

Neonatal characteristics and risk of atopic asthma in schoolchildren: results from a large prospective birth-cohort study

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Abstract

Aim: Asthma is among the most common chronic diseases in childhood and steadily increasing in prevalence. Identification of risk predictors for a hospitalization for atopic asthma in childhood may help design prevention programmes and improve our understanding of disease pathobiology.

Methods: An ongoing birth-cohort study prospectively enrolled all liveborn infants in Tyrol. Between 1994 and 1999 baseline data were collected for 33 808 infants. From 2000 to 2005, all children hospitalized for atopic asthma at an age of 6 years or over ($n = 305$) were identified in a careful search of hospital databases. Disease status was ascertained from the typical medical history, a thorough examination and proof of atopy.

Results: Male sex (relative risk 2.11, 95% CI 1.65–2.70), urban living environment (vs. rural) (1.93, 1.47–2.54), neonatal admission to hospital (1.70, 1.20–2.40), lack of breastfeeding (1.32, 1.02–1.70), postnatal smoking (1.31, 1.00–1.72) and low birth weight (1.45, 0.94–2.23) all emerged as adverse risk predictors for hospitalization for atopic asthma whereas a low risk was found among children living on a farm (0.22, 0.05–0.87) and children with two to three siblings (vs. no or one sibling) (0.71, 0.51–0.97).

Conclusion: In this study a number of neonatal characteristics and environmental exposures were associated with hospitalization for atopic asthma in childhood, suggesting that early life is crucial for disease determination and lending further indirect support to the hygiene hypothesis.

INTRODUCTION

Asthma is among the most common chronic diseases in childhood and imposes an increasing economic and health burden (1). Previous studies have suggested that factors acting early in life and even in the prenatal period may predispose to or render individuals resistant to childhood asthma (2,3). In addition, birth characteristics and sociodemographic variables like birth weight (4,5), sex (6,7), family size (8) and parental educational level (9) have been linked to the risk of asthma manifestation and hospitalization, but the available results are not entirely consistent. In the last decade the hygiene hypothesis has attracted increasing attention (8,10). Early exposure to common pathogens and pathogen products (for instance endotoxin) was postulated to protect against atopy in later life by promoting a shift from the preferential T helper cell type 2 (TH2) response of neonates to a type 1 (TH1) preponderance and by developing immune tolerance for a broad spectrum of natural allergens (11–13).

Identification of early predictors for the manifestation and course of childhood asthma in high-quality epidemiological

studies may deepen our understanding of disease pathobiology and provide a basis for prevention strategies aimed at counteracting the steadily increasing burden of asthma (14). The current study will investigate the association of neonatal and environmental characteristics with hospitalization for atopic childhood asthma in a large prospective birth-cohort study ($n = 33\,808$).

PATIENTS AND METHODS

Study area

The survey area of this study is Tyrol, a federal state in the western part of Austria with 650 000 inhabitants and an area of 12 650 km². It is a mountainous region located in the Alps with a wide range of altitudes of permanent residence (450–1800 m above sea level) and homogeneous climatic conditions. The population of Tyrol is mainly Caucasian. Main sources of income are light industry and tourism.

Farms in Tyrol are primarily traditional and small dairy farms with regular and close contact to animals. Migration rates were low in the study area with only around 1.1% of families with young children moving out of the Tyrol per year

and another 2.1% moving within the Tyrol still contributing to the group of hospitalized asthmatics.

Study population and clinical characteristics

Data on pregnancy, birth and neonatal characteristics were prospectively collected 4–6 weeks after birth for all infants liveborn between April 1994 and December 1999 ($n = 45\,642$). The participation rate was high at 74.1% ($n = 33\,808$).

