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Maternal thyroid disease and adiposity in mother and child

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Summary

Objective: Thyroid hormones are crucial developmental factors and thyroid disease in pregnant women is a concern. Overweight and obesity are also important health concerns, and we hypothesized that *in utero* exposure to maternal thyroid disease could program the fetus to development of adiposity.

Design: Cohort and case-cohort studies

Participants: Pregnant women from the Danish National Birth Cohort and their 7-year old children.

Measurements: Maternal thyroid disease (hyperthyroidism and hypothyroidism) was assessed from registrations of diagnoses and treatment (n = 71,706) or from the measurement of thyroid-stimulating hormone (TSH) in a stored blood sample from the early pregnancy (n = 7,624). Maternal pre-pregnancy body mass index (BMI) and child BMI at 7 years of age were used to define overweight and obesity, and associations were evaluated using regression models adjusting for potential confounders.

Results: No association was found between maternal thyroid disease in pregnancy and child overweight (hyperthyroidism: adjusted risk ratio (aRR): 1.02 (95% confidence interval (CI): 0.58-1.82); hypothyroidism: 1.31 (0.86-1.97)) or obesity (hyperthyroidism: 0.96 (0.53-1.75); hypothyroidism: 1.25 (0.76-2.05)). On the other hand, pregnant women with hypothyroidism in early pregnancy had a higher risk of being overweight (aRR: 1.20 (95% CI: 1.03; 1.41)) and obese (1.45 (1.07; 1.96)), whereas women with hyperthyroidism had a lower risk of being overweight (0.79 (0.64; 0.98)).

Conclusions: Results provide no evidence that maternal thyroid disease in pregnancy programs adiposity in the child, but corroborate an association between maternal thyroid disease and adiposity in the mother.

Key words

Pregnancy, hyperthyroidism, hypothyroidism, bmi, obesity, overweight, fetal programming

Introduction

Fetal development is a complex, tightly and timely regulated process, and an adequate level of thyroid hormones is important. Thyroid hormones present in the fetus in the early pregnancy originate from the mother, and this dependency emphasizes the importance of maternal thyroid function.[1] Consequently, much concern is on thyroid disease in pregnant women which in turn could affect the supply of thyroid hormones to the fetus.[2] The most important consequences of thyroid disease in pregnant women relate to the crucial role of thyroid hormones during brain development.[1] Thus, a hypothesis of fetal programming by maternal thyroid disease via disturbed fetal brain development is biologically plausible and supported by experimental data.[3] Thyroid hormones play a regulatory role in every cell in the human body, and the hypothesis of fetal programming by maternal thyroid disease may extend beyond brain development. Hence, it has been proposed that maternal thyroid disease may program the offspring to later development of asthma, cardiovascular disease, and metabolic alterations.[4–7] Overweight and obesity are important health concerns and much attention is on the identification of risk factors.[8] It has also been proposed that *in utero* exposures could program the fetus to abnormal body weight in later life.[9,10]

We hypothesized that maternal thyroid disease in pregnancy could program the fetus to the development of adiposity in childhood. We evaluated the hypothesis among pregnant women and their 7-year-old children from the Danish National Birth Cohort (DNBC) using different designs and different markers of adiposity. Maternal body mass index (BMI) is a strong determinant of BMI in the child,[9] and maternal BMI could be a possible confounding factor in the association between maternal thyroid disease and child adiposity. Thus, we initially described the association between maternal thyroid disease and adiposity in the mother and subsequently included maternal BMI in the adjusted analyses on child outcomes.

Method and materials

Study design and population

The DNBC was established in Denmark from 1997-2003 and recruited 101,042 pregnancies in which the pregnant woman lived in Denmark and was able to participate in telephone interviews in Danish during the pregnancy.[11] Participants in the present study were pregnant women from the DNBC who gave birth to a singleton, live-born child, and the woman's first-born child during the study period was included. Furthermore, the participants all had a blood sample drawn in the early pregnancy weeks. A total of 71,706 pregnant women fulfilled these criteria and comprised the source population in the present study (Fig. 1).

The DNBC also included the biochemical measurement of maternal thyroid function in early pregnancy within a 12% random sample of the source population (Fig. 1).[12,13] Thus, participants from the source population and from the random sample were included for assessment of maternal (Fig. 1, part I) and child health (Fig. 1, part II).

Maternal health was assessed in cross-sectional studies that evaluated the association between maternal thyroid disease and maternal adiposity (Fig. 1, part I). These studies included all pregnant women from the source population with available data on pre-pregnancy BMI (Fig. 1, part Ia) as well as all pregnant women from the random sample who had information on pre-pregnancy BMI and biochemical assessment of thyroid function in pregnancy (Fig. 1, part Ib).

