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Hyperthyroidism and birth defects

Maternal thyroid function, use of antithyroid drugs in early pregnancy and birth defects

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Context: Antithyroid drug (ATD) therapy in early pregnancy is associated with birth defects, but more data are needed to substantiate the risk associated with different types of ATD. Furthermore, the role of abnormal maternal thyroid function *per se* remains unclarified.
Objective: To evaluate the risk of birth defects associated with the use of ATD in an extended nationwide cohort and the role of abnormal maternal thyroid function in birth cohorts including stored maternal blood samples from the early pregnancy.
Participants: Danish pregnant women and their live-born children including 1,242,353 children from a Nationwide Register-Based Cohort (NRBC), 1997-2016; 8,803 children from the Danish National Birth Cohort (DNBC), 1997-2003; and 14,483 children from the North Denmark Region Pregnancy Cohort (NDRPC), 2011-2015.
Main outcome measures: Birth defects diagnosed before two years of age.
Results: In the NRBC, altogether 2,718 (0.2%) children had been exposed to ATD in early pregnancy. The overall frequency of birth defects was 6.7% (95% confidence interval (CI): 6.7-6.8%) in non-exposed children, and higher after exposure to Methimazole/Carbimazole (9.6% (95% CI: 8.2-11.2%)) and Propylthiouracil (8.3% (6.7-10.3%). On the other hand, the frequency of maternal thyroid dysfunction in early pregnancy was similar in the random cohort and in cases of birth defect in the DNBC (12.4 vs. 12.6%, p=0.8) and the NDRPC (15.1 vs. 15.4%, p=0.8).

Conclusions: Results corroborate an increased risk of birth defects associated with the use of ATD in early pregnancy, and suggest that abnormal maternal thyroid function is not a major risk factor for birth defects.

The risk of birth defects after early pregnancy exposure to antithyroid drugs and abnormal maternal thyroid function was evaluated in a Danish nationwide register-based cohort and in birth cohorts. .

Introduction

Antithyroid drug (ATD) is preferred for the treatment of hyperthyroidism in pregnancy (1,2). The hyperthyroidism of Graves' disease (GD) in pregnant women should be treated to prevent maternal and fetal complications, but raises a concern regarding the risk of birth defects associated with the use of ATD (3). An embryopathy of specific, severe birth defects associated with the use of Methimazole (MMI) and Carbimazole (CMZ) has been known for years, but analytical observational studies were not reported until a decade ago (4). These findings have challenged and re-phrased the clinical guidance for the management of hyperthyroidism in pregnant women, because birth defects have been associated with MMI/CMZ, and also with PTU (5). Thus, a clinical focus on balancing the need for treatment against the potential teratogenic side effects has been introduced in revised clinical guidance, although the evidence regarding ATD withdrawal in early pregnancy is at present inadequate (1,2). An increased risk of birth defects associated with the use of MMI/CMZ has been consistently described (6–8). On the other hand, human observational as well as experimental animal studies have shown divergent results considering the risk of birth defects after exposure to PTU (6–11). Uncertainty remains regarding the risk of birth defects associated with the different types of ATD, and more data are needed.

We previously evaluated the risk of birth defects in a nationwide study of all children in Denmark born from 1996 to 2008 (7). We now extended the cohort and included children born during the 20-year period from 1997 to 2016. Furthermore, we measured maternal thyroid function in stored blood samples from pregnant women who were part of different birth cohorts in Denmark in the years 1997-2003 and 2011-2015. This allowed for the evaluation of the unresolved role of maternal thyroid function *per se* in the development of birth defects.

Materials and methods

Study population

The study included a Nationwide Register-Based Cohort (NRBC), participants from the Danish National Birth Cohort (DNBC) and participants from the North Denmark Region Pregnancy Cohort (NDRPC). The NRBC included all children live-born in Denmark from January 1, 1997 to December 31, 2016 who were identified in the Danish Medical Birth Register (MBR) (12) and had available information on gestational age at birth (Figure 1). The registration procedure in the MBR was changed from January 1, 1997 and only children born from 1997 and onwards were included in the present study to ensure similar registrations throughout the study period. The NRBC was used to evaluate the association between maternal use of ATD and birth defects, but no information on biochemical measurements were available in the register-based cohort.

