

Is neonatal phototherapy associated with an increased risk for hospitalized childhood bronchial asthma?

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This population-based register study examined if factors during the fetal and neonatal period influence the risk for the child to develop bronchial asthma (asthma). From the Swedish Hospital Discharge Register we identified children, born between 1987 and 1999, who had been hospitalized for asthma up to 2001. Thus, the outcome measure contains only hospitalized cases, not all children with asthma. Children younger than 2 yr at admission were excluded because of the uncertainty about the diagnosis of asthma in younger children. The remaining 14,803 children were compared with all children born the same years, recorded in the Swedish Medical Birth Registry, for information on pre- and perinatal characteristics. Odds ratios (ORs) were calculated with Mantel-Haenszel technique and 95% confidence intervals (CIs) with Miettinen's test-based method. The presence of various maternal and neonatal confounders were identified and adjusted for in the analyses. The association between some known factors and childhood asthma were confirmed: young maternal age, maternal smoking, period of unwanted childlessness, low maternal level of education, maternal diabetes, preterm birth, low birth weight, small-for-gestational age, caesarean section, and instrumental vaginal delivery. A number of neonatal characteristics were shown to be independent risk factors: sepsis or pneumonia, neonatal respiratory problems and treatments, neonatal icterus, and/or neonatal phototherapy. The association with icterus and phototherapy remained after exclusion of cases showing other neonatal risk factors and after adjustment for maternal factors (OR 1.27, 95% CI: 1.08–1.50), and increased to 1.5 if the children had been hospitalized for asthma more than once. In conclusion, our results suggest an association between neonatal icterus and/or treatment with neonatal phototherapy and hospitalized childhood asthma. This association needs further exploration.

**Sara Aspberg¹, Gisela Dahlquist²,
Thomas Kahan¹ and Bengt Källén³**

¹Division of Internal Medicine, Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden, ²Department of Clinical Sciences, Pediatrics, Umea University, Umea, Sweden, ³University of Lund, Tornblad Institutet, Lund, Sweden

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Dr. Sara Aspberg, Division of Internal Medicine, Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, S-182 88 Stockholm, Sweden
Tel.: +46 8 655 5000
Fax: +46 8 622 6810
E-mail: sara.aspberg@ds.se

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Bronchial asthma (asthma) is one of the most common diseases in the Western world, and the prevalence is increasing (1). Although susceptibility genes seem to play an important role in the etiology of this disease, such rapid increase in prevalence as that seen over the past decades could not be explained by changes in the gene pool. Asthma is a multifactorial disease, characterized by reversible obstruction, inflammation,

and hyper-responsiveness of the airways. Atopy is a strong risk factor for the development of asthma, especially among children. Atopy is characterized by specific immunoglobulin E (IgE)-mediated immune responses to foreign antigens. Environmental and lifestyle factors may affect the immune responsiveness, such as IgE-type immune responses, which may lead to asthma. The observation of a higher impact of

maternal than paternal asthma and atopy on the risk of asthma in the offspring (1, 2) has focused the interest on the fetal and early perinatal period of life. Fetal and perinatal events can affect the developing immune system and the respiratory system, which might increase the risk of asthma (3, 4). Thus, preterm birth and low birth weight repeatedly have been associated with an increased risk of asthma (2–8). Other complications during pregnancy and delivery, such as antepartum hemorrhage, insufficient placenta, maternal infections, gestational diabetes, and caesarean section have all been linked to childhood asthma (2, 9–12). Among exposures in the perinatal period, respiratory distress syndrome, early viral infections, and neonatal use of antibiotics have been associated with asthma (2, 4).

Another childhood onset disease, which is increasing rapidly in the Western world, is autoimmune diabetes mellitus (13). Although type 1-diabetes is supposed to be mainly a Th₁ mediated disease, whereas asthma would be mainly Th₂ mediated, both diseases seem to increase in frequency in parallel and both diseases result from a dysregulation of the immune system. It has been suggested that allergy and autoimmunity have common pathogenetic effector pathways (14). Several reports show that perinatal risk factors are associated with autoimmune diabetes (15, 16). Blood group incompatibility syndrome and phototherapy seems to have a significant effect on the development of childhood onset diabetes (16, 17).

The aim of this study was to analyze if phototherapy shows the same association with childhood asthma. By analyzing other potential risk factors we tried to identify confounding factors and to validate the data, as some of the factors are well-established risk factors for asthma, and such associations should remain also in this study population.

