

Confirmed association between neonatal phototherapy or neonatal icterus and risk of childhood asthma

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We have previously demonstrated an association between neonatal phototherapy and/or neonatal icterus and risk of hospitalization for childhood asthma. This study included children who were prescribed anti-asthmatic medication on a population basis to study exposures during the foetal and neonatal period and risk of childhood asthma. The Swedish Medical Birth Register was linked to the Swedish Prescribed Drug Register. Perinatal data for singleton children who were prescribed anti-asthmatic medication ($n = 61\,256$) were compared with corresponding data for all singleton children born in Sweden from 1 January 1990 to 30 June 2003 and surviving to 1 July 2005 ($n = 1\,338\,319$). Mantel–Haenszel's odds ratios were calculated after adjustment for various known confounders. Being the first-born child, maternal age above 44 yr, involuntary childlessness for more than 1 yr, maternal smoking during pregnancy, maternal diabetes mellitus of any kind, pre-eclampsia, caesarean section, and instrumental vaginal delivery were all associated with an increased prescription of anti-asthmatic medication during childhood. Preterm birth, low birth weight, being small for gestational age, respiratory problems, mechanical ventilation, and sepsis and/or pneumonia were also associated with increased drug prescriptions. Neonatal phototherapy and/or icterus were risk determinants for children who developed asthma before the age of 12. After controlling for confounders, the odds ratio for phototherapy and/or icterus remained at 1.30 (95% confidence interval 1.16–1.47). In conclusion, this large population-based study confirms an association between some maternal and perinatal factors and childhood asthma, including neonatal phototherapy and/or icterus.

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The incidence of asthma has increased during the last decades (1). Such an increase in incidence during a relatively short time period cannot be explained by genetic changes and is likely because of environmental factors. Many studies have been performed to identify potential environmental risk factors, and several of them have focused on the foetal and neonatal period, when the immune system undergoes a rapid development (2–12).

Large Swedish population-based health registers of high quality offer good possibilities to perform epidemiological research concerning risk factors for different diseases. In one such study, we recently identified several associations between foetal and neonatal factors or events and the risk of childhood asthma (13). To the best of our knowledge, the association between neonatal icterus and/or neonatal phototherapy and risk of asthma has not been previously described. This

was of special interest because phototherapy in some studies has been associated with another disease based on immunological dysregulation, i.e., autoimmune diabetes mellitus (14, 15). Asthma has been described as an autoimmune disease (16), and diabetes mellitus type 1 is a classical autoimmune disease. Thus, both disorders may have common pathogenetic features.

In our previous study, only children hospitalized with a diagnosis of asthma were included (13). This means that a minority of all children with asthma were included, because only few of these patients are hospitalized. Moreover, this study group probably represents children with a more severe disease. The results may thus not be possible to generalize to all children with asthma.

The Swedish Prescribed Drug Register (17) makes it possible to identify all children who have been prescribed and who also have redeemed anti-asthmatic medication. Thus, the aim of this study was to validate our previous findings of associations between exposures during the foetal and neonatal period and risk of asthma in children under the age of 15, with special focus on neonatal icterus and phototherapy, by use of the Swedish Prescribed Drug Register.

Methods

Three large Swedish health registers were used: the Swedish Medical Birth Register, the Swedish Prescribed Drug Register, and the Swedish Hospital Discharge Register.

Linkage between the registers is possible using the personal identification number given to everyone living in the country and widely used in society and in all health care.

The Swedish Medical Birth Register started in 1973 and contains information on the pregnancy, delivery, and neonatal period for nearly all infants born in Sweden. Since 1982, the information is based on copies of medical records from the antenatal care units, the delivery units, and from the paediatric examination of the newborns (18, 19). Children who have immigrated after birth are thus not included in the register.