The DNBC and the NDRPC included the measurement of maternal thyroid function in a stored blood sample from the early pregnancy, and these cohorts were used to evaluate the association between abnormal maternal thyroid function and birth defects. The DNBC was established from 1997-2003 and included 77,671 children live-born in Denmark (Figure 1). For the present case-cohort study, pregnant women were selected as part of a 12% random sub-

cohort (n=7,624) and/or because their child was diagnosed with birth defects within two years of follow-up (n=1,383). The NDRPC was established from 2011-2015. It included all pregnant women in the North Denmark Region who had a blood sample drawn in early pregnancy as part of prenatal screening for chromosomal anomalies and women who gave birth to a singleton live-born children were included in the study (Figure 1).

The study and the data handling were approved by the Danish data protection Agency (J.nr. 2008-58-0028). Furthermore, the biochemical measurements in stored blood samples was approved by the North Denmark Region Committee on Health Research Ethics (N-20130054 and N-20150015).

Exposure definitions

In the NRBC, the exposure of main interest was the use of ATD in early pregnancy, which was assessed from redeemed prescriptions of the drugs in the period ranging from six months prior to pregnancy start up to and including the 10th week of pregnancy, as described previously in detail (7). The Danish National Prescription Register (DNPR) (13) includes information on redeemed prescriptions of drugs coded according to the Anatomical Therapeutical Classification (ATC) system, and drugs used for the treatment of thyroid disease are included in the ATC group: H03. The latest redeemed prescription prior to pregnancy start (or the first in pregnancy if no previous treatment) was used to determine the exposure status in the early pregnancy, and women who redeemed both MMI/CMZ and PTU after pregnancy start were grouped separately and considered 'double' exposed. CMZ is a prodrug to MMI and was combined with MMI and described as MMI exposure in the present study. The non-exposed group was defined as children whose mother had no diagnosis of hyperthyroidism, no registration of thyroid surgery and no redeemed prescription of ATD or Levothyroxine before, during or after the pregnancy under study and up to December 31, 2017.

In the DNBC and NDRPC, the exposure of interest was abnormal maternal thyroid function, which was assessed from the measurement of TSH and free T4 (fT4) in a stored blood sample from the early pregnancy (median week 9-10), as described previously in detail (14,15). Thyroid function parameters were measured using a Dimension Vista (Siemens Healthineers, Germany) immunoassay in the DNBC and an Advia Centaur (Siemens Healthineers, Germany) immunoassay in the NDRPC. In both cohorts, pregnancy week specific reference ranges had been established (14,15) and were used for the classification of maternal thyroid function as normal (euthyroid) or abnormal (overt and subclinical hyper- and hypothyroidism as well as isolated low and high fT4).

Outcome assessment

Information on birth defects in the child was assessed from in- and outpatient hospital diagnoses in the Danish National Hospital Register (DNHR) (16) coded according to the 10th International Classification of Disease (ICD-10). All diagnoses of birth defects (ICD-10: Q00-Q99) diagnosed before the child was two years old were assessed in the NRBC and grouped in accordance with our previous report (7). In the DNBC, children were selected for the study if they had a diagnoses within the eight groups of birth defects (Q10-15 (eyes), Q18 (face and neck, others), Q20-28 (circulatory), Q30-38 (respiratory), Q39-45 (digestive), Q60-64 (urinary), Q79 (musculoskeletal, others), Q80-84 (integumentary system) previously associated with the use of ATD (7), and these groups of birth defects were likewise assessed in the NDRPC.

Statistical analyses

In the NRBC, the frequency of birth defects by ATD exposure was compared using Chi-square test. Furthermore, we reported the results of a Cox proportional hazards model (hazard ratio (HR) with 95% confidence interval (95% CI) adjusting for multiple birth, maternal age, parity, and smoking (from the MBR), origin (from Statistics Denmark), and diabetes (from the DNHR and DNPR). Information on maternal pre-pregnancy body mass index (BMI) was only available in the MBR from 2004 and onwards and was included in a sub-analyses. In the DNBC and NDRPC, the association between abnormal maternal thyroid function and birth defects was evaluated using a Cox proportional hazards model, which was a weighted model in the DNBC to account for the sampling procedure and the overlap between cases and the random sub-cohort, as previously described (17). The adjusted model evaluating these associations included information on maternal age, parity, origin, smoking, BMI, and diabetes.