Patients and methods

Large population-based registers are important for the effective study of risk factors in complex diseases. Sweden offers unique possibilities to perform epidemiological research on early risk determinants for different diseases by the use of nationwide health registers of high quality. In the present study we have used two large nationwide Swedish registers to further analyze the influence of perinatal risk factors on the risk to develop childhood asthma.

We used the Swedish Hospital Discharge Register (18) to identify children hospitalized

for asthma. Information on putative pre- and perinatal risk factors was obtained by linkage with the Swedish Medical Birth Register (19). The Swedish Hospital Discharge Register contains information on all hospitalizations with discharge diagnoses and covers all of Sweden since 1987 (18). From this register, we identified all children born between 1987 and 1999, who had been hospitalized for asthma before the end of 2001. Small children have narrow airways and can have wheezing breath without any atopic predisposition, especially at times of airway infections. Therefore, we only included children who had been treated after the age of 2 yr. A total of 15,409 children included in the Swedish Hospital Discharge Register fulfilled these criteria.

The Swedish Medical Birth Register started in 1973, and contains information on the pregnancy, delivery, and the neonatal period for nearly all infants born in Sweden. The information is (since 1982) based on copies of medical records from the antenatal care units, the delivery units, and the pediatric examinations of the newborns (19, 20). Linkage between the two registers is possible by the personal identification number given to everyone living in Sweden and widely used in health care, including central health registers. Linkage between the two registers was possible for 14,803 (96%) of the children. Absence of linkage can be due to the fact that children who have immigrated after birth are not included in the Medical Birth Register, by absence in that register of a few percent of all infants born, or by errors in the identification numbers.

The children with a diagnosis of asthma were compared with all 1,386,029 children born and registered in Sweden these years in the Swedish Medical Birth Register. The studied variables are shown in Table 1. Small-for-gestational age was determined using sex and parity specific standard growth curves based on the data from the Swedish Medical Birth Register (21).

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

Results

Background data

Among the 14,803 children identified with asthma, 9581 were boys and 5222 girls. The sex ratio (number of boys/number of girls) was 1.83

(95% CI: 1.77–1.90). The sex ratio among all newborns in Sweden is 1.06.

A total of 14,364 of the children with asthma were born as singletons, 427 as twins, and 12 as triplets. The OR for childhood asthma was 1.14 (95% CI 0.99–1.31) for multiple births, after the adjustment for maternal age, parity, smoking habits, and years of involuntary childlessness. Thus, the increase in risk in multiple births for asthma does not quite reach statistical signifi-

cance. The increase in risk is explained by preterm birth, low birth weight and low Apgar score, as the OR was 0.81 (95% CI: 0.13–5.00) after the exclusion of such infants. The average follow up time for all children was 6.8 yr, with a range from 2 to 13 yr.

Maternal characteristics

Fig. 1 shows the associations between certain maternal characteristics and the risk for childhood asthma, after exclusion of infants born preterm (<37 wk), with low birth weight (<2500 g), or with a low 5 min Apgar score (<7). The OR for each variable was adjusted for the other four variables. The results confirm previous observations of an increased risk for asthma with low maternal age, maternal smoking (in our data only if she smoked ≥ 10 cigarettes per day), and with a low maternal level of education. Also involuntary childlessness is a statistically significant risk factor.

Maternal pre-eclampsia (OR = 1.18, 95% CI: 1.05–1.33), maternal diabetes (any type, OR = 1.20, 95% CI: 1.02–1.42), caesarean section (OR = 1.44, 95% CI: 1.37–1.50) vs. vaginal delivery, and instrumental vaginal delivery (OR = 1.08, 95% CI: 1.01–1.17) vs. non-instrumental vaginal delivery, also appeared as significant risk factors. Similar OR values were

Table 1. Maternal and infant characteristics selected for analysis

Maternal characteristics	Infant characteristics
Maternal age in 5-yr classes	Year of birth
Parity (1, 2, 3, and ≥ 4)	Sex
Maternal smoking in early pregnancy (none, <10, and ≥ 10 cigarettes/day)	Multiple births
Duration of pregnancy, completed weeks	Birth weight
Involuntary childlessness, years	Apgar score
Maternal level of education (obtained by linkage from the Education Register of Statistics Sweden, up to 1995)	Some neonatal diagnoses or treatments
	Sepsis or pneumonia
	Respiratory problems
	Mechanical ventilation
	Blood group incompatibility
	Icterus
	Phototherapy

Pre-eclampsia

Diabetes during pregnancy (any type)