Child health was assessed in cohort studies and in a case-cohort study (Fig. 1, part II). The DNBC included a 7-year follow-up of the children in which the parents were asked to fill out a questionnaire about the child. The age of the child at follow-up ensured the possibility to cover the pre-school age since children in Denmark on average start elementary school at 7 years of age. Overall, the rate of participation in this follow-up was 60-65%, and a total of 43,073 pregnant women from the source population participated in the follow-up when the child was median 7.1 years old (range 7.0 to 7.99 years).[14] In the present study, children who participated in this follow-up and had available data on BMI were included in a cohort study (Fig. 1, part IIa). Similarly were children whose mother was part of the random sample and had thyroid function assessed in early pregnancy (Fig. 1, part IIb). Finally, a case-cohort study was performed in which all children in the source population with a BMI corresponding to obesity at 7 years of age were included (cases) together with individuals from the 12% random sample (sub-cohort) (Fig. 1, part IIc).

Exposure

In part Ia and IIa (Fig. 1), maternal thyroid disease was assessed from nationwide health registers and from a telephone interview in the early pregnancy. The Danish National Hospital Register (DNHR) holds information on all in- and outpatients hospital visits including diagnoses of disease coded according to the International Classification of Disease (8th edition from 1977-1993; 10th edition from 1994 and onwards). The Danish National Prescription Register (DNPR) holds information on all prescriptions of drugs redeemed from Danish pharmacies from 1995 including the type of drug coded according to the anatomical therapeutic classification. As previously described in detail,[15] information on maternal thyroid disease was obtained before, during and up to five years after the pregnancy and the different registrations were combined to classify maternal hyperthyroidism and hypothyroidism and the onset of disease.

In part Ib, IIb and IIc (Fig. 1), maternal thyroid disease was assessed from the measurement of thyroid-stimulating hormone (TSH) in a stored blood sample from the early pregnancy. The blood sample had been stored at minus 20 degrees Celsius in the Danish National Biobank since the time of collection and was

thawed in the year 2015 for the measurement of TSH using a Dimension Vista automated immunoassay (Siemens Healthineers, Germany), as previously described in detail.[12] Thyroid hormones are considered stable during long-term storage and freezing/thawing.[16] Maternal thyroid disease was classified according to the method- and pregnancy week-specific reference ranges previously established within the cohort.[12] We *a priori* decided to focus our hypothesis and the analyses on maternal thyroid disease defined by TSH alone.[17] Hyperthyroidism was defined by a TSH below the pregnancy week-specific 2.5 percentile and hypothyroidism by a TSH above the 97.5 percentile. In a sub-analyses, associations were evaluated according to the severity of maternal thyroid disease defined by the level of TSH in early pregnancy.

Outcome

Maternal pre-pregnancy BMI and child BMI at 7 years of age were calculated as body weight in kilograms (kg) divided by the height in meters squared (m^2). Information on maternal height and weight was assessed from the self-reported information in the early pregnancy interview and 70,487 pregnant women from the source population had available data on BMI (Fig. 1, part Ia). Maternal BMI $\geq$ 25.0 kg/m^2 was the main outcome measure, which combined overweight and obesity. Maternal obesity (BMI $\geq$ 30.0 kg/m^2) was less frequent, but also evaluated in a sub-analysis.

The parents reported information on the latest measured height and weight of the child at 7 years of age and 40,585 children had available data for calculation of BMI (Fig.1 , part IIa). The measurements were made by the school doctor, public health nurse, general practitioner or the parent, and the validity is found to be high.[9,18] Among children with available data on BMI, the mean BMI (15.7 kg/m^2) and standard deviation (1.7 kg/m^2) was used for individual calculation of BMI z-score by subtracting the population mean BMI from the individual BMI and dividing the difference with the standard deviation of the population.[9] Child BMI was quite similar among boys and girls in this study population and the age of the children was within a narrow range. Consequently, z-scores were not calculated within sex and age strata. Child overweight was defined by a BMI > 18 kg/m^2, which is the internationally recommended cut-point at 7 years of age for both girls and boys corresponding to a BMI of 25 kg/m^2 at age 18 years.[19] This cut-point corresponded to the 90th percentile in the study population and combined child overweight and obesity. Child obesity was defined by a BMI > 21 kg/m^2, which is the internationally recommended cut-point at 7 years of age for both girls and boys corresponding to a BMI of 30 kg/m^2 at age 18 years.[19] This cut-off corresponded to the 99th percentile in the study population. Child obesity was less frequent and this outcome was evaluated using the case-cohort design. This design allowed for the inclusion of all cases of obesity in the full cohort and comparison to a random sub-cohort. In addition to weight and height, the parents reported on child waist circumference (WC) in centimeters (cm) at 7 years of age and this secondary outcome was also assessed among children with available information (part IIa: n = 37,131, part IIb: n = 3,872).