Results

Study populations

The extended NRBC cohort included 1,242,353 pregnancies (Figure 1 and Table 1) corresponding to the birth year period of the previous cohort (1997-2008) and the later cohort (2009-2016). The DNBC included a total of 8,803 pregnancies and 14,483 pregnancies were included in the NDRPC (Figure 1 and Table 1).

The cohorts were established during a 20-year period, which introduced some differences in maternal characteristics (Table 1). Notably, maternal age increased over time, but was lower in the NDRPC compared with the national cohort around the same time, which is compatible with known regional differences in Denmark. The frequency of maternal smoking in pregnancy decreased over time, whereas the frequency of maternal diabetes and non-Danish origin increased. As expected, the frequency of non-Danish origin was lower in the DNBC (Table 1) since one of the selection criteria in this cohort was the ability to speak Danish well enough to participate in a sequence of telephone interviews.

ATD and birth defects

Altogether 2,718 children (0.2%) had been exposed to maternal use of ATD in early pregnancy in the extended NRBC cohort. MMI was the most frequently used ATD both in the extended and in the previous cohort, and the ratio of MMI to PTU exposure was 2.0 in the previous and 1.8 in the extended cohort (Table 2).

A total of 83,875 children (6.8%) were diagnosed with a birth defect before two years of age in the extended NRPC cohort. An increasing trend in the frequency of birth defects according to birth year of the child was observed throughout the study period (Figure 2), which was less pronounced for the specific subtypes of birth defects previously associated with the use of ATD.

Exposure to MMI was associated with a significantly higher prevalence of birth defects, both when evaluating all birth defects and the defects previously associated with the use of ATD (Table 2). For exposure to PTU, a higher frequency of birth defects was observed in the extended and in the previous cohort compared with non-exposed, but the association was weakened in the extended cohort. Looking at subgroups of birth defects in the extended cohort (Table 3), MMI exposure was associated with birth defects in seven organ systems, whereas PTU revealed an association with face and neck defects and urinary system malformations only.

Exposure to MMI was associated with a high risk (adjusted hazard ratio 20 (95% confidence interval: 12-34)) of the group of specific malformations considered part of an MMI embryopathy (aplasia cutis, esophageal atresia, choanal atresia, and omphalocele). A small group of children (n=255) were exposed to both MMI and PTU in early pregnancy, because the mother shifted

from MMI to PTU after pregnancy start (n=240) or from PTU to MMI (n=15). The frequency of the subgroups of birth defects previously associated with the use of ATD was 5.0% when the mother shifted to PTU after pregnancy start versus 3.1% in non-exposed (p=0.09).

The associations between the use of ATD and birth defects were similar when the period for evaluation of exposure was narrowed to three months prior to pregnancy start or to the early pregnancy weeks. Furthermore, results did not change when the follow-up period for assessment of birth defects in the child was reduced to one month, one year, or extended to five year or complete follow-up (median to age 11 years (range 1-21 years)).

Maternal thyroid function and birth defects

The association between maternal thyroid function in pregnancy and birth defects was evaluated in the DNBC and in the NDRPC (Table 4). The overall frequency of abnormal thyroid function was 12.5% in the DNBC and 15.1% in the NDRPC. In both cohorts, the overall frequency of abnormal thyroid function did not differ between the randomly sampled cohort and cases of birth defects (Table 4). For subtypes of maternal thyroid dysfunction, no associations with birth defects were observed, except for an association with overt hypothyroidism in the DNBC.

When considering subtypes of birth defects in children exposed to overt hypothyroidism in the DNBC, it appeared that this association was dominated by malformations of the eye and of the circulatory system, but numbers were too sparse to perform stratified adjusted analyses. Results were similar when analyses were restricted to pregnancies in which the blood sample was drawn prior to pregnancy week 11 (n=6,715 in the DNBC; n=10,343 in the NDRPC), or to pregnancies in which the mother received no current treatment with ATD or Levothyroxine at the time of blood sampling (n=8,791 in DNBC; n=14,290 in NDRPC).