Caesarean section

Instrumental vaginal delivery

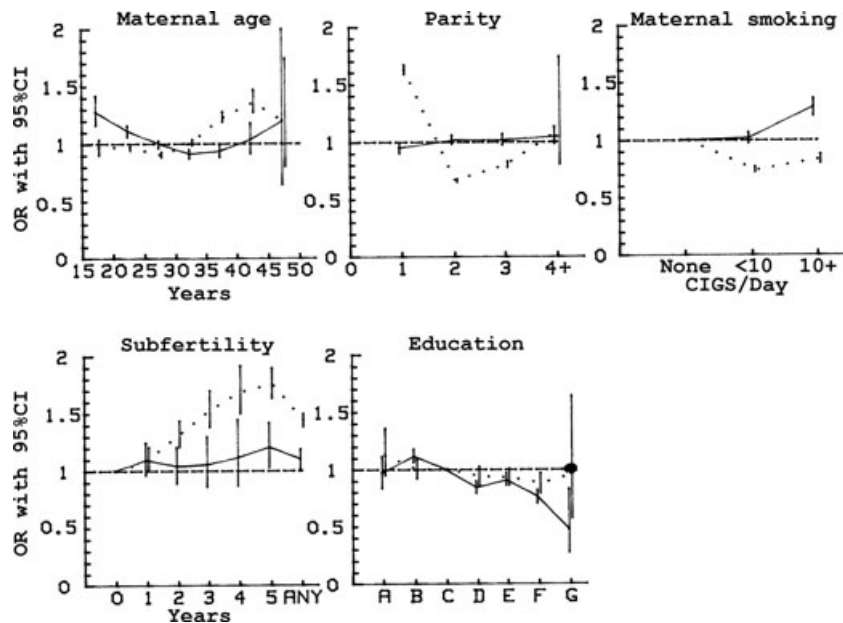


Fig. 1. Odds ratios with 95% confidence intervals (CIs) (95% CI, vertical bars) for various maternal characteristics and childhood asthma (solid lines) and infant icterus (broken lines). Each variable is adjusted for the other four variables and for the year of birth. Maternal level of education was classified as (a) less than compulsory school (<9 yr), (b) compulsory school (9–10 yr), (c) <3 yr gymnasium, (d) 3–4 yr gymnasium, (e) <3 yr post-gymnasium, (f) ≥ 3 yr post-gymnasium and (g) university or equivalent. Swedish 'gymnasium' corresponds to upper secondary school in the UK and to senior high school in USA. Data on education was only available up to and including 1995.

seen also after exclusion of infants who were preterm, of low birth weight, or had low Apgar score.

Neonatal characteristics

Table 2 verifies the observations in the literature that preterm birth, low birth weight, small-for-gestational age, and low Apgar score are risk factors for childhood asthma. Table 3 summarizes the associations between various neonatal conditions and childhood asthma. Adjustment was made for year of birth, maternal age, parity, smoking, and years of involuntary childlessness. Two sets of OR values are given, one including all infants, and the other after exclusion of infants with strong risk factors for childhood asthma, i.e., preterm birth, low birth weight, and low Apgar score. In the latter case the OR values decreased but all associations remained statistically significant.

Two risk factors in Table 3 represent novel observations, icterus and neonatal phototherapy. No effect of blood group incompatibility (mainly ABO) was seen. Fig. 1 shows some maternal risk factors for phototherapy. As seen in Fig. 1 most of the studied factors influence the risk both for asthma and for phototherapy, but often in different ways or with different strength. The

only exception is maternal education, which influences the risk for asthma but not for neonatal phototherapy. Therefore, the results were not adjusted for maternal education in the final analysis of phototherapy.

Table 4 presents the effect of phototherapy for the risk of childhood asthma after exclusion of infants with other strong risk factors: preterm birth, low birth weight, low Apgar score, respiratory problems, sepsis or pneumonia, children delivered by caesarean section or by mothers with diabetes mellitus, or pre-eclampsia. The OR remained increased and statistically significant (Table 4). Two or more hospitalizations for asthma may indicate a more severe disease and perhaps also a more certain diagnosis. Table 4 shows that neonatal phototherapy is a stronger risk factor for asthma in children who have been hospitalized two or more times than in those just hospitalized once.