The Swedish Prescribed Drug Register (17) was established with identification numbers in 2005. It contains information with patient identification on all prescriptions that have been redeemed in Sweden from 1 July 2005 onwards. Drugs are coded with anatomical therapeutic chemical (ATC) codes. From this register, we identified all children who were born between 1990 and 30 June 2003 and who had been prescribed and had redeemed medication against

asthma during the time period 1 July 2005–31 December 2005. For details concerning the selected anti-asthmatic medications, see Table 1. These drugs may or may not have been prescribed for asthma. It is possible in the register to identify prescriptions where asthma was stated as an indication for the medication. This, however, is no requirement for prescriptions, and there will be several anti-asthmatic prescriptions without an indication in the register. We will use the term asthma for the condition of the identified children even though some of them may have got anti-asthmatic drugs for another reason. As the diagnosis of asthma is imprecise in children below 2 yr of age, we excluded these children. Multiple births were also excluded, and only children who were alive on 1 July 2005 were included.

Linkage of these two registers was possible for 97%. Absence of linkage can be because of errors in the identification number, by absence in the register of a few of all infants born in Sweden, or by immigration after birth. Perinatal data for the

Table 1. Anti-asthmatic drugs and systemic glucocorticoids used

ATC Code	Substance	Number of patients
R03AC02	Salbutamol	15,147
R03AC03	Terbutaline	22,374
Adrenergics, inhalation		
R03AC12	Salmeterol	291
R03AC13	Formoterol	2416
R03AK04	Salbutamol and ipratropium	3
R03AK06	Salmeterol and fluticasone	4345
R03AK07	Formoterol and budesonide	6450
Steroids, inhalation		
R03BA01	Beclometasone	117
R03BA02	Budesonide	25,748
R03BA05	Fluticasone	3615
R03BA07	Mometasone	443
Anticholinergics		
R03BB01	Ipratropium	267
R03BB04	Thiotropium	2
Antiallergics		
R03BC01	Cromoglicic acid	148
Adrenergics, systemic		
R03CA02	Ephedrine	89
R03CC02	Salbutamol	3885
R03CC03	Terbutaline	6109
R03CC12	Bambuterol	277
Xantines		
R03DA02	Choline theophyllinate	17,382
Leukotrien receptor antagonists		
R03DC03	Montelukast	4883
Steroids, systemic		
H02AB01	Betamethasone	3983
H02AB02	Dexamethasone	11
H02AB04	Methylprednisolone	7
H02AB06	Prednisolone	153
H02AB09	Hydrocortisone	19

ATC, anatomical therapeutic chemical codes.

children who were prescribed anti-asthmatic medication were then compared with perinatal data for all singleton children born in Sweden during the time period 1990–30 June 2003 and surviving to 30 June 2005 ($n = 1\,337\,472$). The study variables are shown in Table 2. Small-for-gestational age was determined using sex and parity-specific standard growth curves based on data from the Swedish Medical Birth Register (20).

To study the rate of hospitalizations because of asthma among children who had been prescribed anti-asthmatic drugs, the file created above was linked to the Hospital Discharge Register up to and including 2005. This register contains information on all hospitalizations with discharge diagnoses and covers all Sweden since 1987 (21).

Serum bilirubin levels in infants where phototherapy is indicated and when an exchange transfusion should be considered, according to current Swedish national consensus, is illustrated in Fig. 1.

Statistical analysis was made with Mantel–Haenszel analysis after adjustment for various variables, as reported. Odds ratios (OR) were determined as risk estimates, and their 95% confidence intervals (CI) were estimated with Miettinen's test-based method.

Results

During the second half year of 2005, a total of 386 213 children, born during the period 1 January 1990–30 June 2003, were registered in the Swedish Prescribed Drug Register. Of these, 64,204 had been given a prescription with the ATC code R03. For 25,740 (40%) children, the diagnosis of asthma was indicated in the prescription. Linkage was possible for 61,988 children (97%).