Discussion

In a large extended nationwide cohort of more than one million children live-born in Denmark during a 20-year period, an increased risk of birth defects associated with the use of ATD in early pregnancy was corroborated. The sub-types of birth defects associated with the use of MMI and PTU differed, and MMI exposure revealed the highest risk and associations with severe birth defects in several organ systems. On the other hand, birth defects observed after early pregnancy exposure to PTU were mostly located in the urinary system and in the face and neck. The role of maternal thyroid function was addressed in independent birth cohorts, and results did not indicate that abnormalities in maternal thyroid function in early pregnancy *per se* is a major risk factor for birth defects.

The use of ATD for the treatment of hyperthyroidism was discovered in the 1940s and still play a dominant role in the management of patients (18). A main concern about the use of ATD in non-pregnant and pregnant individuals is the risk of severe side effects, and treatment of pregnant women is specific for the risk of birth defects (4). Severe birth defects after the use of MMI in early pregnancy were described in the 1970s (19), but it was not until 2011 that the first observational case-control study was published (20). Since then, a series of observational studies have been conducted (6–8,21–24), and evidence suggests a risk of birth defects associated with the use of MMI, and more recently also with PTU. Nevertheless, the findings differ between studies and many methodological considerations are of importance when studying relatively rare outcomes that need to survive until birth. A notable disparity between the studies that reported an association and those that found no association is the number of exposed children. Thus, the studies that found an association with the use of MMI in early pregnancy included more than 1000 MMI-exposed children (5). Another disparity is the type and timing of outcome assessment

in the child. Birth defects are by definition present at birth, but the defects may not be detected clinically at birth, and less severe malformations may be diagnosed at a later age (4).

The present study is an extension of our previous report published in 2013, in which we reported that both MMI and PTU were associated with birth defects diagnosed before the child was two years old in a nationwide cohort of children born in Denmark from 1996-2008 (7). The finding of an MMI embryopathy was consistent with case reports (25,26) and a large observational study from Japan published in 2012 (6), but the finding of a risk of birth defects associated with PTU was new and merited further investigation (27). We now had data to extend the cohort to include children born in Denmark during a 20-year period from 1997-2016. We strictly applied the same methodology regarding the definition of exposure and outcome and evaluated the overall prevalence of birth defects as well as subgroups of birth defects. Overall, results corroborated an association with MMI, but the association between maternal use of PTU in early pregnancy and birth defects was attenuated and at the border of statistical significance in the extended cohort. This disparity in the association observed in the previous and the extended cohort call into question the accuracy of the previous finding and supports a focus on this association to settle if it was coincidental. Thus, it was an important finding that MMI and PTU revealed associations with the same specific subtypes of birth defects in the extended cohort as in the previous cohort, and the disparity between MMI and PTU for subgroups of birth defects prevailed. This consistency in the associations observed supports an association. For PTU, an association with malformations in the face and neck region and in the urinary system was observed both in the previous and in the extended cohort although no new cases of PTU associated malformations of the face and neck region were identified in the extended cohort, while two new cases of malformation of the urinary system were seen. It is important to notice that subtypes of malformations are rare and face and neck malformations occurred in 0.08% of non-exposed children. Thus, even though we extended the cohort with eight more years, the lack of new cases may reflect the low prevalence of these malformations. This emphasizes the importance of future extended follow-up. Another consideration is the registrations of birth defects. If any, we would expect an increased diagnostic activity, which was apparent from the increase in the overall prevalence of birth defects in the extended cohort. However, for the sub-types of birth defects previously associated with the use of ATD, the prevalence did not show a similar change. In addition, the clinical focus on side effects to the use of ATD brought forward by publications in 2012-2013 (6,7) may have influenced the awareness and the registration although international clinical guidance was revised in 2016-2017 (1,2), which overlaps the end of the study period in the extended cohort. Furthermore, only a slight change in the ratio of MMI to PTU exposure was observed between the previous and the extended cohort indicating no major change in clinical practice.

