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

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31 **Abstract**

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

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

41 **Results:** Of 595,669 children, 3,524 children were born to mothers with hypothyroidism diagnosed
42 before delivery and 4,664 diagnosed after delivery. Overall 48,990 children received treatment for
43 asthma. The IRRs of asthma was 1.16 (95% confidence interval (CI): 1.03–1.30) and 1.12 (95% CI:
44 1.02–1.24) for children born to mothers with hypothyroidism diagnosed before and after delivery,
45 compared to children born to mothers with no thyroid dysfunction. The highest risk was observed
46 among children born to mothers with hypothyroidism diagnosed before delivery who did not receive
47 thyroid hormone treatment during pregnancy (IRR=1.37, 95% CI: 1.04–1.80).

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

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

52 **Introduction**

53 Hypothyroidism is a common endocrine disorder characterized by thyroid hormone deficiency,
54 affecting 2–5% of pregnancies (1, 2). While iodine deficiency is the most common preventable cause
55 of hypothyroidism worldwide (3), in iodine-sufficiency regions, thyroid autoimmunity plays a

56 dominant role in its pathogenesis (4). The clinical manifestation of hypothyroidism spans a broad
57 spectrum of symptoms including tiredness, dry skin, and shortness of breath, which are unspecific and
58 may go unnoticed (5). Hypothyroidism often develops or worsens as gestation progresses (6), and the
59 demands of thyroid hormone is increased during pregnancy (7). Inadequately treated hypothyroidism
60 has been linked to multiple adverse health outcomes, such as pregnancy loss, premature delivery,
61 autism spectrum disorder, and reduced intelligence quotient scores in the offspring (8-11). Although
62 various international guidelines recommend appropriate treatment to maintain euthyroidism in
63 pregnancy (12-14), not all pregnant women with known hypothyroidism receive sufficient thyroid
64 hormone treatment (15).

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

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

84

85 **Methods**

86 ***Study population***

87 We conducted a population-based cohort study using data from national registers in Denmark, where
88 all liveborn and new residents in Denmark are assigned a unique personal identification number, which
89 enables individual-level linkage across registers. We obtained our study cohort from the Danish
90 Medical Birth Register (22), which holds data on all live births and their mothers since 1968. We
91 identified 626,393 live-born singletons born between 1998 and 2007. We excluded 3,794 children with
92 missing or likely errors in gestational age (< 154 or > 315 days). Follow-up started from 5 years of age
93 to comply with our asthma definition, and we further excluded 9,800 children who emigrated and 2,828
94 children who died before their 5th birthday. We excluded 14,302 children whose mothers had records of
95 hyperthyroidism in the study period, i.e. those who had a hospital treatment for hyperthyroidism
96 (242.00–242.29 in the International Classification of Diseases, 8th Revision (ICD)-8 codes and E05 in
97 10th Revision (ICD-10) codes) or received any antithyroid drugs (Anatomical Therapeutic Chemical
98 Classification System (ATC) code H03B) (Figure 1). After exclusion, 595,669 children to 398,200
99 mothers were included in the final analyses.

100

101 ***Identification of maternal hypothyroidism***

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

110 *Hospital treatment for hypothyroidism.* We retrieved information on hospital treatment for
111 hypothyroidism from the Danish National Patient Register (24). The register holds information on all
112 inpatient treatment during 1977–1994 and also contacts in outpatient clinics and emergency rooms
113 from 1995 onwards. The ICD-8 codes were used to encode the diseases until 1994 when the ICD-10

114 codes were introduced. The following ICD codes were used to identify the main or auxiliary diagnosis
115 of hypothyroidism (243.99–244.09 in ICD-8 codes; or E03 and E89.0 in ICD-10 codes)(25).

116 *Pharmaceutical treatment with thyroid hormones.* Information on redeemed prescriptions of
117 thyroid hormones was retrieved from the Danish National Prescription Registry (26). The registry
118 includes all prescriptions redeemed from the community pharmacies since 1995 and also holds data on
119 the ATC codes of the drug, redemption date, and the number of packages dispensed. The ATC code for
120 thyroid hormones is H03A.