Table 2. Variables studied

Maternal characteristics	Infant characteristics
Maternal age (<20, 20–39, ≥40)	Year of birth
Parity (1, ≥2)	Multiple births
Maternal smoking in early pregnancy (unknown, yes, no)	Preterm birth
Involuntary childlessness (yes, no)	Low birth weight
Pre-eclampsia	Small for gestational age
Diabetes mellitus during pregnancy (any type)	Sepsis or pneumonia
Caesarean section	Respiratory problems
Instrumental vaginal delivery	Mechanical ventilation
	Low Apgar score (<7 at 5 min)
	Blood group incompatibility
	Icterus
	Phototherapy

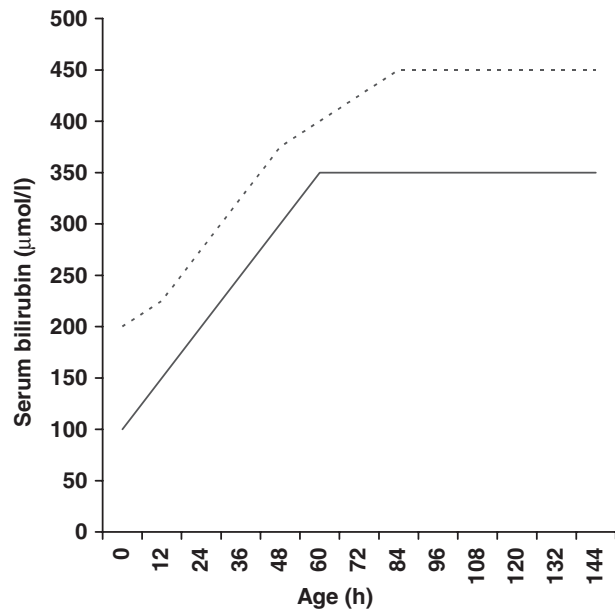


Fig. 1. Serum bilirubin levels ($\mu\text{mol/l}$) in infants where phototherapy is indicated (solid line) and when an exchange transfusion should be considered (broken line) in relation to age (hours), according to current Swedish national consensus (30).

To estimate the validity of the prescription of an anti-asthmatic drug as a proxy for asthma, the rates of hospitalization were studied for cases with or without a diagnosis of asthma stated on the prescription. During the years 1990–2005, 5641 (9.1%) children who had got a prescription of anti-asthmatic drugs were hospitalized and discharged with the diagnosis of asthma. Among the children where at least one prescription stated the indication asthma, 3113 (12.5%) were hospitalized because of asthma. Among those without such an indication in the prescription, 2528 (6.8%) were hospitalized with this diagnosis.

The further analysis was restricted to singleton infants ($n = 61,256$). Among them, 4152 (6.8%) also had a prescription for glucocorticoids. Among these, 2025 had in any prescription the indication asthma marked (49%), while among children without a prescription for glucocorticoids, this occurred in 22,675 among 57,104 children (40%).

Maternal and delivery risk markers for asthma are summarized in Table 3. Teenage mothers had a lower risk, and mothers above the age of 45 seemed to have a higher risk of having a child who would be prescribed anti-asthmatic medication. Being the first-born child was associated with an increased risk. Involuntary childlessness for more than 1 yr, maternal smoking during pregnancy, maternal diabetes mellitus of any kind, pre-eclampsia, caesarean section, and

Table 3. Maternal characteristics as risk determinants for childhood asthma

Variables	Number of children with asthma	Total number	OR	95% CI
Maternal age*				
<20	1230	30,451	0.84	0.79–0.90
20–39	58,581	1,277,229	1.00	Reference
≥40	1445	29,792	1.07	1.01–1.13
Parity*				
1	28,109	568,395	1.14	1.12–1.16
≥2	33,147	759,077	1.00	Reference
Smoking*				
Unknown	3648	76,918		
No	47,874	1,042,683	1.00	Reference
Yes	9734	216,671	1.08	1.05–1.10
Involuntary childlessness*				
No	57,170	1,265,376	1.00	Reference
Yes	4086	72,096	1.18	1.14–1.22
Diabetes mellitus†	916	16,257	1.19	1.12–1.28
Pre-eclampsia†	2466	41,389	1.24	1.19–1.29
Caesarean section†	9600	160,677	1.30	1.27–1.33
Instrumental vaginal delivery†,‡	4509	88,134	1.09	1.06–1.13

OR, odds ratio. CI, confidence interval.