A strength of the present study was the large extended study population, which enabled us to study a relatively rare exposure and outcomes. Another register-based study using Korean National Health Insurance databases was published in 2018 and included more than two million live-born children (8). Similar to our findings, both MMI and PTU exposure was associated with birth defects in this study, and the authors further showed a dose-dependent association with MMI. We did not have information on the dose of ATD in the Danish nationwide registers, and we do not know if the women actually took the prescribed drug, but a strength of our study was the detailed assessment of ATD exposure. We considered all prescriptions of ATD in the period before and in early pregnancy and the last redeemed prescription prior to pregnancy start defined the type of ATD exposure in the first pregnancy weeks. This methodological aspect is important

when using indirect measures of exposure from redeemed prescriptions of drugs (28). A clinical focus is on the timing of a shift in therapy from MMI to PTU around pregnancy start and the possibility of ATD withdrawal (1,2). In our previous and extended cohort and in the study from Korea (8), a higher risk of birth defects was observed in women who shifted from MMI to PTU treatment after pregnancy start. We previously evaluated these cases in detail and although the number of exposed cases was limited, this evaluation showed that the timing of a shift in therapy may be important to reduce MMI exposure (29). Further studies are needed to evaluate the outcomes of birth defects in women who shifted from MMI to PTU before or during the early pregnancy period as well as the outcomes of ATD withdrawal in early pregnancy, and large study populations are required to obtain a sufficient number of exposed cases.

The role of maternal thyroid function *per se* in early pregnancy for the risk of birth defects remains unclarified. A study by Momotani et al. published in 1984 concluded that uncontrolled maternal hyperthyroidism may cause congenital malformations and that the beneficial role of MMI treatment outweighs its teratogenic risks (30). Only few studies addressed this role of maternal hyperthyroidism since then (6,31). We now had the opportunity to investigate the role of maternal thyroid function in two independent birth cohorts. The assessment was based on a single measurement of TSH and fT4 in a blood sample from early pregnancy, and we acknowledge that repeated testing would have been preferred. The overall findings did not indicate that abnormal maternal thyroid function was a risk factor for birth defects. This observation is in line with the study from Japan (6) in which the authors had access to the review of medical records and thereby results of thyroid function testing from women with GD, who became pregnant. We observed that maternal overt hypothyroidism was a risk factor for birth defects in one cohort, and the exposed cases predominantly had malformations of the circulatory system. This finding extends a previous case-control study in which maternal hypothyroidism was associated with congenital heart disease in the offspring (32). These observations encourage further investigations and it may be speculated if hypothyroidism secondary to overtreatment of maternal hyperthyroidism with ATD could be a risk factor for birth defects. However, we observed similar findings when women who received current treatment for thyroid disease at the time of blood sampling were excluded from the analyses. The mechanisms by which ATD exposure increases the risk of birth defects is not known, and the role of thyroid autoimmunity *per se* is intriguing and unclarified. However, in the Danish (7) and Swedish (24) nationwide studies we did not see a higher risk of birth defects in women who were diagnosed with hyperthyroidism and received no ATD treatment in the pregnancy.

From a clinical perspective, results of the present study corroborates a risk of severe birth defects associated with the use of MMI in early pregnancy and supports the use of PTU in early pregnancy as put forward in clinical guidance (1,2). Further and large studies are needed to investigate the risk associated with PTU and to evaluate outcomes of a shift in therapy. Detailed assessment of the timing of exposure up to and after the start of a pregnancy is crucial to inform this debate.

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Disclosure summary:
the authors have nothing to disclose

Data Availability

Restrictions apply to the availability of data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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Figure 1. Flowchart illustrating the selection of the study populations.

Figure 2. Prevalence of birth defects (all types combined as well as the subtypes previously associated with the use of antithyroid drug in early pregnancy) diagnosed before two years of age in children live-born in Denmark from 1997 to 2015.

