Maternal hypothyroidism in the perinatal period and childhood asthma in the offspring

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Abstract

Background: There is increasing interest in the possible link between maternal hypothyroidism in the perinatal period and childhood asthma risk. We explored this in the present study while accounting for the timing of hypothyroidism diagnosis. Further, we evaluated whether the risk was moderated by thyroid hormone treatment during pregnancy.

Methods: We conducted a population-based cohort study using Danish national registers. All liveborn singletons in Denmark from 1998 to 2007 were identified. Maternal hypothyroidism and asthma in the children were defined by data from the Patient Register and Prescription Registry. We estimated incidence rate ratios (IRRs) of asthma among children born to hypothyroid mothers versus children born to mothers with no recorded thyroid dysfunction using Poisson regression models.

Results: Of 595,669 children, 3,524 children were born to mothers with hypothyroidism diagnosed before delivery and 4,664 diagnosed after delivery. Overall 48,990 children received treatment for asthma. The IRRs of asthma was 1.16 (95% confidence interval (CI): 1.03–1.30) and 1.12 (95% CI: 1.02–1.24) for children born to mothers with hypothyroidism diagnosed before and after delivery, compared to children born to mothers with no thyroid dysfunction. The highest risk was observed among children born to mothers with hypothyroidism diagnosed before delivery who did not receive thyroid hormone treatment during pregnancy (IRR=1.37, 95% CI: 1.04–1.80).

Conclusion: Our findings suggest that maternal hypothyroidism, especially when it is untreated, increases childhood asthma risk. Early detection and appropriate treatment of hypothyroidism in pregnant women may be an area for possible prevention of childhood asthma.

Keywords: Asthma, childhood, cohort study, hypothyroidism, perinatal

Introduction

Hypothyroidism is a common endocrine disorder characterized by thyroid hormone deficiency, affecting 2–5% of pregnancies (1, 2). While iodine deficiency is the most common preventable cause of hypothyroidism worldwide (3), in iodine-sufficiency regions, thyroid autoimmunity plays a dominant role in its pathogenesis (4). The clinical manifestation of hypothyroidism spans a broad spectrum of symptoms including tiredness, dry skin, and shortness of breath, which are unspecific and may go unnoticed (5). Hypothyroidism often develops or worsens as gestation progresses (6), and the demands of thyroid hormone is increased during pregnancy (7). Inadequately treated hypothyroidism has been linked to multiple adverse health outcomes, such as pregnancy loss, premature delivery, autism spectrum disorder, and reduced intelligence quotient scores in the offspring (8-11). Although various international guidelines recommend appropriate treatment to maintain euthyroidism in pregnancy (12-14), not all pregnant women with known hypothyroidism receive sufficient thyroid hormone treatment (15).

Empirical evidence implicates that inadequately treated maternal hypothyroidism in the perinatal period may be associated with increased asthma risk in the offspring. Transfer of maternal thyroid hormones is essential for a developing fetus (16), since the fetal thyroid is not functional until midgestation (17). In case of maternal hypothyroidism, the transfer of thyroid hormones from the mother to the fetus may be compromised (7). This in turn may impair the fetal lung development (18), and increase asthma risk in the children (19). Furthermore, women with chronic autoimmune hypothyroidism have elevated titer of autoantibodies, which cross the placenta (20), and may act directly on fetal lung development (21). Nonetheless, epidemiological evidence on the association between maternal hypothyroidism and childhood asthma is lacking. Additionally, it remains unresolved

whether thyroid hormone treatment moderates any potential adverse effect of hypothyroidism during pregnancy.

Our primary aim was to evaluate the association between maternal hypothyroidism and the risk of childhood asthma while taking into consideration the timing of hypothyroidism diagnosis. We hypothesized that maternal hypothyroidism increases the risk of asthma in the offspring. As mothers with hypothyroidism diagnosed after delivery may have abnormal thyroid hormone levels and/or antoantibodies during pregnancy already, it is likely that children born to mothers with hypothyroidism diagnosed after delivery as well as before delivery will be at an increased risk of childhood asthma. The secondary objective was to assess whether thyroid hormone treatment in pregnancy moderates the association between maternal hypothyroidism and childhood asthma.

