 (94.3)	450 (94.5)	510 (95.1)	1,323 (94.7)	49,149 (95.6)
No	6 (7.4)	8 (5.7)	26 (5.5)	26 (4.8)	74 (5.3)	2,241 (4.4)
Parity						
Multiparity	41 (50.6)	65 (46.4)	271 (56.9)	334 (62.3)	756 (54.1)	26 986 (52.5)
Primiparity	40 (49.3)	75 (53.6)	205 (43.0)	202 (37.7)	641 (45.9)	24 404 (47.5)
Education-ongoing (y)						
<9	2 (2.5)	2 (1.4)	5 (1.0)	7 (1.3)	30 (2.1)	847 (1.6)
9-12	28 (34.6)	34 (24.3)	111 (23.3)	131 (24.4)	407 (29.1)	12 830 (24.9)
13-16	24 (29.6)	53 (37.9)	206 (43.3)	231 (43.1)	535 (38.3)	21 412 (41.7)
>16	23 (28.4)	50 (35.7)	143 (30.0)	158 (29.5)	400 (28.6)	15 328 (29.8)
Missing	3 (3.7)	1 (0.7)	11 (2.3)	9 (1.7)	25 (1.8)	973 (1.8)
Income[a]						
<16 013 USD	24 (29.6)	35 (25.0)	124 (26.0)	119 (22.2)	371 (26.6)	12 111 (23.6)
16 013-54 443 USD	40 (49.4)	67 (47.8)	271 (56.9)	309 (57.6)	812 (58.1)	30 199 (58.8)
>54 443 USD	14 (17.3)	29 (20.7)	70 (14.7)	88 (16.4)	168 (12.0)	7431 (14.5)
Missing	3 (3.7)	9 (6.4)	11 (2.3)	20 (3.7)	46 (3.3)	1649 (3.2)
Smoking during pregnancy (1st and 2nd trimester)						
Yes	3 (3.7)	4 (2.9)	19 (3.9)	18 (3.4)	108 (7.7)	2851 (5.5)
No	62 (76.5)	107 (76.4)	370 (77.7)	413 (77.0)	1017 (72.8)	39 337 (76.5)
Stopped	3 (3.7)	11 (7.9)	24 (5.0)	34 (6.3)	95 (6.8)	3209 (6.2)
Missing	13 (16.0)	18 (13.0)	63 (13.0)	71 (13.0)	177 (12.6)	5993 (11.5)
Alcohol use during pregnancy[b] (1st and 2nd trimester)						
Yes	21 (25.9)	34 (24.3)	86 (18.0)	102 (19.0)	320 (22.9)	11,862 (23.0)
No	56 (69.1)	98 (70.0)	374 (78.6)	407 (75.0)	1016 (72.7)	37,530 (73.0)
Missing	4 (4.9)	8 (5.7)	16 (3.4)	27 (5.0)	61 (4.4)	1998 (3.8)
Mental comorbidities (1st and 2nd trimester)						
Medicated	9 (11.1)	5 (3.6)	29 (6.1)	25 (4.7)	51 (3.7)	1232 (2.4)
Nonmedicated	13 (16.0)	13 (9.3)	48 (10.1)	73 (13.6)	193 (13.8)	4938 (9.6)
No	59 (72.8)	122 (87.1)	399 (83.8)	438 (81.7)	1153 (82.5)	45 220 (87.9)

(Continues)

TABLE 1 (Continued)

Variables, n (%)	Decreasing-Low, n = 81	Increasing-Medium, n = 140	Constant-Medium, n = 476	Constant-High, n = 536	THRT after delivery, n = 1397	Nonhypothyroid group, n = 51 390
Somatic comorbidities[c] (1st and 2nd trimester)						
Medicated	10 (12.3)	15 (10.7)	46 (9.7)	80 (14.9)	90 (6.4)	1959 (3.8)
Nonmedicated	14 (17.3)	19 (13.6)	59 (12.4)	64 (11.9)	112 (8.0)	3462 (6.7)
No	57 (70.4)	106 (75.7)	371 (77.9)	392 (73.1)	1195 (85.6)	45 969 (89.4)
Gestational diabetes mellitus diagnosis	2 (2.5)	3 (2.1)	4 (0.8)	11 (2.0)	14 (1.0)	465 (0.9)
Recommended supplement use (1st and 2nd trimester)						
Yes	59 (72.8)	92 (65.7)	345 (72.5)	400 (74.6)	970 (69.4)	34 234 (66.7)
No	23 (28.4)	48 (34.3)	131 (27.5)	136 (25.4)	427 (30.6)	17 156 (33.3)
Fiber intake						
≥29.8 g/d	41 (50.6)	60 (42.8)	235 (49.4)	249 (46.5)	646 (46.2)	23 731 (46.2)
<29.8 g/d	40 (49.4)	80 (57.2)	241 (50.6)	287 (53.5)	751 (53.8)	27 659 (53.8)
Gender						
Boy	44 (54.3)	60 (42.8)	265 (55.7)	280 (52.2)	740 (52.9)	26 412 (51.4)
Girl	37 (45.7)	80 (57.2)	211 (44.3)	256 (47.8)	657 (47.0)	24 978 (48.6)
Thyroid diagnoses, n (%)						
Hypothyroidism[d] (ICD-10 code "e03")						
Yes	29 (35.8)	82 (58.6)	339 (71.2)	384 (71.6)	14 (1.0)	26 (0.05)
Hyperthyroidism (ICD-10 code "e05" from NPR only)						
Yes	1 (1.2)	0 (0.0)	2 (0.4)	3 (0.6)	0 (0.0)	2 (0.01)