121 The timing of hypothyroidism diagnosis was defined as the day of the first prescription of
122 thyroid hormones redeemed or first hospital treatment for hypothyroidism, whichever came first.
123 We categorized children into three exclusive groups according to the presence and timing of maternal
124 hypothyroidism diagnosis relating to the delivery: 1) no maternal recorded thyroid dysfunction, 2)
125 maternal hypothyroidism diagnosed before delivery, and 3) maternal hypothyroidism diagnosed within
126 5 years after delivery.

127

128 *Incident asthma in the offspring—outcome of interest*

129 Since a clinical diagnosis of asthma can be made with certainty first by age 5 years (27), we defined
130 childhood asthma as asthma treatment after 5 years of age, i.e. at least one hospital treatment for
131 asthma or two or more redeemed prescriptions of an asthma medication within one year. Asthma
132 hospital treatment was defined as having at least one inpatient, outpatient, or emergency room visit for
133 asthma (ICD-10 codes J45 and J46), retrieved from the Danish National Patient Register (24).
134 Information on the prescriptions for an asthma medication was obtained from the Danish National
135 Prescription Registry (26). The ATC codes for inhaled asthma drugs were: inhaled β 2-agonists
136 (R03AC02–04, -12, and -13), inhaled glucocorticoids (R03BA01, -02 and -05), fixed-dose combination
137 of inhaled β 2-agonists and glucocorticoids (R03AK06 and -07), leukotriene receptor antagonists
138 (R03DC03), and anti-IgE therapies (R03DX05)(28).

139

140 *Statistical analysis*

141 Statistical analyses were performed with Stata 13.1 (StataCorp, College Station, TX, USA). Each child
142 was followed from age 5 years up to 14 years until the end of 2012, emigration, death, or the date of
143 first asthma diagnosis, whichever came first. We estimated incidence rate ratios (IRRs) of childhood

144 asthma and their 95% confidence intervals (CIs) using Poisson regression models. Children born to
145 mothers with hypothyroidism were compared to children whose mothers had no recorded thyroid
146 dysfunction. To account for the dependence between siblings, we used robust sandwich variance
147 estimator for correction of standard errors. A p-value of less than 0.05 (2-sided) was judged statistically
148 significant. Adjustment was made for the following covariates: maternal age at delivery (<25, 25–34,
149 or ≥35 years), primiparity (yes/no), smoking during pregnancy (yes/no), highest education level
150 attained at delivery (elementary school/ above elementary school), annual income at delivery (lowest
151 quartile/above lowest quartile), calendar year at delivery (1998–2000, 2001–2003, or 2004–2007),
152 maternal asthma (yes/no), maternal diabetes (249 and 250 in ICD-8 codes or E10–E14, H36.0, and O24
153 in ICD-10 codes; yes/no), and paternal asthma at delivery (yes/no). We defined maternal or paternal
154 asthma at delivery as one or more hospital contact for asthma or at least two asthma medication
155 prescriptions redeemed within one year before delivery of the index child. Data on covariates were
156 extracted from the registers mentioned above as well as from Statistics Denmark’s registers on
157 education level and annual income (29). About 5.1% of the values were missing for smoking during
158 pregnancy, maternal highest education level and annual income status at delivery, and we consequently
159 applied 20 imputations using the Markov Chain Monte Carlo technique for imputing missing values
160 (30).

161 To examine whether the associations between maternal hypothyroidism and childhood asthma
162 were moderated by thyroid hormone treatment during pregnancy, we classified children born to
163 mothers with hypothyroidism diagnosed before delivery into two groups according to thyroid hormone
164 treatment during pregnancy, which was defined by at least one redeemed prescription of thyroid
165 hormones in the period from 6 months before pregnancy until delivery. Pregnancy was counted from
166 the first day of the last menstrual period until delivery. To further examine whether the association
167 between maternal hypothyroidism and childhood asthma depended on the timing of diagnosis, we
168 categorized maternal hypothyroidism diagnosed after delivery into hypothyroidism diagnosed within 2
169 years after delivery and 3–5 years after delivery.