Methods

Study population

We conducted a population-based cohort study using data from national registers in Denmark, where all liveborn and new residents in Denmark are assigned a unique personal identification number, which enables individual-level linkage across registers. We obtained our study cohort from the Danish Medical Birth Register (22), which holds data on all live births and their mothers since 1968. We identified 626,393 live-born singletons born between 1998 and 2007. We excluded 3,794 children with missing or likely errors in gestational age (< 154 or > 315 days). Follow-up started from 5 years of age to comply with our asthma definition, and we further excluded 9,800 children who emigrated and 2,828 children who died before their 5th birthday. We excluded 14,302 children whose mothers had records of hyperthyroidism in the study period, i.e. those who had a hospital treatment for hyperthyroidism (242.00–242.29 in the International Classification of Diseases, 8th Revision (ICD)-8 codes and E05 in

10th Revision (ICD-10) codes) or received any antithyroid drugs (Anatomical Therapeutic Chemical Classification System (ATC) code H03B) (Figure 1). After exclusion, 595,669 children to 398,200 mothers were included in the final analyses.

Identification of maternal hypothyroidism

The identification of maternal hypothyroidism was based on hospital (inpatient or outpatient) treatment for hypothyroidism and pharmaceutical treatment with thyroid hormones. Autoimmune hypothyroidism persists during pregnancy even if it is diagnosed before pregnancy. Similarly, hypothyroidism symptoms may go unnoticed for prolonged time periods (23). To capture maternal hypothyrodism and to acknowledge a possible delay in time to diagnosis, we defined maternal hypothyroidism requiring treatment based on the following two criteria: 1) one hospital treatment for hypothyroidism and at least one redeemed prescription of thyroid hormones at any time before 5 years after delivery; or 2) two or more redeemed prescriptions of thyroid hormones at any time before 5 years after delivery.

Hospital treatment for hypothyroidism. We retrieved information on hospital treatment for hypothyroidism from the Danish National Patient Register (24). The register holds information on all inpatient treatment during 1977–1994 and also contacts in outpatient clinics and emergency rooms from 1995 onwards. The ICD-8 codes were used to encode the diseases until 1994 when the ICD-10 codes were introduced. The following ICD codes were used to identify the main or auxiliary diagnosis of hypothyroidism (243.99–244.09 in ICD-8 codes; or E03 and E89.0 in ICD-10 codes)(25).

Pharmaceutical treatment with thyroid hormones. Information on redeemed prescriptions of thyroid hormones was retrieved from the Danish National Prescription Registry (26). The registry includes all prescriptions redeemed from the community pharmacies since 1995 and also holds data on

the ATC codes of the drug, redemption date, and the number of packages dispensed. The ATC code for thyroid hormones is H03A.

The timing of hypothyroidism diagnosis was defined as the day of the first prescription of thyroid hormones redeemed or first hospital treatment for hypothyroidism, whichever came first. We categorized children into three exclusive groups according to the presence and timing of maternal hypothyroidism diagnosis relating to the delivery: 1) no maternal recorded thyroid dysfunction, 2) matenral hypothyroidism diagnosed before delivery, and 3) maternal hypothyroidism diagnosed within 5 years after delivery.

Incident asthma in the offspring—outcome of interest

Since a clinical diagnosis of asthma can be made with certainty first by age 5 years (27), we defined childhood asthma as asthma treatment after 5 years of age, i.e. at least one hospital treatment for asthma or two or more redeemed prescriptions of an asthma medication within one year. Asthma hospital treatment was defined as having at least one inpatient, outpatient, or emergency room visit for asthma (ICD-10 codes J45 and J46), retrieved from the Danish National Patient Register (24). Information on the prescriptions for an asthma medication was obtained from the Danish National Prescription Registry (26). The ATC codes for inhaled asthma drugs were: inhaled β2-agonists (R03AC02–04, -12, and -13), inhaled glucocorticoids (R03BA01, -02 and -05), fixed-dose combination of inhaled β2-agonists and glucocorticoids (R03AK06 and -07), leukotriene receptor antagonists (R03DC03), and anti-IgE therapies (R03DX05)(28).