Abbreviations: ICD-10 codes, International Classification of Diseases-10th Revision of diagnoses codes; MBRN, Medical Birth Registry of Norway; NPR, Norwegian Patient Registry; SD, standard deviation; US, United States of America; USD, US Dollar.

[a]Women's income status (USD/year): 1.00 NOK = 0.13 USD.

[b]Alcohol consumption, No stands for "less than once a month" and Yes for "once or more a month."

[c]Somatic comorbidity includes epilepsy, arthritis, anemia, diabetes mellitus (including gestational diabetes mellitus), and cardiovascular disorders.

[d]ICD-10 codes "e03" from NPR and MBRN. Thyroid diagnoses are available only for a subsample of the study population, because (a) reporting thyroid diagnoses is not mandatory in MBRN, and (b) information in NPR is incomplete if women got a diagnosis before 2008.

In the complete analysis of the trajectory analysis, birth weight (weighted mean difference [β] = 88; 95% CI, 30-145) and head circumference (β = .22; 95% CI, 0.05-0.39) in the Constant-High trajectory were significantly larger than in the nonhypothyroid group (Table S6).

4 | DISCUSSION

This study is the first to examine the impact of THRT trajectories in pregnancy on immediate perinatal outcomes and to include information on maternal thyroid hormone blood levels during gestation.

An increased risk of LGA infants was observed among women in the Increasing-Medium (69% magnitude) and THRT after delivery (19% magnitude) groups compared with the nonhypothyroid group. Given that the fetus relies entirely on maternal thyroid hormone production in the first 20 weeks,[37] late initiation of treatment during early gestation in the Increasing-Medium group might explain the observed increased risk of LGA.[38] Pregestational THRT use might also be necessary for women with diagnosed hypothyroidism to maintain maternal thyroid hormone levels within the reference range during early gestation.[39]

Hypothyroidism might be latent, for some time, before it is diagnosed and treated.[40] An underlying thyroid disorder during gestation among women in the THRT after delivery group might explain the LGA results.[40] Currently, there is no consensus about whether pregnant women should be screened for hypothyroidism in pregnancy.[40] Our results support current guidelines of selective screening of pregnant women for hypothyroidism early in gestation. Moreover, we recommend monitoring and tailoring of THRT to women with hypothyroidism in need of pharmacological treatment. There is however a need to further examine potential benefits of universal screening for the health of mother and child.

We found no significant risk of LGA infant for women that consistently used THRT (ie, women in the Constant-High and Constant-Medium groups). This is in contrast to results from a recent Finnish study, which showed that consistent users of THRT had a 26% increased risk magnitude of LGA infant (aOR = 1.26; 95% CI, 1.10-1.45) when compared with mothers without thyroid disease.[6] However, we excluded pregnancies with gestational age before 32 weeks,

TABLE 2 Trajectory analysis: Mean difference (β) and Odds Ratio (OR) in pregnancy outcomes (n = 54 020)