*Adjusted for year of birth and the other three of the first four variables.

†Adjusted for year of birth, maternal age, parity, smoking, and involuntary childlessness. ‡Restricted to deliveries which did not start with a caesarean section (51,656 with asthma, 116,649 in population).

instrumental vaginal delivery were all also associated with an increased risk but no odds ratio was above 1.30.

Some neonatal risk markers for asthma are described in Table 4. Preterm birth, low birth weight, being small for gestational age, respiratory problems, mechanical ventilation, and sepsis and/or pneumonia were associated with an increased risk. Neonatal phototherapy and/or neonatal icterus appeared as a risk determinant. Table 5 shows the results concerning phototherapy and/or icterus for different subgroups of children. The highest estimates were obtained when a diagnosis of asthma was stated on the prescription or when systemic glucocorticoids had been given, but the differences in OR are not large.

After extensive exclusions of children with other risk factors, the OR for phototherapy and/or icterus decreased somewhat and lost statistical significance. However, this effect was restricted to the first four birth cohorts of children, born 1990–93, OR = 1.13 (95% CI 0.96–1.34). For children born after 1993, the OR remained at 1.30 (95% CI 1.16–1.47). Without exclusions, the OR for children born after 1993 was 1.41 (95% CI 1.32–1.50).

Fig. 2 shows the OR for asthma in the presence of some selected variables for four different birth cohorts: 1990–93, 1994–97, 1998–2000, and 2001–03. There were only small differences in

Table 4. Infant characteristics as risk determinants for childhood asthma

Variables	Number of children with asthma	Total number	OR	95% CI
Preterm <37 wk*	4330	63,843	1.52	1.47–1.57
Preterm <32 wk*	739	7586	2.18	2.02–2.35
Birth weight <2500 g†	2806	40,751	1.52	1.42–1.63
Birth weight <1500 g†	607	6062	2.23	1.64–3.03
Small for gestational age‡	1639	28,545	1.22	1.11–1.35
Apgar <7 at 5 minutes§	958	13,868	1.50	1.40–1.60
Sepsis and/or pneumonia	995	15,246	1.42	1.33–1.52
Mechanical ventilation	148	1318	2.47	2.09–2.92
Respiratory diagnoses	2370	32,580	1.61	1.54–1.68
Blood group incompatibility	339	6718	1.11	0.99–1.24
Icterus	3018	45,353	1.45	1.40–1.51
Phototherapy	1525	24,953	1.35	1.28–1.42

OR, odds ratio. CI, confidence interval.

*Singletons with known gestational duration (61,155 with asthma, 1,325,195 in population).

†Singletons with known birth weight (60,972 with asthma, 1,322,506 in population).

‡Singletons with known gestational duration, birth weight, and sex (60,882 with asthma, 1,320,407 in population).

§Infants with known Apgar score (51,656 with asthma, 1,166,649 in population). All other variables were studied on all children (61,256 with asthma, 1,337,472 in population). Adjustments were made for year of birth, maternal age, parity, smoking during pregnancy, and years of involuntary childlessness.

Table 5. Phototherapy as a risk determinant for different subgroups of childhood asthma

Group studied	Number with phototherapy and asthma	Number with asthma	OR	95% CI
All asthma	1525	24,953	1.35	1.28–1.43
Asthma stated in prescription	658	24,700	1.42	1.31–1.54
Asthma not stated in prescription	867	36,556	1.28	1.20–1.37
Systemic corticosteroids	116	4152	1.47	1.22–1.77
No systemic corticosteroid	1409	57,104	1.34	1.27–1.41
Asthma after some exclusions*	438	41,303	1.24	0.90–1.72

OR, odds ratio. CI, confidence interval.