Statistical analysis

Statistical analyses were performed with Stata 13.1 (StataCorp, College Station, TX, USA). Each child was followed from age 5 years up to 14 years until the end of 2012, emigration, death, or the date of first asthma diagnosis, whichever came first. We estimated incidence rate ratios (IRRs) of childhood asthma and their 95% confidence intervals (CIs) using Poisson regression models. Children born to mothers with hypothyroidism were compared to children whose mothers had no recorded thyroid dysfunction. To account for the dependence between siblings, we used robust sandwich variance estimator for correction of standard errors. A p-value of less than 0.05 (2-sided) was judged statistically significant. Adjustment was made for the following covariates: maternal age at delivery (<25, 25–34, or ≥35 years), primiparity (yes/no), smoking during pregnancy (yes/no), highest education level attained at delivery (elementary school/ above elementary school), annual income at delivery (lowest quartile/above lowest quartile), calendar year at delivery (1998–2000, 2001–2003, or 2004–2007), maternal asthma (yes/no), maternal diabetes (249 and 250 in ICD-8 codes or E10–E14, H36.0, and O24 in ICD-10 codes; yes/no), and paternal asthma at delivery (yes/no). We defined maternal or paternal asthma at delivery as one or more hospital contact for asthma or at least two asthma medication prescriptions redeemed within one year before delivery of the index child. Data on covariates were extracted from the registers mentioned above as well as from Statistics Denmark's registers on education level and annual income (29). About 5.1% of the values were missing for smoking during pregnancy, maternal highest education level and annual income status at delivery, and we consequently applied 20 imputations using the Markov Chain Monte Carlo technique for imputing missing values (30).

To examine whether the associations between maternal hypothyroidism and childhood asthma were moderated by thyroid hormone treatment during pregnancy, we classified children born to mothers with hypothyroidism diagnosed before delivery into two groups according to thyroid hormone

157 treatment during pregnancy, which was defined by at least one redeemed prescription of thyroid
158 hormones in the period from 6 months before pregnancy until delivery. Pregnancy was counted from
159 the first day of the last menstrual period until delivery. To further examine whether the association
160 between maternal hypothyroidism and childhood asthma depended on the timing of diagnosis, we
161 categorized maternal hypothyroidism diagnosed after delivery into hypothyroidism diagnosed within 2
162 years after delivery and 3–5 years after delivery.
163
164 ***Sensitivity analysis***
165 Five sensitivity analyses were done to validate our findings. First, asthma is highly heritable (31), and
166 the association between maternal hypothyroidism and childhood asthma may differ between children
167 born to mothers with and without asthma. We, therefore, repeated our analyses by stratification on
168 maternal asthma diagnosis. Second, to test whether there was gender-specific difference in the
169 vulnerability to maternal hypothyroidism, we repeated the analyses by stratifying on the sex of the
170 child. Third, to further address the possible secular trends in diagnostic practices, we repeated our
171 analyses stratified on the calendar year of birth (1998–2000, 2001–2003, or 2004–2007). Fourth, as
172 maternal elevated body mass index (BMI) increases the risk of hypothyroxinemia and asthma in the
173 offspring (32, 33), we further investigated the role of maternal hypothyroidism on childhood asthma by
174 inclusion of an interaction term between maternal prepregnancy BMI (<18.5, 18.5–29.9, or ≥30 kg/m^2)
175 and maternal hypothyroidism in a subcohort of children born during 2004–2007 when information on
176 BMI was available in the registers. Fifth, to evaluate whether the associations were influenced by the
177 definition of childhood asthma and to account for the fact that some children may receive asthma
178 diagnosis before age 5 years, we also investigated the association between maternal hypothyroidism
179 and childhood asthma using a different asthma definition according to asthma treatment during 0–3

years and 4–6 years based on the schema from Martinez *et al*., i.e., early-onset transient, early-onset persistent, and late-onset asthma (34).

Ethics

The study was approved by the Danish Data Protection Agency (No. 2015-57-0002) and identity of the individuals was blinded to the investigators. The study did not need approval from the ethics committee according to Danish legislation.

Results

During the period from 1998 to 2007, we included 595,669 liveborn singletons, of whom, 3,524 children were born to mothers with a hypothyroidism diagnosed before delivery and 4,664 diagnosed after delivery. Table 1 summarizes the characteristics of the study population. Mothers with hypothyroidism tended to be older at delivery, to smoke less, to have a lower income, to have diabetes and asthma before delivery, and to have a preterm delivery, compared to mothers with no recorded thyroid dysfunction. There were no differences between these groups regarding paternal asthma before delivery, low birth weight, or sex of the child.