Discussion

This large study makes it possible to identify also relatively low frequency events as risk factors for childhood asthma. Diagnoses in health registers are sometimes not perfect and a certain misclassification will occur. On the other hand, the registration of all factors analyzed was made

Table 2. The risk of development of childhood asthma in relation to duration of pregnancy, birth weight, small for gestational age, and low Apgar score (<7 at 5 min) in singleton infants

Variable	Population (n)	Asthma (n)	OR (95% CI)	p-value
<32 wk	7566	289	3.67 (3.28–4.11)	<0.0001
<37 wk	65,470	1278	1.86 (1.62–2.15)	<0.0001
<1500 g	6406	250	3.79 (1.68–8.58)	<0.001
<2500 g	42,449	902	1.97 (1.63–2.37)	<0.0001
>4500 g	47,094	487	1.04 (0.80–1.34)	0.79
SGA	35,383	571	1.43 (1.11–1.84)	0.003
Low Apgar score	14,258	319	2.24 (2.00–2.50)	<0.0001

CI, confidence interval; OR, odds ratio; SGA, small for gestational age (<2 standard deviations below expected weight at that week, infant sex, and maternal parity).

Table 4. Odds ratios (ORs) for neonatal phototherapy as a risk factor for childhood asthma in relation to number of hospitalizations for asthma

Number of hospitalizations for asthma	Phototherapy (n)		OR (95% CI)	p-value
	Yes	No		
≥1	147	10,367	1.27 (1.08–1.50)	0.002
≥2	65	3891	1.52 (1.19–1.95)	0.0004
≥3	31	1,953	1.46 (1.02–2.09)	0.04

Adjustments were made for year of birth, maternal age, parity, smoking during pregnancy, and involuntary childlessness. Excluded were infants with preterm birth, low birth weight, low Apgar score, respiratory problems, sepsis, pneumonia, caesarean section, instrumental vaginal delivery, maternal diabetes mellitus, or pre-eclampsia.

CI, confidence interval.

Table 3. Some neonatal diagnoses and treatments and the risk of childhood asthma

	Population (n)	Asthma (n)	OR (95% CI) all subjects	OR (95% CI) and p-value after exclusions
Sepsis or pneumonia	15,887	331	1.96 (1.76–2.18)	1.74 (1.50–2.01) p < 0.0001
Respiratory problems	36,316	784	2.11 (1.97–2.27)	1.58 (1.40–1.79) p < 0.0001
Mechanical ventilation	1560	64	3.62 (2.85–4.60)	2.95 (1.34–6.50) p = 0.007
Blood group incompatibility	6967	83	1.11 (0.89–1.39)	1.09 (0.85–1.40) p = 0.51
Icterus	50,616	858	1.64 (1.53–1.75)	1.37 (1.22–1.54) p < 0.0001
Phototherapy	29,640	494	1.51 (1.38–1.65)	1.34 (1.16–1.54) p < 0.0001

After exclusion denotes exclusion for preterm birth (<37 wk), low birth weight (<2500 g), and low Apgar score (<7 at 5 min).

CI, confidence interval; OR, odds ratio.

during pregnancy or at delivery, ensuring that data cannot be biased by the fact that the child developed asthma. Misclassification will therefore affect risk estimates little, and if anything will bias them towards 1.

This study confirms an increased risk of childhood asthma if the mother is young or has a short duration of education (2, 7, 22). These associations could in part be explained by differences in tendency to seek hospital care, and may not reflect a true difference in the prevalence of asthma. Nevertheless, environmental and socioeconomic factors are likely to contribute to the development of asthma. Maternal smoking during pregnancy is a well-established risk factor for childhood asthma. In our study it was not possible to evaluate whether the mother continued to smoke after delivery, and maternal smoking during pregnancy may be a proxy for exposure to cigarette smoke postpartum. Studies designed to distinguish between maternal smoking during pregnancy and postpartum smoking have found an independent association between exposure for cigarette smoke in utero and childhood asthma (22–24).

Maternal diabetes mellitus and pre-eclampsia are also associated with an increased risk of childhood asthma (2). Both diagnoses are associated with an increased rate of pregnancy disturbances and neonatal complications and treatments, and can thereby also influence other factors of possible importance for childhood asthma. Also delivery method and a number of neonatal conditions have been associated with an increased risk of childhood asthma (2–5, 7, 8, 10). These findings were confirmed by the current study. Further confounding factors may exist, which have not been possible to take into account. One such factor could be breast feeding. There are conflicting data regarding the influence of breast feeding on the risk to develop childhood asthma. However, most studies have demonstrated that breast feeding either has no effect or provides a protective effect against the development of childhood asthma (25).

As in most reports, it was not possible to adjust for maternal asthma in this study. This might confound some results because of the genetic trait for asthma, and as maternal asthma has been associated with complications for both mother and child. It was therefore important that we made exclusions and adjustments for such factors in the final analyses.