*Exclusion of maternal diabetes mellitus, pre-eclampsia, caesarean section, instrumental vaginal delivery, preterm birth (<37 wk), low birth weight (<2500 g), respiratory diagnoses, Apgar score <7 at 5 min, mechanical ventilation, sepsis, and/or pneumonia. Adjustments were made for year of birth, maternal age, parity, smoking during pregnancy, and years of involuntary childlessness.

the odds ratio estimates for maternal diabetes mellitus, pre-eclampsia, or caesarean section, while the association with preterm birth, low birth weight, respiratory diagnoses, sepsis and/or pneumonia and as mentioned, phototherapy and/or neonatal icterus increased in younger cohorts.

In an effort to distinguish between the effect of icterus and phototherapy, the OR for either exposure was determined. When a diagnosis of icterus was present but not phototherapy, the

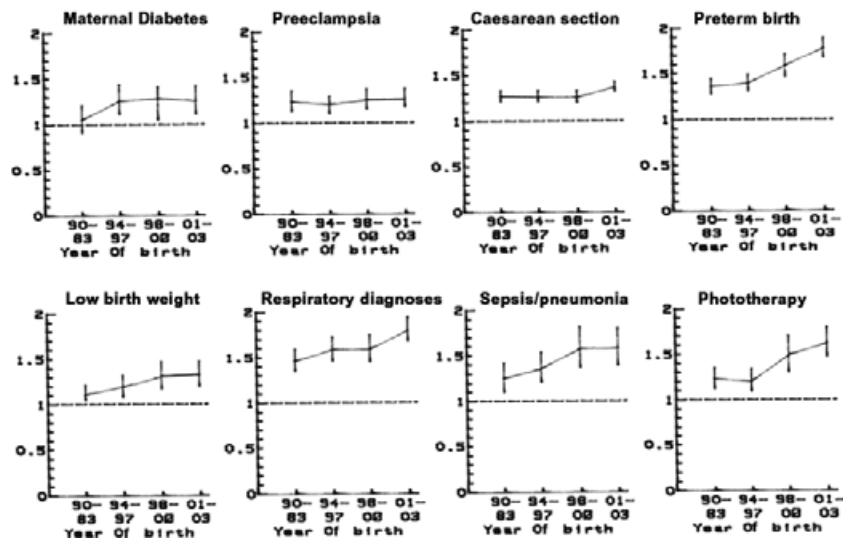


Fig. 2. Diagrams showing OR estimates with 95% CI (vertical lines) for eight risk determinants and for each one of four periods of year of births.

OR was 1.26 (95% CI 1.21–1.32) and when both a diagnosis of icterus and phototherapy was present, the OR was higher, 1.41 (95% CI 1.29–1.53). These two OR differs significantly, $z = 2.32$, $p = 0.03$.

Discussion

This study confirms and strengthens our previous findings of an association between childhood asthma and neonatal icterus and/or neonatal phototherapy (13). The results of this study were obtained in a larger population of children with asthma than our previous investigation. Neonatal phototherapy and icterus are closely related to the other risk factors. However, the association remained for children who developed asthma before the age of 12, after exclusions and adjustments made to minimize the possibility that the association was secondary to other known perinatal risk factors. We found the highest OR among the youngest children.

Childhood asthma is not a well-defined diagnosis, and prescription of anti-asthmatic drugs may not correspond to true asthma. Children with other unspecific diagnoses will therefore be included in the study. However, this will underestimate an association and will not give false-positive results. We tried to limit such effects by only including children older than 2 yr of age and by comparing children with prescriptions with and without the indication of asthma stated. Large population-based registers will identify also rather low risks, but because of the dilution effect of a poorly defined diagnosis, the risks may still be clinically relevant. Also the risk determinants studied may suffer from low precision in the Swedish Medical Birth Register, and clearly

the treatment diagnosis phototherapy may in some cases not be recorded. However, it is unlikely that this would lead to a bias, because the disorder leading to the prescription was not known at the time of registration. Again, the possible consequence would be a slight underestimation of the risk. Maternal asthma will increase the risk of asthma in the child because of a genetic component in the disease. If maternal asthma was associated with an increased risk for jaundice and phototherapy treatment in the child, it could act as a confounder. Maternal asthma and use of anti-asthmatic drugs during pregnancy were associated with neonatal icterus in one study, but when children born preterm were excluded, the risk of neonatal icterus decreased and lost statistical significance. It was concluded that the association mainly was an expression of risk of preterm birth (22).