170

171 **Sensitivity analysis**

172 Five sensitivity analyses were done to validate our findings. First, asthma is highly heritable (31), and
173 the association between maternal hypothyroidism and childhood asthma may differ between children

174 born to mothers with and without asthma. We, therefore, repeated our analyses by stratification on
175 maternal asthma diagnosis. Second, to test whether there was gender-specific difference in the
176 vulnerability to maternal hypothyroidism, we repeated the analyses by stratifying on the sex of the
177 child. Third, to further address the possible secular trends in diagnostic practices, we repeated our
178 analyses stratified on the calendar year of birth (1998–2000, 2001–2003, or 2004–2007). Fourth, as
179 maternal elevated body mass index (BMI) increases the risk of hypothyroxinemia and asthma in the
180 offspring (32, 33), we further investigated the role of maternal hypothyroidism on childhood asthma by
181 inclusion of an interaction term between maternal prepregnancy BMI (<18.5, 18.5–29.9, or ≥ 30 kg/m²)
182 and maternal hypothyroidism in a subcohort of children born during 2004–2007 when information on
183 BMI was available in the registers. Fifth, to evaluate whether the associations were influenced by the
184 definition of childhood asthma and to account for the fact that some children may receive asthma
185 diagnosis before age 5 years, we also investigated the association between maternal hypothyroidism
186 and childhood asthma using a different asthma definition according to asthma treatment during 0–3
187 years and 4–6 years based on the schema from Martinez *et al.*, i.e., early-onset transient, early-onset
188 persistent, and late-onset asthma (34).

189

190 **Ethics**

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

194

195 **Results**

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

203 Overall 48,990 children received treatment for asthma during follow-up in the entire cohort.
204 Table 2 shows the IRRs of asthma according to the presence and the timing of maternal
205 hypothyroidism diagnosis. After adjusting for potential confounders, children born to mothers with
206 hypothyroidism had a slightly increased risk of childhood asthma (IRR=1.14, 95% CI: 1.06–1.23),
207 compared to children born to mothers with no recorded thyroid dysfunction. The IRRs were 1.16 (95%
208 CI: 1.03–1.30) for children born to mothers with hypothyroidism diagnosed before delivery and 1.12
209 (95% CI: 1.02–1.24) diagnosed after delivery.

210 Of the 3,524 children born to mothers with hypothyroidism diagnosed before delivery, 515
211 (14.6%) were born to mothers who received no thyroid hormone treatment, and 3,009 (85.4%) to
212 mothers with at least one redeemed prescription for thyroid hormones in a period from 6 months prior
213 to pregnancy until delivery. In comparison to children born to mothers with no thyroid dysfunction, a
214 slightly higher risk was observed among children whose mothers received no thyroid hormone
215 treatment in the pregnancy (IRR=1.37, 95% CI: 1.04–1.80) versus children born to mothers with
216 thyroid treatment (IRR=1.12, 95% CI: 0.99–1.27).

217 The associations between maternal hypothyroidism and childhood asthma were comparable
218 between children born to mothers with and without asthma, indicating that genetic susceptibility to
219 asthma did not modify the association between maternal hypothyroidism and childhood asthma (Figure
220 2). Similar associations were observed in girls and boys (all p-values for interaction of timing of
221 maternal hyperthyroidism and sex of the child on the multiplicative scale were greater than 0.1), albeit
222 that the magnitude of the associations was non-statistically higher in girls than in boys (Figure S1 in the
223 supplement). There was no strong evidence that the associations varied by study period (Figure S2 in
224 the Supplement), with all p-values for the interaction of timing of maternal hypothyroidism diagnosis
225 and calendar year of birth greater than 0.2. Maternal pre-pregnancy BMI did not modify the estimated
226 effect of maternal hyperthyroidism on childhood asthma (all p-values for interaction were greater than
227 0.2). The associations remained identical when we used different asthma definition. Moreover, the
228 associations did not differ among different phenotypes of childhood asthma (early-onset transient,
229 early-onset persistent, and late-onset asthma) (Table S1 in the supplement).

230 Discussion

231 To the best of our knowledge, our study is the first to investigate the association between maternal
232 hypothyroidism and childhood asthma. In this population-based cohort study, we found that maternal

233 hypothyroidism was associated with a modest but statistically significantly increased risk of childhood
234 asthma. Notably, the association was observed both when maternal hypothyroidism was diagnosed
235 before delivery and also when the disorder was first diagnosed and treated after delivery. The highest
236 risk was observed among children whose mothers had hypothyroidism diagnosed before delivery but
237 received no thyroid hormone treatment during pregnancy.