Covariates

Information on covariates was obtained from the DNBC interviews in the pregnancy (maternal smoking and pre-pregnancy alcohol intake), from the Danish Medical Birth Register (maternal age, parity, child's sex, gestational age at birth, and birth weight), from Statistics Denmark (maternal country of birth, geographical residence, and educational level), and from the DNHR and DNPR (maternal diabetes mellitus before, during and up to five years after the pregnancy).

Statistical analyses

Linear regression was used to estimate crude and adjusted mean differences (MD) for the association between maternal hyper- and hypothyroidism and outcomes of maternal BMI and child BMI z-score as well as child WC. Results of the linear regression models were robust against non-normality and variance heterogeneity when bootstrapping was applied. Modified Poisson regression was used to estimate crude and adjusted risk ratios (RR) for the association between maternal hyper- and hypothyroidism and outcomes of maternal and child overweight and obesity.[20] Finally, the method for analyses of case-cohort studies with binary outcome described by Schouten et al. was used to estimate crude and adjusted RR for the association between maternal hyper- and hypothyroidism and the outcome of child obesity.[21] Child's sex, birth weight, and gestational age at birth were not included in the main adjusted model, but considered separately in a sub-analysis. To substantiate the findings, median maternal TSH within non-overweight, overweight and obese pregnant women and children, respectively, were estimated and compared using Mann-Whitney U test.

All participating mothers provided written informed consent. The study was approved by The North Denmark Region Committee on Health Research Ethics (N-20130054), the Danish Data Protection Agency (2008-58-0028) and the DNBC Steering Committee (2013-23). Statistical analyses were performed using STATA 16 (Stata Corp., College Station, Texas, USA).

Results

Altogether 70,487 pregnant women were included in early pregnancy for maternal health assessment (Fig 1, part I), and 40,585 of the women were included in the follow-up investigation on health of the child at 7 years of age (Fig. 1, part II). These groups of women were comparable on the majority of maternal characteristics (Table 1), however, there was a tendency towards higher age and educational level in the follow-up population.

For the association between maternal thyroid disease and adiposity (Table 2), maternal hypothyroidism as defined from diagnosis and treatment (part Ia) was associated with a higher BMI and a higher risk of maternal overweight and obesity. This association was predominantly seen among women with known

hypothyroidism at the time of pregnancy (Table 2, part Ia). Altogether 7,504 pregnant women had thyroid function assessed in the early pregnancy from the measurement of TSH (Table 2, part Ib). In this group, maternal TSH was median 1.19 mIU/l in non-overweight women and higher in women (n = 2,053) with overweight (median 1.31 mIU/l, $p < 0.001$) as well as in women (n = 628) with obesity (median 1.38 mIU/l, $p < 0.001$). When maternal hyper- and hypothyroidism were defined from TSH in early pregnancy (Table 2, part Ib), an association between hypothyroidism and BMI was corroborated. Moreover, hyperthyroidism was associated with a lower BMI and a lower risk of overweight (Table 2, part Ib).

For the association between maternal thyroid disease and child adiposity defined by BMI at 7 years of age (Table 3 and 4), no association was observed except that maternal hypothyroidism diagnosed after the pregnancy marginally associated with a higher BMI z-score in the child (Table 3, part IIa). Altogether 4,255 of the randomly selected pregnant women had thyroid function in the early pregnancy assessed from the measurement of TSH (Table 3, part IIb). In this group, maternal TSH was median 1.21 mIU/l in non-overweight children and similar in children (n = 318) with overweight (median 1.24 mIU/l, $p = 0.4$). Furthermore, the case-cohort study included 372 obese children (Table 5, part IIc) and maternal TSH in this group was median 1.29 mIU/l and not different from the random sub-cohort (median 1.21 mIU/l, $p = 0.4$).

Similar to child BMI, no associations between maternal thyroid disease and child WC at 7 years of age was found (Table 5). The association between maternal thyroid disease and markers of adiposity in the child did not change when child's sex, gestational age, and birth weight were considered in the analyses. Furthermore, results did not change when the severity of maternal thyroid disease was considered from the level of TSH in early pregnancy.