Our study is limited to hospitalized cases with childhood asthma. This will have various effects. The case definition will probably result in a selection of relatively severe cases of asthma and

the findings may only be relevant for that group. The risk factors identified will be a combination of risk for asthma and risk for being hospitalized for asthma. Thus, for instance, young maternal age could be a risk factor if young mothers may be more prone to seek medical advice than older mothers. It seems less probable that the risk under study (icterus/phototherapy) can affect the hospitalization risk years later. Only a small part of all children with a diagnosis of asthma is hospitalized, and other cases will incorrectly be labeled as controls in this study. This will result in an underestimate of the risk and will not give false-positive results. The group of children hospitalized with a diagnosis of asthma is probably heterogeneous, consisting of, for instance children with atopic and non-atopic asthma, and risk factors for the various subgroups may differ. Our estimates refer to the total group. Further subdivision is not reliable when based on hospital discharge diagnoses.

A novel finding, as far as we know, is that neonatal icterus and neonatal phototherapy appear as risk factors for childhood asthma. These associations remained also when extensive exclusions and adjustments were done to exclude that this association was secondary to other risk factors. The diagnoses given in the Swedish Medical Birth Register are not always complete and some mothers or infants with one or more of these diagnoses may have remained in the analysis. However, it is unlikely that this can explain the observations made. As an example, the OR for icterus before exclusion of preterm birth or low birth weight infants and infants with a low Apgar score was 1.64; after such exclusions it was 1.37. After further exclusions of specific diagnoses and other conditions, the OR remained similar for infants with any hospitalization for asthma (OR 1.27; see Table 4). If this increase in OR were the effect of inclusion of infants in the analysis who should have been excluded, it would mean that about 80% of diagnoses should be missing in the register, which is out of question.

The strong association between neonatal icterus and neonatal phototherapy makes it nearly impossible to separate the effect of the two, and it was not possible to do so in this study. We can expect that there is an excess of mothers with asthma among children with the disease and maternal asthma or the medication for the disease taken during pregnancy might be associated with an increased risk for neonatal icterus and phototherapy. In an analysis of 14,324 singleton infants whose mothers had reported the use of anti-asthmatic drugs during pregnancy and with the same exclusions as given in Table 4,

284 children had a neonatal diagnosis of icterus. The OR was 1.06 (95% CI: 0.70–1.61), adjusting for year of birth, maternal age, parity, smoking, and years of involuntary childlessness (B. Källén, personal communication). Thus, there was no evidence of an association between maternal asthma and neonatal icterus.

Phototherapy is widely used for mild and moderately jaundiced infants and is thought to be very safe. The main acute complications are severe watery stools, skin rashes, and dehydration. Potential side effects of the photo breakdown products of bilirubin may still have long-term effects. Experimental studies indicate that phototherapy can induce DNA strand breaks and mutations (26). Phototherapy is not only used during the neonatal period but also later in life for the treatment of different kinds of skin diseases. Thus, eczema mediated by T-lymphocyte activation is successfully treated by phototherapy (27). The light reduces T-lymphocyte activity in the skin and thereby cures the eczema. This kind of phototherapy usually is based on ultraviolet light, while phototherapy during the neonatal period is based on wavelengths in the visible range. However, also phototherapy free of ultraviolet light can successfully be used for the treatment of atopic eczema (28). Phototherapy might influence the immature immune system of the newborn, maybe by direct effects on T-lymphocytes in the thin skin, with possible long-term effects for developing the immune system. Suppression of T-lymphocyte activity by phototherapy during the immunologically important neonatal period can theoretically slow the shift from a mainly Th₂ mediated immune response towards a Th₁ mediated reaction, and thereby increase the risk for asthma.

Another interesting theory describes asthma as an example of an autoimmune disease, as both asthma and autoimmune diseases are based on immunologic dysregulation and may have common pathophysiological mechanisms (14). Studies from Sweden and other European countries have found that perinatal events including neonatal phototherapy were associated with an increased risk to develop autoimmune diabetes mellitus (16, 17).

In conclusion, this large population-based study confirmed previous findings of some maternal and perinatal factors to be associated with hospitalized childhood asthma. In addition, we show that neonatal phototherapy or the underlying condition, neonatal icterus, is apparently independently associated with an increased risk to develop childhood asthma. The mechanism behind this association is unknown. In view

of the rapidly rising prevalence of childhood asthma in western countries potentially preventable factors must be further studied.

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