238

239 ***Maternal hypothyroidism and childhood asthma***

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

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

248 Secondly, autoimmunity is a common cause of hypothyroidism among women of reproductive
249 age (4). Women with chronic autoimmune hypothyroidism have elevated titer of antibodies, which
250 cross the placenta (20). Another possible explanation for the association between maternal
251 hypothyroidism and childhood asthma is that maternal autoantibodies impair beta-adrenergic
252 responsiveness and bronchial epithelium of the fetus, contributing to the pathogenesis of asthma (21).
253 Further studies are needed that more precisely examine potential mechanisms underlying the
254 association.

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

261

262 ***Thyroid hormone treatment of hypothyroidism during pregnancy and childhood asthma***

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

270

271 *Strengths and limitations*

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

276 Our study also has limitations. First, we followed children from 5 years and excluded 2,828
277 (0.5%) children who died before 5 years, which may lead to selection bias. However, there was no
278 statistical difference in the mortality rate before age 5 years between children born to mothers with and
279 without hypothyroidism. Therefore, any bias due to conditioning on the survival is likely to be small.
280 Second, we identified maternal hypothyroidism and childhood asthma from records in hospitals and
281 prescription register, and misclassification cannot be ruled out. Actual measurement of maternal
282 thyroid function in stored biobank sera from Danish pregnant women has shown that 4.5% of the
283 women had undetected hypothyroidism in the early pregnancy (23). In the present study, to account for
284 undetected hypothyroidism during pregnancy, we included women who were diagnosed and treated for
285 hypothyroidism both before and within 5 years after delivery. Still, we may have misclassified some
286 cases of undetected hypothyroidism. Similarly, we may have misclassified asthma due to
287 undertreatment of asthmatics and overtreatment of transient wheeze. We expect all these
288 misclassifications to be non-differential and therefore would have biased our results toward no
289 association. Third, redeemed prescriptions of thyroid hormones do not reflect actual use, while women
290 without prescription redeemed may take medication that was redeemed outside of the defined period.
291 However, studies indicated that adherence to thyroid hormone treatment was good during pregnancy
292 (35, 38), and the bias is non-differential and probably biases our finding on thyroid treatment during

293 pregnancy toward the null. Fourth, we did not have information on laboratory tests on thyrotropin and
294 thyroid hormone levels. We were not able to differentiate the effects of overt and subclinical
295 hypothyroidism. Fifth, we excluded children born to mothers with hyperthyroidism, which imposes
296 constraints on the generalization of our findings to children born to mothers with hypothyroidism
297 following treatment for hyperthyroidism. Last, our study is an observational study. Despite careful
298 adjustment for possible confounders, our findings do not prove causality. The findings of the present
299 study await confirmation in future studies.

300

301 **Conclusion**

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

307

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316 publication.

317 **Conflicts of interests:** None to declare.