The following variables were assessed by means of a standardized questionnaire completed by the infant's mother: (a) infant's data: age, sex, birth weight and gestation (<37 and ≥ 37 weeks); (b) sociodemographic background: marital status, educational level and profession of the parents; (c) pregnancy characteristics: mother's age at delivery, number of previous pregnancies and deliveries, maternal smoking habits during pregnancy and after birth of the child; (d) postnatal factors: neonatal hospitalization, child care practices such as the usual sleeping position and feeding practices; (e) place of residence. The questionnaire used in the current study is part of the public health programme in Tyrol and was approved by the appropriate committee of the local Board of Health. Categorization of all variables was prespecified. Low birth weight was defined by a cut-off of <2500 g. Season of birth was categorized as 'cold months' (November–February) or 'other months'. Feeding practice during the first 4–6 weeks of life was coded 'breast-fed' if the main type of milk given was breast milk. Parental educational level was documented in years of education (<12 years, 12 years, and >12 years). A farming environment was assumed if farm work was given as a full-time occupation. Living environment was coded 'urban' (large towns with $>100\,000$ inhabitants), 'suburban' (towns with $10\,000$ – $100\,000$ inhabitants), or 'rural' (villages with $<10\,000$ inhabitants).

Ascertainment of asthma cases

Data on hospitalization for atopic asthma of children aged 6–10 years (born April 1994 to December 1999) were extracted from computer databases of all children's hospitals in Tyrol. Children aged 5 years and under were not included in the current investigation, because there are many different causes for wheezing in this age range. In a first step, a search was made for diagnoses 493.0 (ICD-9) and J45.0 (ICD-10) which identified 721 infants. In a second step the diagnosis was confirmed by two paediatric pulmonologists (E.H., D.M.) based upon a critical review of the hospital medical records. A diagnosis of asthma required a medical history of at least 3 episodes of wheezing confirmed by clinical examination on hospital admission and proof of atopy (a positive skin-prick test reaction to at least one common aeroallergen and/or elevation of specific IgE in serum). The skin-prick test reaction to common aeroallergens (grass pollen mix, hazel, birch pollen, cat dander, house dust mite (*Dermatophagoides pteronyssinus*), *Alternaria alternata*, *Cladosporium herbarum*) was considered positive if the wheal diameter was at least 3 mm greater than a negative control with saline solution 15 min after testing.

The level of specific IgE was measured by radioallergo sorbent assay (RAST) and considered elevated if the level was ≥ 3.5 kU per litre for the specific allergen. A total of 367 (50.9%) out of 721 children satisfied these criteria.

Statistical analysis

Data analysis was performed using SPSS 12.0 for Windows. Associations between categorized baseline variables and hospitalization for atopic childhood asthma were analyzed with the χ^2 test. Relative risks were estimated from logistic regression analysis applying hospitalization for asthma as the dependent variable. Models were fitted with a forward-stepwise selection procedure (probability values for entry and removal of variables, 0.10 and 0.15) and variables selected for inclusion from all those listed in Table 1. The test procedure was based on maximum-likelihood estimators, and the goodness of fit of each model was assessed by the test of Hosmer and Lemeshow. Differential associations in subgroups were tested by the inclusion of interaction terms. All p -values were two-sided.

RESULTS

A critical review of hospital admission records identified 367 children with atopic asthma in the survey area, who required at least one hospitalization in the period between 2000 and 2005. Neonatal questionnaires had been returned in 305 of the cases.

Descriptive characteristics of the overall birth cohort (33 808) are shown in Table 1.

Univariate analysis showed hospital admission for asthma to be significantly associated with male sex, low birth weight, urban living environment, parental educational level, neonatal admission to hospital, lack of breastfeeding and smoking.

Detailed analyses indicated that the increase in asthma risk equally applied to women who smoked during and after pregnancy ($n = 4645$, RR [95% CI] 1.36 [1.01–1.84]) and those who abstained during pregnancy but restarted smoking after delivery ($n = 1445$, RR [95% CI] 1.57 [0.98–2.52]) whereas the number of women who smoked during pregnancy and quit thereafter was too low to assess reliable risk estimates ($n = 259$).