IPTW analysis[a]						
	Decreasing-Low, n = 81	Increasing-Medium n = 140	Constant-Medium, n = 476	Constant-High, n = 536	THRT after delivery, n = 1397	Nonhypothyroid group, n = 51 390
Outcome, β (95% CI)						**Reference**
Gestational age (d)	1.78 (−1.14 to 4.72)	−0.74 (−2.98 to 1.51)	−0.80 (−2.07 to 0.45)	−0.56 (−1.79 to 0.65)	−0.34 (−0.98 to 0.30)	279 (279,280)
Birth weight (g)	13 (−121 to 147)	38 (−70 to 145)	2 (−56 to 60)	32 (−24 to 87)	4 (−26 to 34)	3,593 (3,588,3,597)
Head circumference (cm)	0.05 (−0.31 to 0.36)	0.02 (−0.31 to 0.36)	−0.02 (−0.18 to 0.14)	0.13 (−0.03 to 0.30)	0.04 (−0.05 to 0.13)	35.27 (35.26,35.29)
LGA infant, n (%)	9 (11.1)	24 (17.1)	48 (10.0)	70 (13.0)	176 (12.6)	5,274 (10.3)
Outcome, OR (95% CI)						Reference
LGA infant	1.10 (0.52-2.32)	1.69 (1.06-2.73)	0.92 (0.66-1.28)	1.12 (0.84-1.52)	1.19 (1.01-1.42)	1
Crude analysis						
Outcome, β (95% CI)	Decreasing-Low, n = 81	Increasing-Medium n = 140	Constant-Medium n = 476	Constant-High, n = 536	THRT after delivery, n = 1397	Nonhypothyroid group, n = 51 390 Reference
Gestational age (d)	1.27 (−1.17 to 3.70)	−1.64 (−3.63 to 0.36)	−0.94 (−2.14 to 0.27)	−0.92 (−1.88 to 0.03)	−0.59 (−1.21 to 0.03)	279 (279-280)
Birth weight (g)	12 (−102 to 126)	16 (−78 to 113)	−1 (−53 to 51)	55 (10-100)	10 (−18 to 39)	3592 (3587-3597)
Head circumference (cm)	0.10 (−0.21 to 0.42)	−0.05 (−0.32 to 0.21)	0.00 (−0.14 to 0.15)	0.15 (0.02-0.28)	0.07 (−0.01 to 0.16)	35.27 (35.26-35.29)
Outcome, OR (95% CI)						Reference
LGA infant	1.09 (0.55-2.18)	1.80 (1.16-2.80)	0.98 (0.72-1.32)	1.31 (1.01-1.69)	1.26 (1.07-1.47)	1

Abbreviations: cm, centimeter; CI, confidence interval; g, gram; IPTW, inverse probability of treatment weighting; LGA, Large for gestational age (>90th percentile); OR, Odds Ratio; β, mean difference in pregnancy outcome.

[a]IPTW in the trajectory analysis: Weights were truncated at the 99th percentile.

and this might have introduced bias because of the selection of healthier pregnancies. Therefore, if more severe hypothyroidism would had been associated with (very) early preterm birth and LGA infant, this might explain why we observe no increase in risk for LGA infant for consistent THRT users, as opposed to Turunen et al.[6]

In the complete case analysis, infants of women in the Constant-High group had significantly higher birth weight and head circumference. This could be explained by the fact that women in this group were most often obese and had gestational diabetes.[41,42] Although we adjusted for BMI and maternal diabetes in the analysis, residual confounding and a role for unobserved maternal metabolic factors cannot be ruled out. Greater risk of selection bias in the complete case analysis might explain these significant effects, which disappeared after multiple imputation.

4.1 | Strengths

The clear strengths of this study are the large size of the study population, the combination of multifaceted data sources, inclusion of thyroid hormone blood levels, and advanced statistical analysis. To our knowledge, combining the generalized propensity score with exposure trajectories is a novel approach. This approach enabled us to minimize confounding bias;[43] in particular, we reduced the confounding by severity by including maternal thyroid hormone blood levels. A potential concern might be the use of prescription records rather than maternal self-reported THRT use. Prescription records do not necessarily represent actual medication use.[14] However, our approach is supported by results from Frank et al,[8] which showed "perfect" agreement (Cohen Kappa coefficient [κ] = 0.91; 95% CI, 0.89-0.92) between self-report and prescription records for THRT among Norwegian data sources during gestation.

To limit the risk of indication bias, we used information on thyroid diagnosis from the MBRN and NPR (ICD-10 codes "e03" and "e05") and additionally accounted for disease severity (blood levels, FT3, FT4, TSH, and TPOAb). This enabled us to verify that half of the women with hypothyroidism used medication to treat their condition. An effect can however not completely be rule out, because sensitivity and specificity of NPR and MBRN data have not been assessed for thyroid diagnoses.[44]