Discussion

Principal findings

This study evaluated the association between maternal thyroid disease in pregnancy and markers of maternal and child adiposity within a large, well-defined and nationwide cohort. Across the different designs, no substantial evidence was found that maternal thyroid disease programs adiposity in the child at 7 years of age. However, an association between maternal thyroid disease and markers of adiposity in the mother was seen.

Adiposity in the mother

The topic of thyroid disease and body weight has long attracted attention from clinicians and scientists. From patient complaints and clinical observations of changes in body weight before and after the treatment of thyroid disease to the scientific curiosity about the underlying mechanisms.[22] In line with our findings, it has been observed in non-pregnant and in pregnant individuals that BMI is higher in patients suffering from hypothyroidism with a positive association between the level of TSH and BMI.[23–25] Furthermore, weight

loss after treatment of hypothyroidism and weight gain after treatment of hyperthyroidism are often seen in clinical practice and in observational studies.[22,26] However, even when associations are consistently observed, the difficult part is on the determination of the underlying mechanisms and causality. Our investigation on maternal health was cross-sectional and relied on maternal pre-pregnancy BMI and assessment of maternal thyroid disease from indirect measures or from a single biochemical measurement of thyroid function in early pregnancy. Self-reported pre-pregnancy BMI has been shown to correlate well with measured BMI and with BMI at the first antenatal visit in pregnancy.[27,28] Considering thyroid disease, we previously showed that a large proportion of women diagnosed with thyroid disease after the pregnancy had abnormal biochemical thyroid function in the early pregnancy.[13] This observation suggests that the thyroid function abnormality identified in early pregnancy was likely to persist and to reflect actual thyroid disease. On the other hand, women with known thyroid disease diagnosed before the pregnancy may be insufficiently treated in pregnancy,[13] and we observed an association with maternal adiposity in this group specifically. We had only markers of thyroid disease and adiposity in pregnancy, and we cannot determine the direction of the association observed. This relationship is also not clear from studies in non-pregnant individuals, and it is a notable finding that thyroid disease may affect weight status, but also that obesity potentially affects thyroid function.[22] Furthermore, the higher body weight in hypothyroid individuals and the weight loss associated with treatment seem related to water excess and subsequent water loss and not a higher content of fat.[22,26] One may speculate how the physiological alterations in body composition during a pregnancy interact with this hypothesis.

Another aspect relates to the clinical implications of an association between thyroid disease and body weight. For the management of thyroid disease in pregnancy, it remains uncertain if the diagnostic procedure would benefit from the use of reference ranges for thyroid function tests that are stratified by categories of maternal BMI.[12,29] Moreover, measurement of TSH should be considered in clinical practice when maternal BMI is above 40 kg/m^2 (morbid obesity).[2] A scientific consideration is also on the establishment of reference ranges for thyroid function tests and the potential influence of maternal BMI on reports of prevalence and incidence of maternal thyroid disease in pregnancy. Furthermore, considerations are on the possible implications for pregnancy outcome studies. Much focus is on fetal programming by maternal obesity and various outcomes of pregnancy and child development have been investigated.[9,10] Thus, studies investigating the consequences of maternal thyroid disease in pregnancy should preferably include data on maternal body weight and height.

Adiposity in the child

The concept of fetal programming by *in utero* exposure has long been considered and is yet still emerging.[3] A fetal programming effect of maternal thyroid disease in pregnancy has mainly been proposed in relation to brain development and the risk of adverse neurodevelopmental and neurocognitive outcomes in the

child.[3] Such hypothesis is supported by experimental data and by clinical data from women with severe overt abnormalities in thyroid function.[17] On the other hand, the impact of smaller abnormalities in maternal thyroid function on child neurocognitive development is not clear.[17]

The hypothesis of fetal programming by maternal thyroid disease has also been proposed in relation to metabolic and cardiovascular outcomes in the offspring. Considering the diverse role of thyroid hormones in humans and during development it can be hypothesized that peripheral metabolic effects as well as alterations of central hormonal regulation may play a role.[30,31] Thus, experimental data have proposed an association and observational studies within birth cohorts from Denmark, the Netherlands, and the United Kingdom have investigated the hypothesis in humans.[4,5,7] Notably, previous results were not consistent, and studies were heterogeneous in terms of design, exposure, and outcome assessment. The timing of exposure assessment in early pregnancy varied from early to late pregnancy and the age of the child at outcome evaluation ranged from 6 to 20 years.[4,5,7] Furthermore, it varied between studies whether variation in maternal thyroid function within the normal range or deviations outside the reference ranges were considered.[4,5,7]