Table 1 Maternal **c**haracteristics in the extended, previous and later Nationwide Register-Based Cohort (NRBC), in the Danish National Birth Cohort (DNBC) and in the North Denmark Region Pregnancy Cohort (NDRPC)

	NRBC (extended)		**NRBC (previous)**		**NRBC (later)**		**DNBC**		**NDRPC**	
Pregnancies (n)	1,242,353		771,103		472,250		8,803		14,483	
Birth year of the child	1997-2016		1997-2008		2009-2016		1997-2003		2011-2015	
Maternal characteristics	n	%	n	%	n	%	n	%	n	%
Maternal age										
< 30 years	574,412	46.2	368,977	47.8	205,448	43.5	4,326	49.0	7,520	51.9
≥ 30 years	668,928	53.8	402,126	52.2	266,802	56.5	4,504	51.0	6,963	48.1
Maternal parity[1]										
Nulliparous	550,134	44.8	331,264	43.6	218,870	46.7	4,415	50.0	6,719	46.4
Multiparous	678,810	55.2	428,654	56.4	250,156	53.3	4,415	50.0	7,761	53.6
Maternal smoking in pregnancy[2]										
No smoking	959,795	84.1	549,024	81.3	410,771	88.3	6,436	72.9	12,789	88.4
Smoking	180,816	15.9	126,578	18.7	54,238	11.7	2,392	27.1	1,678	11.6
Maternal pre-pregnancy BMI[3]										
< 30 kg/m^2	668,213	87.7	265,623	88.4	402,590	87.2	7.963	91.7	12,156	84.0
≥ 30 kg/m^2	93,563	12.3	34,698	11.6	58,865	12.8	724	8.3	2,312	16.0
Maternal co-morbidity										
No diabetes	1,156,212	93.0	723,104	93.8	433,108	91.7	8,550	96.8	13,183	91.0
Diabetes	87,141	7.0	47,999	6.2	39,142	8.3	280	3.2	1,300	9.0
Maternal origin[4]										
Born in Denmark	1,054,494	84.8	669,121	86.8	385,373	81.7	8,644	97.9	12,838	88.6
Not born in Denmark	188,508	15.2	101,936	13.2	86,572	18.3	183	2.1	1,645	11.4

Abbreviations: BMI; body mass index
[1]Missing information on parity (n=14,409) not included.
[2]Missing information on maternal smoking in pregnancy only available from 1998 onwards, missing information (n=102,742) not included.
[3]Information on maternal pre-pregnancy BMI only available from 2004 and onwards, missing information (n=481,577) not included.
[4]Missing information on maternal origin (n=351) not included.

Table 2 Frequency of birth defects diagnosed before 2 years of age and corresponding crude hazard ratio (cHR) and adjusted hazard ratio (aHR) with 95% confidence intervals (95% CI) according to maternal use of antithyroid drug (ATD) in early pregnancy.

	Children	All birth defects[1]						Subtypes of birth defects[2]					
	n	n	%	p[3]	cHR	aHR[4]	95% CI	n	%	p[3]	cHR	aHR[4]	95% CI
Cohort 1997-2016													
Non-exposed[5]	1,159,181	77,791	6.7	ref.	ref.	ref.	ref.	35,953	3.1	ref.	ref.	ref.	ref.
Methimazole	1,574	151	9.6	< 0.001	1.46	1.41	1.19-1.67	100	6.4	< 0.001	2.08	2.04	1.66-2.51
Propylthiouracil	889	74	8.3	0.060	1.25	1.17	0.91-1.49	39	4.4	0.031	1.42	1.36	0.98-1.92
Cohort 1997-2008													
Non-exposed[5]	713,683	41,717	5.9	ref.	ref.	ref.	ref.	19,067	2.7	ref.	ref.	ref.	ref.
Methimazole	1,050	94	9.0	< 0.001	1.56	1.46	1.17-1.81	64	6.1	< 0.001	2.33	2.25	1.73-2.93
Propylthiouracil	528	47	8.9	0.003	1.55	1.48	1.08-2.02	27	5.1	0.001	1.94	1.89	1.26-2.85

[1]ICD-10 diagnoses: Q00-99.
[2]ICD-10 diagnoses: Q10-15, Q18, Q20-28, Q30-38, Q39-45, Q60-64, Q79, and Q80-84.
[3]p-value is the result of comparison with the non-exposed group using Chi-square test.
[4]Adjusted for maternal age, parity, multiple birth, origin, diabetes, and smoking.
[5]No diagnosis of hyperthyroidism, no redeemed prescription of antithyroid drugs or Levothyroxine, and no thyroid surgery from 1995-2017.