318 **Author contributions**

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

322 **References**

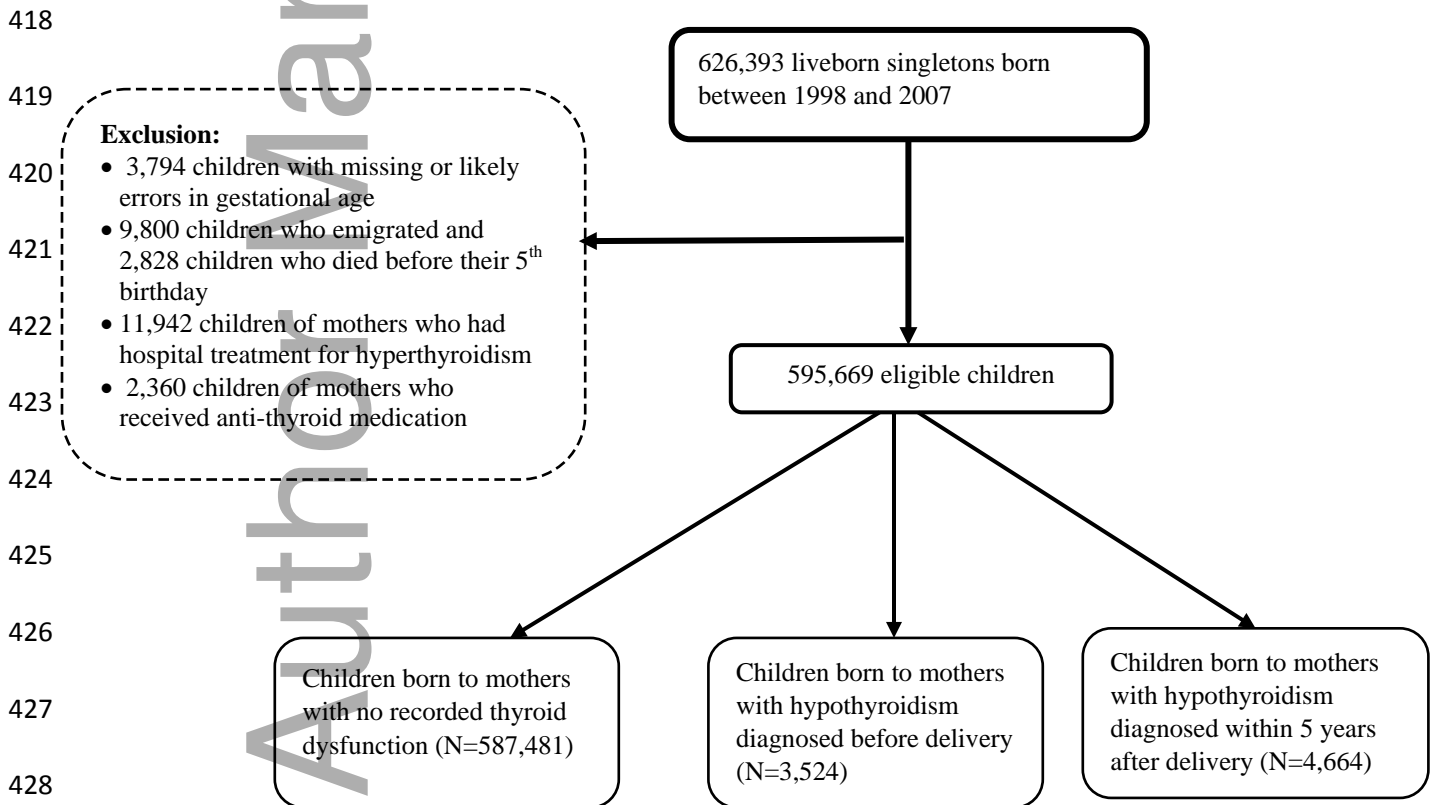
- 323 1. Lazarus JH. Thyroid function in pregnancy. *Br Med Bull* 2011;**97**:137-148.
- 324 2. Casey BM, Dashe JS, Wells CE, McIntire DD, Byrd W, Leveno KJ, et al. Subclinical
325 hypothyroidism and pregnancy outcomes. *Obstet Gynecol* 2005;**105**(2):239-245.
- 326 3. Glinoe D, Abalovich M. Unresolved questions in managing hypothyroidism during pregnancy.
327 *BMJ* 2007;**335**(7614):300-302.
- 328 4. Carle A, Laurberg P, Pedersen IB, Knudsen N, Perrild H, Ovesen L, et al. Epidemiology of
329 subtypes of hypothyroidism in Denmark. *Eur J Endocrinol* 2006;**154**(1):21-28.
- 330 5. Carle A, Pedersen IB, Knudsen N, Perrild H, Ovesen L, Laurberg P. Hypothyroid symptoms and
331 the likelihood of overt thyroid failure: a population-based case-control study. *Eur J Endocrinol*
332 2014;**171**(5):593-602.
- 333 6. Glinoe D, Riahi M, Grun JP, Kinthaert J. Risk of subclinical hypothyroidism in pregnant women
334 with asymptomatic autoimmune thyroid disorders. *J Clin Endocrinol Metab* 1994;**79**(1):197-204.
- 335 7. Alexander EK, Marqusee E, Lawrence J, Jarolim P, Fischer GA, Larsen PR. Timing and
336 magnitude of increases in levothyroxine requirements during pregnancy in women with
337 hypothyroidism. *N Engl J Med* 2004;**351**(3):241-249.
- 338 8. De Vivo A, Mancuso A, Giacobbe A, Moleti M, Maggio Savasta L, De Dominicis R, et al.
339 Thyroid function in women found to have early pregnancy loss. *Thyroid* 2010;**20**(6):633-637.
- 340 9. Andersen SL, Laurberg P, Wu CS, Olsen J. Attention deficit hyperactivity disorder and autism
341 spectrum disorder in children born to mothers with thyroid dysfunction: a Danish nationwide
342 cohort study. *BJOG* 2014;**121**(11):1365-1374.
- 343 10. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, et al. Maternal thyroid
344 deficiency during pregnancy and subsequent neuropsychological development of the child. *N*
345 *Engl J Med* 1999;**341**(8):549-555.
- 346 11. Andersen SL, Olsen J, Wu CS, Laurberg P. Low Birth Weight in Children Born to Mothers with
347 Hyperthyroidism and High Birth Weight in Hypothyroidism, whereas Preterm Birth Is Common
348 in Both Conditions: A Danish National Hospital Register Study. *Eur Thyroid J* 2013;**2**(2):135-
349 144.