Overall 48,990 children received treatment for asthma during follow-up in the entire cohort. Table 2 shows the IRRs of asthma according to the presence and the timing of maternal hypothyroidism diagnosis. After adjusting for potential confounders, children born to mothers with hypothyroidism had a slightly increased risk of childhood asthma (IRR=1.14, 95% CI: 1.06–1.23), compared to children born to mothers with no recorded thyroid dysfunction. The IRRs were 1.16 (95%

CI: 1.03–1.30) for children born to mothers with hypothyroidism diagnosed before delivery and 1.12 (95% CI: 1.02–1.24) diagnosed after delivery.

Of the 3,524 children born to mothers with hypothyroidism diagnosed before delivery, 515 (14.6%) were born to mothers who received no thyroid hormone treatment, and 3,009 (85.4%) to mothers with at least one redeemed prescription for thyroid hormones in a period from 6 months prior to pregnancy until delivery. In comparison to children born to mothers with no thyroid dysfunction, a slightly higher risk was observed among children whose mothers received no thyroid hormone treatment in the pregnancy (IRR=1.37, 95% CI: 1.04–1.80) versus children born to mothers with thyroid treatment (IRR=1.12, 95% CI: 0.99–1.27).

The associations between maternal hypothyroidism and childhood asthma were comparable between children born to mothers with and without asthma, indicating that genetic susceptibility to asthma did not modify the association between maternal hypothyroidism and childhood asthma (Figure 2). Similar associations were observed in girls and boys (all p-values for interaction of timing of maternal hyperthyroidism and sex of the child on the multiplicative scale were greater than 0.1), albeit that the magnitude of the associations was non-statistically higher in girls than in boys (Figure S1 in the supplement). There was no strong evidence that the associations varied by study period (Figure S2 in the Supplement), with all p-values for the interaction of timing of maternal hypothyroidism diagnosis and calendar year of birth greater than 0.2. Maternal pre-pregnancy BMI did not modify the estimated effect of maternal hyperthyroidism on childhood asthma (all p-values for interaction were greater than 0.2). The associations remained identical when we used different asthma definition. Moreover, the associations did not differ among different phenotypes of childhood asthma (early-onset transient, early-onset persistent, and late-onset asthma) (Table S1 in the supplement).

Discussion

To the best of our knowledge, our study is the first to investigate the association between maternal hypothyroidism and childhood asthma. In this population-based cohort study, we found that maternal hypothyroidism was associated with a modest but statistically significantly increased risk of childhood asthma. Notably, the association was observed both when maternal hypothyroidism was diagnosed before delivery and also when the disorder was first diagnosed and treated after delivery. The highest risk was observed among children whose mothers had hypothyroidism diagnosed before delivery but received no thyroid hormone treatment during pregnancy.

Maternal hypothyroidism and childhood asthma

Although the underlying mechanisms linking hypothyroidism during pregnancy and offspring asthma remain to be determined, existing knowledge provides biologically plausible explanations for our findings. Overall, maternal hypothyroidism may increase the risk of childhood asthma in two ways.

Firstly, in the presence of hypothyroidism, mothers may be unable to produce sufficient thyroid hormones to meet the needs of both the mother and the fetus (7). Insufficient thyroid hormones in the intra-uterine period may subsequently result in an abnormal structural development of lungs with larger air spaces and less alveolar septae, which predisposes children to the development of asthma later in life (19). This mechanism has been observed in mice (18).

Secondly, autoimmunity is a common cause of hypothyroidism among women of reproductive age (4). Women with chronic autoimmune hypothyroidism have elevated titer of antibodies, which cross the placenta (20). Another possible explanation for the association between maternal hypothyroidism and childhood asthma is that maternal autoantibodies impair beta-adrenergic responsiveness and bronchial epithelium of the fetus, contributing to the pathogenesis of asthma (21).

Further studies are needed that more precisely examine potential mechanisms underlying the association.