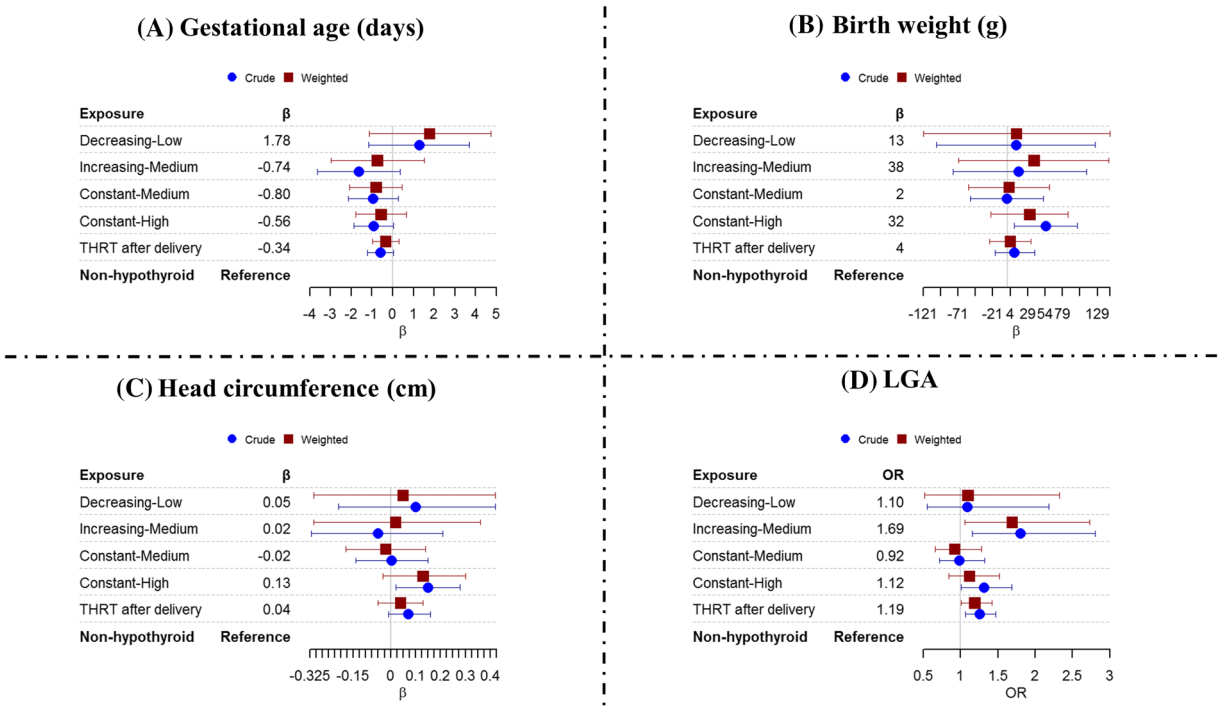

FIGURE 3 Trajectory analysis: Mean difference (*β*) and Odds Ratio (OR) in pregnancy outcomes. Abbreviations: LGA, large-for-gestational-age infant; OR, adjusted odds ratio; OR, odds ratio; *β*, weighted mean difference in pregnancy outcome; *β*, mean difference in pregnancy outcome [Colour figure can be viewed at wileyonlinelibrary.com]

To date, few pregnancy safety studies have investigated the effect of thyroid hormone exposure patterns on pregnancy outcomes.[45,46] Similar to a study by Hurault-Delarue et al[46], we captured an effect of treatment on the risk of LGA infants by splitting the medicated group into disjointed trajectories.

4.2 | Limitations

Selection bias is a well-known, acknowledged limitation of the MoBa cohort study.[9] Compared with the general Norwegian population, women in MoBa are known to be older, healthier, have higher educational levels, and are less likely to smoke during pregnancy.[10] All pregnancy outcomes were however within the normal range for a Norwegian infant.

Although we adjusted for measured confounders and thyroid hormone blood levels, we cannot rule out, for example, the influence of residual confounding by maternal disease severity in mid-late pregnancy, given that blood samples were taken in gestational week 18.

Given that Biobank is a nonrandom sample of MoBa, there is a possibility that information on blood levels is missing not at random. However, imputation of blood levels based on MAR assumption did not bias our results, as sensitivity analysis without inclusion of blood levels showed. This study warrants the need for future methodological development on using biological material from small, selected (non or) random subsamples in statistical analysis.[9]

According to power calculations, the present study could only detect large effect sizes.

5 | CONCLUSIONS

We found an increased risk of LGA infants among women initiating THRT late in pregnancy or after delivery. However, there was no evidence that the various THRT patterns had a substantial, differential effect on the other outcomes. The results of this study support current guidelines on the importance of THRT use during pregnancy and selective screening of pregnant women for hypothyroidism.

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CONFLICT OF INTEREST

The authors declare no conflict of interest related to this study.

ORCID

Anna S. Frank https://orcid.org/0000-0002-3728-3476
Angela Lupattelli https://orcid.org/0000-0002-8787-3183
Hedvig Nordeng https://orcid.org/0000-0001-6361-2918

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SUPPORTING INFORMATION

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