- 350 12. Lazarus J, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R, Vaidya B. 2014
351 European thyroid association guidelines for the management of subclinical hypothyroidism in
352 pregnancy and in children. *Eur Thyroid J* 2014;**3**(2):76-94.
- 353 13. De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH, et al. Management of
354 thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice
355 guideline. *J Clin Endocrinol Metab* 2012;**97**(8):2543-2565.
- 356 14. Dansk Thyreoidea Selskab. Kliniske retningslinjer for behandling af thyroideasygdomme hos
357 gravide og nyfødte. 2011. Available online at:
358 [http://www.endocrinology.dk/PDF/NBV/Kliniske_Retningslinier_for_behandling_af_thyroideas](http://www.endocrinology.dk/PDF/NBV/Kliniske_Retningslinier_for_behandling_af_thyroideas_ygdomme_hos_gravide_og_nyfoedte_Apr2011.pdf)
359 [ygdomme_hos_gravide_og_nyfoedte_Apr2011.pdf](http://www.endocrinology.dk/PDF/NBV/Kliniske_Retningslinier_for_behandling_af_thyroideas_ygdomme_hos_gravide_og_nyfoedte_Apr2011.pdf) (accessed Jan 2, 2017).
- 360 15. Giden K, Andersen JT, Torp-Pedersen AL, Enghusen Poulsen H, Torp-Pedersen C, Jimenez-
361 Solem E. Use of thyroid hormones in relation to pregnancy: a Danish nationwide cohort study.
362 *Acta Obstet Gynecol Scand* 2015;**94**(6):591-597.
- 363 16. Forhead AJ, Fowden AL. Thyroid hormones in fetal growth and parturition maturation. *J*
364 *Endocrinol* 2014;**221**(3):R87-R103.
- 365 17. Fisher DA, Nelson JC, Carlton EI, Wilcox RB. Maturation of human hypothalamic-pituitary-
366 thyroid function and control. *Thyroid* 2000;**10**(3):229-234.
- 367 18. van Tuyl M, Blommaert PE, de Boer PA, Wert SE, Ruijter JM, Islam S, et al. Prenatal exposure
368 to thyroid hormone is necessary for normal postnatal development of murine heart and lungs. *Dev*
369 *Biol* 2004;**272**(1):104-117.
- 370 19. Holt PG, Upham JW, Sly PD. Contemporaneous maturation of immunologic and respiratory
371 functions during early childhood: implications for development of asthma prevention strategies. *J*
372 *Allergy Clin Immunol* 2005;**116**(1):16-24; quiz 25.
- 373 20. Seror J, Amand G, Guibourdenche J, Ceccaldi PF, Luton D. Anti-TPO antibodies diffusion
374 through the placental barrier during pregnancy. *PLoS One* 2014;**9**(1):e84647.
- 375 21. Rottem M, Gershwin ME, Shoenfeld Y. Allergic disease and autoimmune effectors pathways.
376 *Dev Immunol* 2002;**9**(3):161-167.
- 377 22. Knudsen LB, Olsen J. The Danish Medical Birth Registry. *Dan Med Bull* 1998;**45**(3):320-323.