Our finding on the increased risk of asthma among children born to mothers with hypothyroidism diagnosed both before and after the delivery questions the hypothesis on the specificity of the intrauterine effect. However, given symptoms of hypothyroidism may be unspecific, and hypothyroidism may persist for a period before the diagnosis is made (23), both findings support an intrauterine effect. It is possible that women diagnosed with hypothyroidism in the years after delivery may have already suffered from hypothyroidism in the pregnancy which was undetected and untreated.

Thyroid hormone treatment of hypothyroidism during pregnancy and childhood asthma

We observed a higher risk of asthma in children whose mothers were diagnosed with hypothyroidism before delivery but did not receive current treatment during pregnancy, compared to those who were treated. Current guidelines advocate that overt and subclinical hypothyroidism arising before or during pregnancy should be treated with levothyroxine, but the active management of smaller aberrations in thyroid function is less evident (12). Given thyroid hormones are considered safe to take during pregnancy, if replicated, our findings add to the literature on a potential beneficial effect of thyroid hormone treatment among pregnant women with hypothyroidism (35-37).

Strengths and limitations

The use of national registers with complete coverage enables us to include the whole population. We have almost complete follow-up and thus eliminated attrition bias. Information on hypothyroidism and childhood asthma were collected independently, which rules out differential reporting bias. The large sample size allowed for detailed analyses in subgroups.

Our study also has limitations. First, we followed children from 5 years and excluded 2,828 (0.5%) children who died before 5 years, which may lead to selection bias. However, there was no statistical difference in the mortality rate before age 5 years between children born to mothers with and without hypothyroidism. Therefore, any bias due to conditioning on the survival is likely to be small. Second, we identified maternal hypothyroidism and childhood asthma from records in hospitals and prescription register, and misclassification cannot be ruled out. Actual measurement of maternal thyroid function in stored biobank sera from Danish pregnant women has shown that 4.5% of the women had undetected hypothyroidism in the early pregnancy (23). In the present study, to account for undetected hypothyroidism during pregnancy, we included women who were diagnosed and treated for hypothyroidism both before and within 5 years after delivery. Still, we may have misclassified some cases of undetected hypothyroidism. Similarly, we may have misclassified asthma due to undertreatment of asthmatics and overtreatment of transient wheeze. We expect all these misclassifications to be non-differential and therefore would have biased our results toward no association. Third, redeemed prescriptions of thyroid hormones do not reflect actual use, while women without prescription redeemed may take medication that was redeemed outside of the defined period. However, studies indicated that adherence to thyroid hormone treatment was good during pregnancy (35, 38), and the bias is non-differential and probably biases our finding on thyroid treatment during pregnancy toward the null. Fourth, we did not have information on laboratory tests on thyrotropin and thyroid hormone levels. We were not able to differentiate the effects of overt and subclinical hypothyroidism. Fifth, we excluded children born to mothers with hyperthyroidism, which imposes constraints on the generalization of our findings to children born to mothers with hypothyroidism following treatment for hyperthyroidism. Last, our study is an observational study. Despite careful

adjustment for possible confounders, our findings do not prove causality. The findings of the present study await confirmation in future studies.

Conclusion

The present study investigates the association betweem maternal hypotyroidism and childhood asthma. Our findings suggest that maternal hypothyroidism, especially untreated, may increase the risk of childhood asthma. Potential mechanisms underlying this association need to be explored in mechanistic studies. If replicated, appropriate treatment of pregnant women with hypothyroidism may be an area for possible prevention of childhood asthma.

Acknowledgements

Funding: This study is funded by the Danish Council for Independent Research (Project No. DFF-5053-00156B). Munk-Olsen T. and Agerbo E. is supported by iPSYCH, the Lundbeck Foundation Initiative for Integrative Psychiatric Research (R155-2014-1724). Agerbo E. is also supported by Niels Bohr Professorship Grant from the Danish National Research Foundation and the Stanley Medical Research Institute. The investigators conducted the research independently. The funders had no role in study design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflicts of interests: None to declare.

Author contributions

XL conceived the study. XL, SLA, and TMO designed the study. XL analyzed the data and drafted the manuscript. XL, SLA, JO, EA, VS, SCD, and TMO interpreted the data and revised the manuscript critically. All authors approved the final manuscript as submitted.