An association between maternal thyroid function and blood pressure in the offspring was observed in two studies,[4,5] and one study found that lower levels of maternal TSH in early pregnancy associated with lower BMI in the child at 6 years of age as well as lower abdominal subcutaneous fat mass area and total fat mass.[4] Contrary to this report[4] and in line with other reports,[5,7] we observed no association between maternal thyroid disease in pregnancy and child BMI at 7 years of age. We used various methods to identify maternal hyper- and hypothyroidism in pregnancy and regardless of the method used, the association between maternal hyperthyroidism and markers of adiposity in the child was robust with point estimates being close to no effect. We also found no effect of maternal hypothyroidism, however, results for this type of thyroid disease varied to some extent by the method of exposure assessment, and the adjusted RR for overweight and obesity in the child were slightly above one, but non-significant. We previously showed that marked maternal hypothyroidism in early pregnancy (TSH above 10 mIU/l) was associated with lower intelligence quotient in the child at 6 years of age.[32] However, results of the present study did not change when the severity of maternal hypothyroidism was considered. A strength of our study was the comprehensive information on maternal characteristics and the possibility to adjust for potential confounders including maternal BMI. Furthermore, the case-cohort design is feasible to study rare outcomes, and the fact that we observed no association between maternal thyroid disease and child obesity even using this design provides evidence of no association. Thus, the findings may favor a scientific focus on alternative hypotheses and other outcomes of child development.

The definition of child obesity may be inconsistent across studies and international guidelines. We used the 99th percentile of BMI to define child obesity, which corresponded to an internationally recommended cut-off,[19] but others recommend that the 95th percentile defines child obesity.[33] In that respect, the cases we

identified were severely obese, and we cannot exclude that an association would be seen with less severe obesity. Notably, our findings were consistent when WC was used as a different marker of adiposity in the child. BMI is the most commonly used marker of adiposity, but other markers are increasingly used, and the predictive role of different markers on the risk of cardiovascular disease and metabolic syndrome is considered in children and in adults.[34] Furthermore, it is considered how these indirect markers correlate with more direct measures of body fat content and distribution.[34] We cannot exclude that an association between maternal thyroid disease and alternative markers of child adiposity would be seen. Furthermore, we had no information on thyroid function in the child which would be of interest considering that both maternal thyroid function and obesity have been associated with alterations in offspring thyroid function.[35] Finally, thyroid disease in women of fertile age are predominantly of autoimmune origin,[2] and it remains uncertain whether autoimmune mechanism could be involved in a fetal programming effect. No measurements of thyroid autoantibodies were performed in this study and would be of interest in future investigations.

Conclusion

In a Danish nationwide birth cohort, various investigations using different designs provided no evidence that maternal thyroid disease programs adiposity in the child. Results corroborated an association between maternal thyroid disease in pregnancy and adiposity in the mother and call for further studies to address the clinical impact of deviations in body weight among women with thyroid disease who are or may become pregnant. These findings inform the debate on the management of thyroid disease in pregnant women including the consequences of abnormal maternal thyroid function for later development of the child and considerations on how and when to diagnose thyroid disease in pregnant women.

Conflict of interest

Nothing to declare.

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Data availability

Research data cannot be shared due to regulatory restrictions that apply to the availability of data generated and analysed during this study to preserve patient confidentiality and according to the GDPR regulations.

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Table 1 Maternal characteristics at time of the pregnancy among women from the source population (part Ia) and among the women who participated in the 7-year follow-up (part IIa).

	Part Ia		Part IIa	
	n	%	n	%
Pregnant women[a]	70,487		40,585	
Year of child's birth				
1997-2000	41,769	59.3	24,450	60.2
2001-2003	28,718	40.7	16,135	39.8
Age at child's birth				
< 30 years	34,591	49.1	19,229	47.4
≥ 30 years	35,896	50.9	21,356	52.6
Previous births				
Nulliparous	35,338	50.1	20,597	50.8
Multiparous	35,149	49.9	19,988	49.2
Country of birth				
Denmark	68,918	97.8	39,808	98.1
Outside Denmark	1,550	2.2	769	1.9
Geographical residence[b]				
East Denmark	27,237	38.8	15,571	38.4
West Denmark	43,014	61.2	24,964	61.6
Educational level				
Low	16,016	22.8	8,009	19.8
Middle	28,673	40.8	16,261	40.1
High	25,556	36.4	16,238	40.1
Smoking in pregnancy				
Yes	19,016	27.0	9,780	24.1
No	51,449	73.0	30,792	75.9
Pre-pregnancy body mass index				
< 18.5 kg/m^2	3,205	4.5	1,694	4.2
18.5-24.9 kg/m^2	47,882	67.9	28,410	70.0
25.0-29.9 kg/m^2	13,639	19.4	7,583	18.7
≥ 30.0 kg/m^2	5,761	8.2	2,898	7.1
Pre-pregnancy alcohol intake				
0-7 units/week	64,049	91.0	36,871	91.0
> 7 units/week	6,345	9.0	3,669	9.0
Diabetes mellitus[c]				
Yes	2,009	2.8	1,079	2.7
No	68,478	97.2	39,506	97.3