- 378 23. Andersen SL, Olsen J. Early Pregnancy Thyroid Function Test Abnormalities in Biobank Sera
379 from Women Clinically Diagnosed with Thyroid Dysfunction Before or After Pregnancy.
380 *Thyroid* 2017;**27**(3):451-459.
- 381 24. Andersen TF, Madsen M, Jorgensen J, Mellekjoer L, Olsen JH. The Danish National Hospital
382 Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999;**46**(3):263-
383 268.
- 384 25. Andersen SL, Olsen J, Laurberg P. Hypothyroidism and pregnancy loss: comparison with
385 hyperthyroidism and diabetes in a Danish population-based study. *Clin Endocrinol (Oxf)* 2016;
386 **85**(6):962-970.
- 387 26. Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. *Scand J*
388 *Public Health* 2011;**39**(7 Suppl):38-41.
- 389 27. Bacharier LB, Boner A, Carlsen KH, Eigenmann PA, Frischer T, Gotz M, et al. Diagnosis and
390 treatment of asthma in childhood: a PRACTALL consensus report. *Allergy* 2008;**63**(1):5-34.
- 391 28. Liu X, Agerbo E, Schlunssen V, Wright RJ, Li J, Munk-Olsen T. Maternal asthma severity and
392 control during pregnancy and risk of offspring asthma. *J Allergy Clin Immunol* 2017. doi:
393 10.1016/j.jaci.2017.05.016.
- 394 29. Petersson F, Baadsgaard M, Thygesen LC. Danish registers on personal labour market affiliation.
395 *Scand J Public Health* 2011;**39**(7 Suppl):95-98.
- 396 30. Royston P, White IR. Multiple Imputation by Chained Equations (MICE): Implementation in
397 Stata. *Journal of Statistical Software* 2011;**45**(4):1-20.
- 398 31. Burke W, Fesinmeyer M, Reed K, Hampson L, Carlsten C. Family history as a predictor of
399 asthma risk. *Am J Prev Med* 2003;**24**(2):160-169.
- 400 32. Reinehr T. Obesity and thyroid function. *Mol Cell Endocrinol* 2010;**316**(2):165-171.
- 401 33. Forno E, Young OM, Kumar R, Simhan H, Celedon JC. Maternal obesity in pregnancy,
402 gestational weight gain, and risk of childhood asthma. *Pediatrics* 2014;**134**(2):e535-546.
- 403 34. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and
404 wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med*
405 1995;**332**(3):133-138.

- 406 35. Maraka S, Mwangi R, McCoy RG, Yao X, Sangaralingham LR, Singh Ospina NM, et al. Thyroid
 407 hormone treatment among pregnant women with subclinical hypothyroidism: US national
 408 assessment. *BMJ* 2017;**356**:i6865.
- 409 36. Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Universal
 410 screening versus case finding for detection and treatment of thyroid hormonal dysfunction during
 411 pregnancy. *J Clin Endocrinol Metab* 2010;**95**(4):1699-1707.
- 412 37. Maraka S, Singh Ospina NM, O'Keeffe DT, Rodriguez-Gutierrez R, Espinosa De Ycaza AE, Wi
 413 CI, et al. Effects of Levothyroxine Therapy on Pregnancy Outcomes in Women with Subclinical
 414 Hypothyroidism. *Thyroid* 2016;**26**(7):980-986.
- 415 38. Olesen C, Sondergaard C, Thrane N, Nielsen GL, de Jong-van den Berg L, Olsen J. Do pregnant
 416 women report use of dispensed medications? *Epidemiology* 2001;**12**(5):497-501.