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Figure 1. Flowchart illustrating the identification of the study population

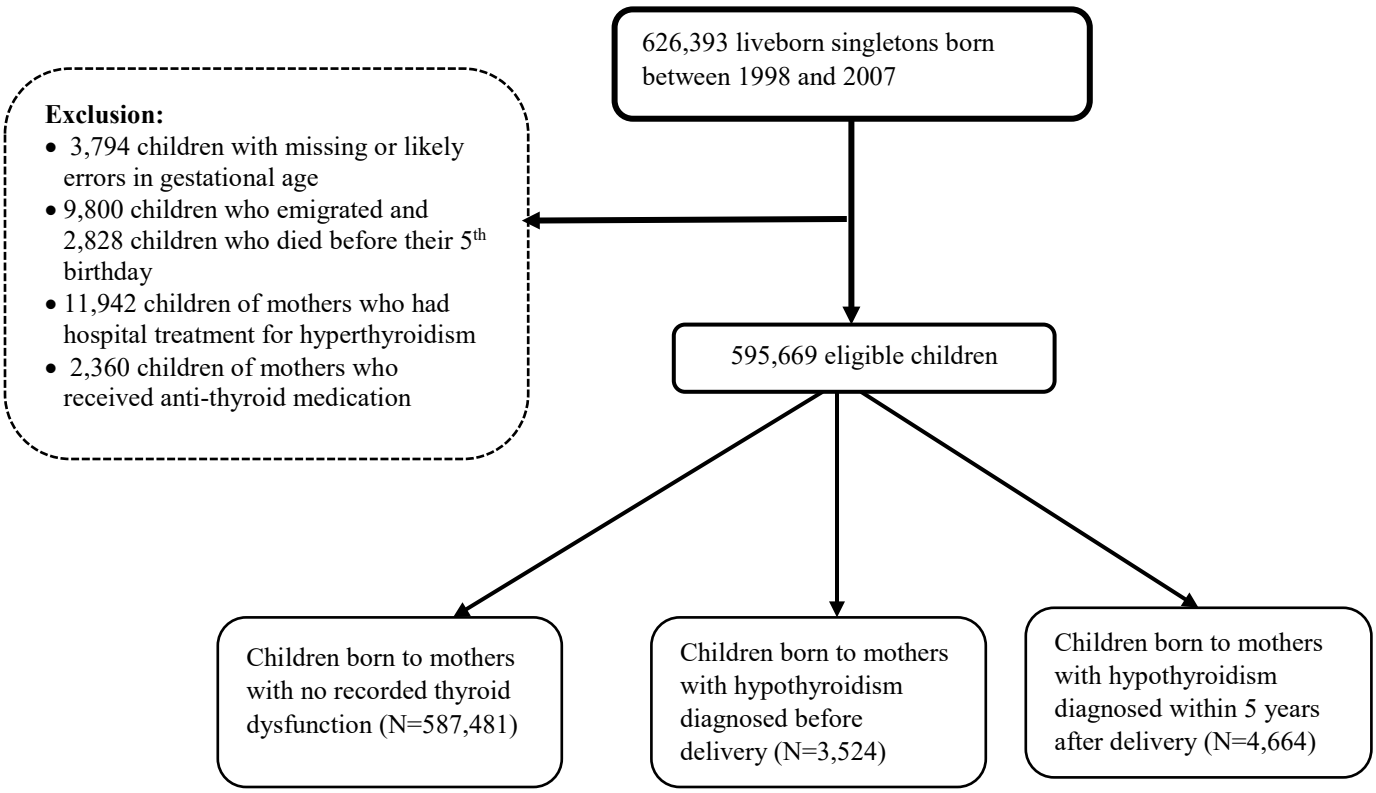


Table 1. Characteristics of the study population.