Table 3 Frequency of subgroups of birth defects diagnosed before 2 years of age in the combined NRBC cohort of children born 1997-2016 according to maternal use of antithyroid drug (ATD) in early pregnancy.

	Non-exposed[1]		Methimazole			Propylthiouracil		
	n = 1,159,181		n = 1,574			n = 889		
	n	%	n[2]	%	p[3]	n[2]	%	p[3]
Subgroups of birth defects (Q00-99)								
Nervous system (Q00-07)	1,180	0.10	<3	<0.3	0.6	<3	<0.3	0.9
Eye (Q10-15)	2,480	0.21	7	0.44	0.05	0	0.00	0.2
Ear (Q16-17)	773	0.07	<3	<0.3	0.4	<3	<0.3	0.07
Face and neck, others (Q18)	907	0.08	0	0.00	0.3	3	0.34	0.006
Circulatory system (Q20-28)	15,195	1.31	39	2.48	<0.001	16	1.80	0.2
Respiratory system (Q30-38)	9,636	0.83	23	1.46	0.006	12	1.35	0.09
Digestive system (Q39-45)	3,251	0.28	16	1.02	<0.001	<3	<0.3	0.8
Genital organs (Q50-56)	12,182	1.05	15	0.95	0.7	9	1.01	0.9
Urinary system (Q60-64)	4,125	0.36	12	0.76	0.007	7	0.79	0.03
Musculoskeletal system (Q65-78)	29,260	2.52	34	2.16	0.4	26	2.92	0.4
Muscoloskeletal system, others (Q79)	925	0.08	7	0.44	<0.001	0	0.00	0.4
Integumentary system (Q80-84)	2,002	0.17	11	0.70	<0.001	<3	<0.3	0.7
Others (Q85-99)	5,532	0.48	9	0.57	0.6	4	0.45	0.9

[1]No diagnosis of hyperthyroidism, no redeemed prescription of antithyroid drugs or Levothyroxine, no thyroid surgery 1995-2017.
[2]Subgroups with less than three cases were reported as <3 according to the regulations for the use of register-based data.
[3]p-value is the result of comparison with the non-exposed group using Chi-square test.

Table 4 Frequency of subtypes of birth defects diagnosed before 2 years of age and the associated crude hazard ratio (cHR) and adjusted hazard ratio (aHR) with 95% confidence interval (95% CI) according to maternal thyroid function in early pregnancy.

	Sub-cohort		Birth defects[1]				
	n	%	n	%	cHR	aHR[2]	95% CI

Danish National Birth Cohort (DNBC)							
No thyroid dysfunction	6,673	87.5	1,209	87.4	ref.	ref.	ref.
Thyroid dysfunction	951	12.5	174	12.6	1.02	1.02	0.86-1.22
Hyperthyroidism							
Overt hyperthyroidism	118	1.55	16	1.16	0.75	0.77	0.46-1.30
Subclinical hyperthyroidism	153	2.01	26	1.88	0.94	0.91	0.60-1.39
Isolated high free T4	149	1.95	25	1.81	0.95	1.01	0.66-1.55
Hypothyroidism							
Overt hypothyroidism	55	0.72	19	1.37	1.98	1.91	1.12-3.25
Subclinical hypothyroidism	302	3.96	53	3.83	0.95	0.95	0.70-1.29
Isolated low free T4	174	2.28	35	2.53	1.11	1.15	0.79-1.65
North Denmark Region Pregnancy Cohort (NDRPC)							
No thyroid dysfunction	12,300	84.9	490	84.6	ref.	ref.	ref.
Thyroid dysfunction	2,183	15.1	89	15.4	1.03	1.03	0.82-1.30
Hyperthyroidism							
Overt hyperthyroidism	218	1.51	12	2.07	1.39	1.49	0.84-2.64
Subclinical hyperthyroidism	330	2.28	10	1.73	0.75	0.79	0.42-1.48
Isolated high free T4	249	1.72	6	1.04	0.59	0.60	0.27-1.34
Hypothyroidism							
Overt hypothyroidism	145	1.00	5	0.86	0.86	0.86	0.36-2.09
Subclinical hypothyroidism	752	5.19	33	5.70	1.11	1.08	0.76-1.53
Isolated low free T4	489	3.89	23	3.97	1.19	1.19	0.79-1.82

[1]ICD-10 diagnoses: Q10-15, Q18, Q20-28, Q30-38, Q39-45, Q60-64, Q79, and Q80-84.
[2]Adjusted model included: maternal age, parity, origin, smoking, bmi, and diabetes.