417 **Figure 1.** Flowchart illustrating the identification of the study population



429

431 **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)

432 Figures are numbers (%)

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

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

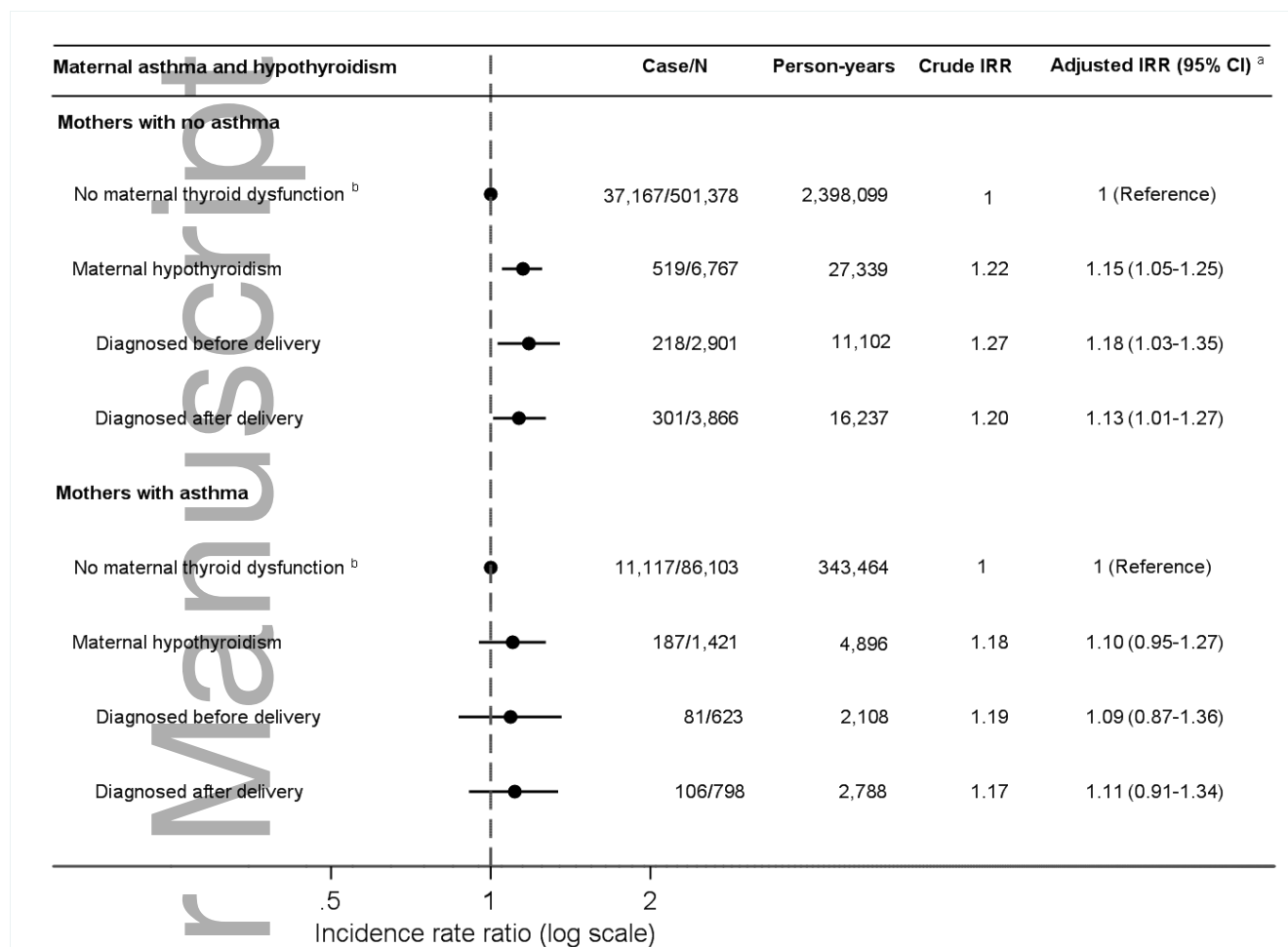
Maternal hypothyroidism and treatment	N	Cases	Person-years	Crude IRRs	Adjusted IRRs ^a (95% CI)
No maternal thyroid dysfunction^b	587,481	48,284	2,741,563	1	1 (reference)
Maternal hypothyroidism	8,188	706	32,235	1.24	1.14 (1.06 – 1.23)
<i>Diagnosed before delivery</i>	3,524	299	13,210	1.29	1.16 (1.03 – 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)
<i>Diagnosed after delivery</i>	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.

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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.



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