[a]Individuals with missing information on country of birth (study part Ia: n = 19; study part IIa: n = 8), geographical residence (n = 236; n = 50), educational level (n = 242; n = 77), smoking in pregnancy (n = 22; n = 13), and pre-pregnancy alcohol intake (n = 93; n = 45) were not included in the table.

[b]Divided by the Great Belt.

[c]Hospital diagnosis or redeemed prescription of drugs before and up to 5 years after the child's birth.

Table 2 Association between maternal thyroid disease and maternal pre-pregnancy body mass index (BMI). Maternal thyroid disease was assessed from hospital diagnosis and redeemed prescriptions of drugs (part Ia) and from biochemical measurement of thyroid function in thearly pregnancy (part Ib).

		BMI (kg/m^2)	Mean difference in BMI			Risk ratio for overweight[a]			Risk ratio for obesity[b]		
	n	Mean	cMD	aMD[c]	95% CI[d]	cRR	aRR[c]	95% CI[d]	cRR	aRR[c]	95% CI[d]
Part Ia	**70,487**										
Non-exposed[e]	68,529	23.5	Ref.	Ref.		Ref.	Ref.		Ref.	Ref.	
Hyperthyroidism	1,113	23.7	0.11	-0.09	-0.33; 0.16	1.08	1.01	0.93; 1.11	1.19	1.08	0.90; 1.29
Before or during pregnancy	615	23.6	0.06	-0.15	-0.49; 0.18	1.03	0.63	0.84; 1.09	1.16	1.04	0.81; 1.32
After pregnancy	498	23.7	0.17	-0.01	-0.37; 0.36	1.14	1.09	0.95; 1.23	1.21	1.12	0.86; 1.46
Hypothyroidism	845	24.3	0.74	0.64	0.36; 0.93	1.24	1.21	1.10; 1.33	1.40	1.34	1.11; 1.63
Before or during pregnancy	362	24.8	1.24	1.09	0.66; 1.52	1.39	1.33	1.17; 1.53	1.67	1.58	1.21; 2.07
After pregnancy	483	23.9	0.37	0.31	-0.06; 0.69	1.13	1.12	0.98; 1.27	1.20	1.16	0.88; 1.52
Part Ib	**7,504**										
Non-exposed[f]	6,884	23.6	Ref.	Ref.		Ref.	Ref.		Ref.	Ref.	
Hyperthyroidism	270	23.1	-0.45	-0.61	-1.12; -0.10	0.84	0.79	0.64; 0.98	0.90	0.80	0.52; 1.23
Hypothyroidism	350	24.3	0.75	0.81	0.35; 1.26	1.17	1.20	1.03; 1.41	1.42	1.45	1.07; 1.96

Abbreviations: cMD: crude mean difference; aMD: adjusted mean difference; cRR: crude risk ratio; aRR: adjusted risk ratio; CI: confidence interval; ref.: reference group.

[a]BMI ≥ 25.0 kg/m^2.

[b]BMI ≥ 30.0 kg/m^2.

[c]Adjusted model included: year of child's birth, maternal age, parity, country of birth, geographical residence, educational level, smoking in pregnancy, pre-pregnancy alcohol intake, and diabetes mellitus.

[d]95% confidence interval for the adjusted estimate.

[e]No registration of maternal hyper- or hypothyroidism up to 5 years after the pregnancy.

[f]TSH within the method- and pregnancy week-specific reference range.

Table 3 Association between maternal thyroid disease and body mass index (BMI) of the child at 7-years of age. Maternal thyroid disease was assessed from hospital diagnosis and redeemed prescriptions of drugs (part IIa) and from biochemical measurement of thyroid function in the early pregnancy (part IIb).