Figure 1

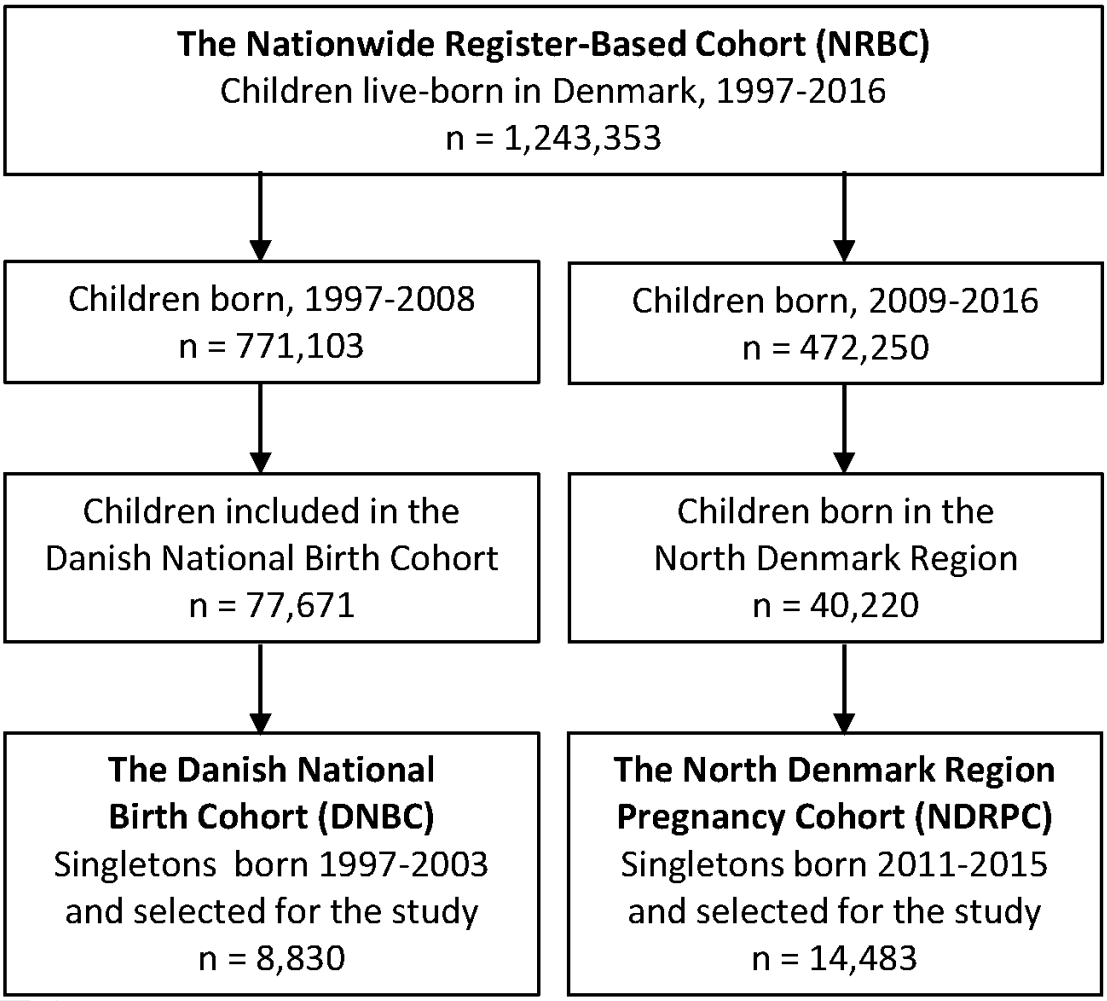

Figure 2