Characteristics	No maternal thyroid dysfunction (N=587,481)	Maternal hypothyroidism	
		Diagnosed before delivery (N=3,524)	Diagnosed after delivery (N=4,664)
Maternal age at delivery (years)			
<25	78,850 (13.4)	209 (5.9)	420 (9.0)
25–34	413,975 (70.5)	2,363 (67.1)	3,310 (71.0)
≥35	94,656 (16.1)	952 (27.0)	934 (20.0)
Parity			
1	254,370 (43.3)	1,104 (31.3)	1,983 (42.5)
≥2	333,111 (56.7)	2,420 (68.7)	2,681 (57.5)
Maternal smoking during pregnancy			
Yes	112,351 (19.1)	428 (12.1)	614 (13.2)
No	458,071 (78.0)	2,983 (84.7)	3,917 (84.0)
Missing	17,059 (2.9)	113 (3.2)	133 (2.9)
Maternal annual income status at delivery [a]			
Lowest quartile	125,689 (21.4)	921 (26.1)	1,171 (25.1)
Above lowest quartile	461,528 (78.6)	2,603 (73.9)	3,493 (74.9)
Missing	264 (<0.1)	0 (0.0)	0 (0.0)
Maternal highest education level at delivery			
Elementary school	117,938 (20.1)	589 (16.7)	847 (18.2)
Above elementary school	456,124 (77.6)	2,862 (81.2)	3,689 (79.1)
Missing	13,419 (2.3)	73 (2.1)	128 (2.7)
Calendar year of birth			
1998–2000	181,023 (30.8)	684 (19.4)	1,088 (23.3)
2001–2003	174,706 (29.7)	952 (27.0)	1,329 (28.5)
2004–2007	231,752 (39.5)	1,888 (53.6)	2,247 (48.2)
Maternal diabetes at delivery	11,557 (2.0)	282 (8.0)	205 (4.4)
Maternal asthma at delivery	86,103 (14.7)	623 (17.7)	798 (17.1)
Paternal asthma at delivery	62,380 (10.6)	419 (11.9)	553 (11.9)
Sex of the child			
Boys	301,379 (51.3)	1,807 (51.3)	2,351 (50.4)
Girls	286,102 (48.7)	1,717 (48.7)	2,313 (49.6)
Preterm delivery (<37 weeks)	28,247 (4.8)	213 (6.0)	247 (5.3)
Low birth weight (<2500 g)	20,154 (3.4)	125 (3.5)	161 (3.5)
Fetal growth [b]			
Small for gestational age	98,606 (16.8)	497 (14.1)	733 (15.7)
Appropriate for gestational age	416,419 (70.9)	2,542 (72.1)	3,221 (69.1)
Large for gestational age	72,456 (12.3)	485 (13.8)	710 (15.2)

Figures are numbers (%)

[a] Maternal annual income status at delivery was categorized by the sex and age; [b] Small for gestational age is defined as a birth weight below the 10th percentile of birth weight by the gestational age and sex, and large for gestational age as above the 90th percentile. The p-values for the comparison of differences among these three groups were all less than 0.001, using chi-square tests.