		BMI (kg/m^2)	Mean difference in BMI z-score			Risk ratio for overweight[a]		
	n	Mean	cMD	aMD[b]	95% CI[c]	cRR	aRR[b]	95% CI[c]
Part IIa	**40,585**							
Non-exposed[d]	39,466	15.7	Ref.	Ref.		Ref.	Ref.	
Hyperthyroidism	625	15.7	-0.01	-0.04	-0.12; 0.04	1.07	0.99	0.78; 1.27
Before or during pregnancy	343	15.6	-0.03	-0.07	-0.17; 0.04	0.99	0.88	0.63; 1.24
After pregnancy	282	15.7	0.01	-0.01	-0.13; 0.10	1.17	1.14	0.80; 1.62
Hypothyroidism	494	15.9	0.13	0.10	0.01; 0.18	1.18	1.12	0.86; 1.46
Before or during pregnancy	202	15.8	0.06	-0.01	-0.14 0.13	1.09	0.96	0.62; 1.50
After pregnancy	292	16.0	0.18	0.16	0.05; 0.28	1.25	1.24	0.89; 1.72
Part IIb	**4,255**							
Non-exposed[e]	3,889	15.6	Ref.	Ref.		Ref.	Ref.	
Hyperthyroidism	156	15.5	-0.10	-0.10	-0.25; 0.06	0.96	1.02	0.58; 1.82
Hypothyroidism	210	15.7	0.04	0.02	-0.12; 0.15	1.36	1.31	0.86; 1.97

Abbreviations: cMD: crude mean difference; aMD: adjusted mean difference; cRR: crude risk ratio; aRR: adjusted risk ratio; CI: confidence interval; ref.: reference group.

[a]BMI > 18.0 kg/m^2.

[b]Adjusted model included: year of child's birth, maternal age, parity, country of birth, geographical residence, educational level, smoking in pregnancy, pre-pregnancy alcohol intake, pre-pregnancy BMI, and diabetes mellitus.

[c]95% confidence interval for the adjusted estimate.

[d]No registration of maternal hyper- or hypothyroidism up to 5 years after the pregnancy.

[e]TSH within the method- and pregnancy week-specific reference range.

Table 4 Association between maternal thyroid disease and obesity in the child at 7 years of age in a case-cohort study (part IIc). Maternal thyroid disease was assessed from biochemical measurement of thyroid function in the early pregnancy.

	Sub-cohort		**Cases**		**Risk ratio of obesity[a]**		
	n	**%**	**n**	**%**	**cRR**	**aRR[b]**	**95% CI[c]**
Part IIc	**4,255**		**372**				
Non-exposed[d]	3,889	91.4	336	90.3	Ref.	Ref.	
Hyperthyroidism	156	3.7	13	3.5	0.96	0.96	0.53; 1.75
Hypothyroidism	210	4.9	23	6.2	1.27	1.25	0.76; 2.05

Abbreviations: cRR: crude risk ratio; aRR: adjusted risk ratio; CI: confidence interval; ref.: reference group

[a]BMI > 21.0 kg/m^2.

[b]Adjusted model included: year of child's birth, maternal age, parity, country of birth, geographical residence, educational level, smoking in pregnancy, pre-pregnancy alcohol intake, pre-pregnancy body mass index, and diabetes mellitus.

[c]95% confidence interval for the adjusted estimate.

[d]TSH within the method- and pregnancy week-specific reference range.

Table 5 Association between maternal thyroid disease and waist circumference (WC) of the child at 7 years of age. Maternal thyroid disease was assessed from hospital diagnosis and redeemed prescriptions of drugs (part IIa) and from biochemical measurement of thyroid function in the early pregnancy (part IIb).

		WC (cm)	Mean difference in WC		
	n	**Mean**	**cMD**	**aMD[a]**	**95% CI[b]**
Part IIa	**37,131**				
Non-exposed[c]	36,128	57.0	Ref.	Ref.	
Hyperthyroidism	564	57.2	0.16	0.06	-0.35; 0.47
Before or during pregnancy	308	57.1	0.08	-0.04	-0.59; 0.51
After pregnancy	256	57.3	0.25	0.17	-0.43; 0.77
Hypothyroidism	439	57.5	0.42	0.26	-0.20; 0.72
Before or during pregnancy	177	57.5	0.49	0.24	-0.49; 0.96
After pregnancy	262	57.4	0.37	0.28	-0.32; 0.87
Part IIb	**3,872**				
Non-exposed[d]	3,544	56.9	Ref.	Ref.	
Hyperthyroidism	138	56.4	-0.50	-0.38	-1.18; 0.43
Hypothyroidism	190	57.3	0.41	0.37	-0.32; 1.07

Abbreviations: WC: waist circumference; cMD: crude mean difference; aMD: adjusted mean difference; CI: confidence interval; ref.: reference group.