Phototherapy is a common treatment for mild and moderate neonatal icterus. In experimental studies, phototherapy has induced DNA strand breaks and mutations (23). The strong association between icterus and phototherapy makes it difficult to separate them from each other, also in this study. The observed effect can thus be caused by bilirubin or its degradation products and/or by an effect of phototherapy. We found a significantly higher OR if phototherapy had been given than when only a diagnosis of icterus but no phototherapy was indicated. This could suggest an effect of phototherapy itself but most likely treated cases had higher bilirubin values than non-treated cases, which do not exclude a sole effect of icterus. A further complication is that in all large databases, diagnoses or treatments could be absent so the apparent effect of icterus in the absence of phototherapy could

be because of an under-recording of the latter if the true cause is phototherapy.

Phototherapy suppresses T-lymphocyte activity and inflammation in the skin and is successfully used among older children and adults with skin diseases (24). Also phototherapy in the visible wave length range can reduce inflammation in the skin (25). It seems likely that phototherapy could influence the immature immune system of the newborn child, maybe by direct effects on T-lymphocytes in the thin skin. Asthma has been described mainly as a Th-2-mediated disease. During the rapid immunological development in the newborn, the immune system shifts from mainly Th-2 immune responses towards more Th-1 activity. If the T-lymphocytes are suppressed during this time by e.g., phototherapy, this shift may be delayed. Bilirubin is supposed to be an antioxidant at least at moderately elevated levels, with capability to reduce complement activation (26) and to slow leucocyte migration (27), and thus also to some extent has an immunosuppressive effect. These mechanisms could have implications for the development of diseases caused in part by a dysregulated immune response.

Neonatal complications like preterm birth, low birth weight, being small for gestational age, respiratory distress, low Apgar score, and severe infections including sepsis or pneumonia were all associated with an increased risk of getting later anti-asthmatic medication. Also, procedures like respiratory treatment, caesarean section, and instrumental vaginal delivery were associated with an increased risk. This is in agreement with previous results by us and by others (4–6, 8–13). Various neonatal complications may cause disturbances, inflammation, and epithelial damage in the airways, which could predispose for later development of airway disease.

We show that the first-born child had an increased risk of childhood asthma. Having older siblings often means exposure to airway infections, which in accordance with the hygiene hypothesis would decrease the risk of atopy. This hypothesis, however, is under debate, and repeated early infections have in some studies been associated with an increased risk of asthma (28, 29). Several of the perinatal risk determinants seemed strongest in the youngest, suggesting that children with such perinatal exposures and who are genetically susceptible may develop the disease at a younger age.

We confirm that maternal smoking during pregnancy and childhood is associated with an increased risk of childhood asthma (30–32). Young maternal age was not associated with a

risk of childhood asthma, in contrast with our previous study, where young mothers had an increased risk of having a child hospitalized for asthma (13). The explanation could be that young mothers may seek medical care more often than older mothers. Maternal diabetes mellitus during pregnancy and pre-eclampsia were risk determinants for childhood asthma in our study. Both conditions are associated with pregnancy complications of possible importance for childhood asthma. Type 1 diabetes and pre-eclampsia are associated (14), and both have links to immunological disturbances that could be of importance for the development of childhood asthma by inheritance and by influence on the foetal environment.

In conclusion, this large population-based study confirms associations between some maternal and perinatal factors and childhood asthma. We furthermore extend our previous observation of an independent association between neonatal phototherapy and/or icterus and the risk of childhood asthma. The mechanism behind this association needs further exploration.

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