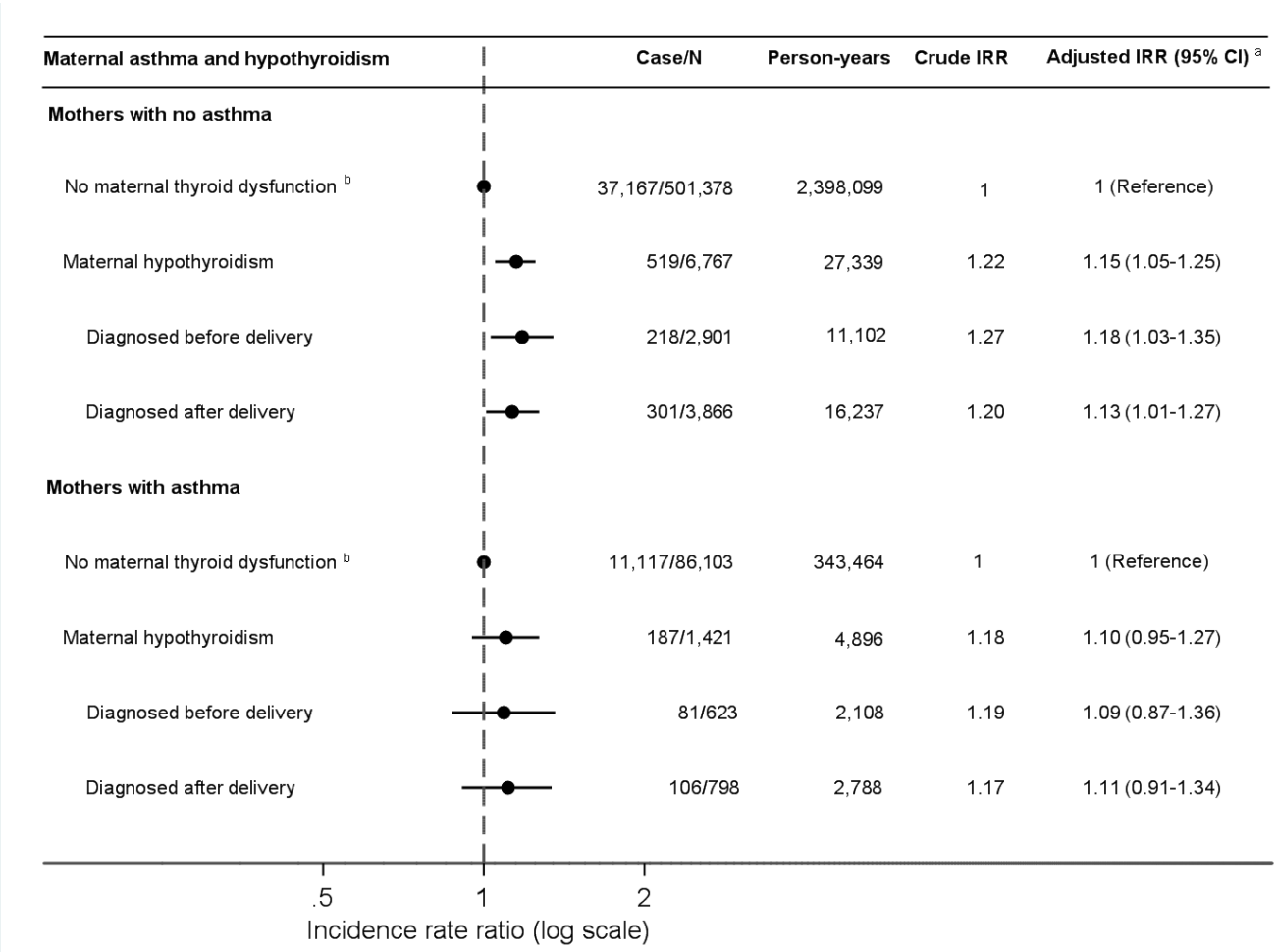
Table 2. Incidence rate ratios of childhood asthma according to the presence and timing of maternal hypothyroidism diagnosis

Maternal hypothyroidism and treatment	N	Cases	Person-years	Crude IRRs	Adjusted IRRs [a] (95% CI)
No maternal thyroid dysfunction [b]	587,481	48,284	2,741,563	1	1 (reference)
Maternal hypothyroidism	8,188	706	32,235	1.24	1.14 (1.06 – 1.23)
Diagnosed before delivery	3,524	299	13,210	1.29	1.16 (1.03 – 1.30)
No thyroid hormone treatment during pregnancy	515	53	1,998	1.51	1.37 (1.04 – 1.80)
With thyroid treatment during pregnancy	3,009	246	11,212	1.25	1.12 (0.99 – 1.27)
Diagnosed after delivery	4,664	407	19,025	1.21	1.12 (1.02 – 1.24)
Diagnosed within 2 years after delivery	1,975	182	8,104	1.28	1.19 (1.03 – 1.38)
Diagnosed between 3–5 years after delivery	2,689	225	10,921	1.17	1.08 (0.94 – 1.23)

Abbreviation: IRR, incidence rate ratio; CI, confidence interval

[a] Adjusted for maternal age, primiparity, smoking during pregnancy, education status, income status, calendar year of birth, maternal diabetes, maternal asthma, paternal asthma at delivery, and the index child's age at observation (each year) during the study period; [b] Children born to mothers with no thyroid dysfunction was used as the reference group for estimating the incidence rate ratio of asthma among children born to mothers with hypothyroidism.

Figure 2. Incidence rate ratios of childhood asthma according to the timing of maternal hypothyroidism diagnosis stratification on maternal asthma



Abbreviation: IRR, incidence rate ratio; CI, confidence interval

[a] Adjusted for maternal age, primiparity, smoking during pregnancy, education status, income status, calendar year of birth, maternal diabetes, paternal asthma at delivery, and the index child's age at observation (each year) during the study period; [b] Children born to mothers with no thyroid dysfunction was used as the reference group for estimating the incidence rate ratio of asthma among children born to mothers with hypothyroidism.