[a]Adjusted model included: year of child's birth, maternal age, parity, country of birth, geographical residence, educational level, smoking in pregnancy, pre-pregnancy alcohol intake, pre-pregnancy B, and diabetes mellitus.

[b]95% confidence interval for the adjusted estimate.

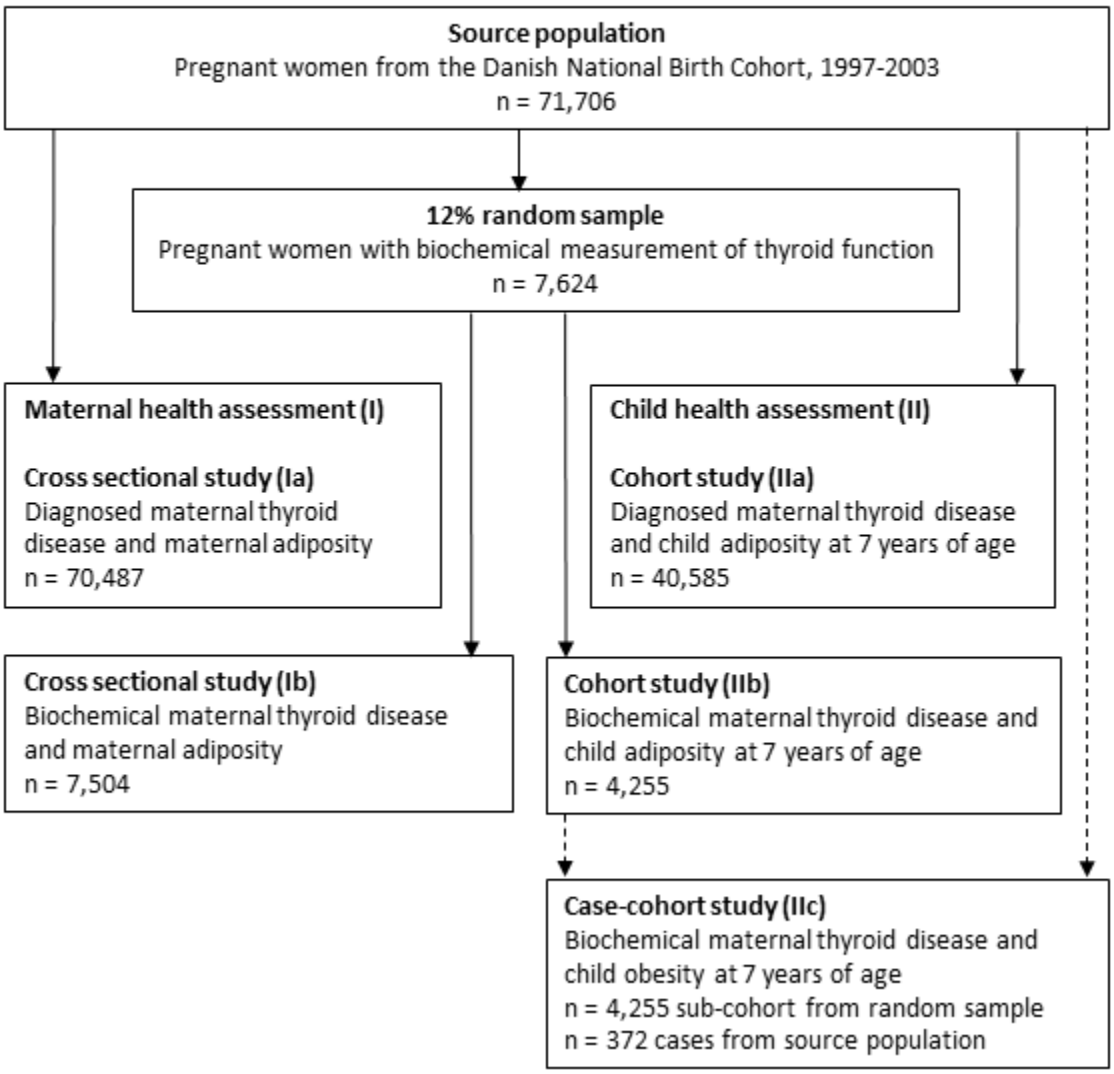
[c]No registration of maternal hyper- or hypothyroidism up to 5 years after the pregnancy.

[d]TSH within the method- and pregnancy week-specific reference range.

Figure legends

Fig. 1 Flowchart illustrating the selection of the study population within the Danish National Birth Cohort for the study on maternal health assessment (part I) and child health assessment (part II).

Figure 1



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