In addition, the risk for hospitalization for atopic asthma was lower in children who live on a farm and those having 2–3 siblings, and in children of parents with a low education level. In detail, relative risks of asthma amounted to 1.00, 0.71 and 1.25 for children with 1, 2–3 and 4 siblings when compared with those without a sibling. Finally, there were no relations with maternal age at delivery, season of birth, single parenthood or infant's sleeping position.

In a multivariate step-forward logistic regression analysis the following variables were selected for inclusion: male sex and urban environment ($p < 0.001$, each), neonatal admission to hospital ($p = 0.003$), lack of initial breastfeeding ($p = 0.034$), postnatal smoking ($p = 0.048$) and low birth weight ($p = 0.091$). Living on a farm ($p = 0.032$) and living in families with two to three siblings ($p = 0.033$) emerged as inverse risk predictors (Table 2). Parental educational

Table 1 Association of neonatal, sociodemographic and environmental characteristics with hospitalization for atopic childhood asthma (n = 38 808)

Variable	Subjects at risk	Hospitalizations for asthma	Frequency of hospitalizations per 1000 PYs*	p-value†
Sex				
Male	17 219	210	6.3	<0.001
Female	16 589	95	3.0	
Season of birth				
Cold months	10 126	92	4.8	0.935
Other months	23 682	213	4.6	
Birth weight				
<2500 g	1666	26	8.4	0.004
≥2500 g	32 142	279	4.5	
Mother's age at delivery				
<23 years	3886	33	4.2	0.711
≥23 years	19 922	272	4.7	
Number of siblings				
≤1 sibling	25 655	248	5.0	0.028
2 or 3 siblings	7171	46	3.3	
≥4 siblings	982	11	5.7	
Single parenthood				
No	30 381	278	4.8	0.455
Yes	3427	27	3.6	
Educational level‡				
<12 years	22 032	163	4.3	0.042
12 years	4012	45	6.8	
≥12 years	4441	38	5.1	
Farming				
No	32 658	303	4.8	0.004
Yes	1150	2	1.0	
Living environment				
Urban	4186	70	8.1	<0.001
Suburban	4010	24	3.3	
Rural	25 612	211	4.2	
Neonatal admission to hospital				
No	31 269	263	4.3	<0.001
Yes	2539	42	8.7	
Initial breast feeding				
No	4580	54	6.0	0.033
Yes	29 228	251	4.4	
Prone sleeping position				
No	32 071	289	4.7	0.932
Yes	1737	16	4.1	
Postnatal smoking				
No	27 718	233	4.3	0.011
Yes	6 090	72	6.1	
Prenatal smoking				
No	28 904	250	4.4	0.079
Yes	4904	55	6.0	

*Frequency of hospitalizations for atopic asthma per 1000 person-years (PYs) of follow-up.

†Information on social status was available in 30 485 subjects only.

‡p-value for a comparison of frequencies of hospitalizations for asthma between variable categories.

Table 2 Multivariate association between risk variables and hospitalization for atopic childhood asthma (n = 33 808)

Variable	RR (95% CI)	p value
Male sex	2.11 (1.65–2.70)	<0.001
Living environment		<0.001
Rural	1.00	
Suburban	0.70 (0.46–1.07)	0.097
Urban	1.93 (1.47–2.54)	<0.001
Neonatal admission to hospital	1.70 (1.20–2.40)	0.003
Farming	0.22 (0.05–0.87)	0.032
Lack of breastfeeding	1.32 (1.02–1.70)	0.034
Postnatal smoking	1.31 (1.00–1.72)	0.048
Number of siblings		0.058
≤1 sibling	1.00	
2 or 3 siblings	0.71 (0.51–0.97)	0.033
≥4 siblings	1.26 (0.68–2.31)	0.462
Low birth weight	1.45 (0.94–2.23)	0.091

Relative risks (RR) and 95% confidence intervals (95% CI) were estimated from logistic regression analysis. The multivariate analysis was fitted with a forward-stepwise selection procedure allowing for all variables in Table 1 (probability values for entry and removal of variables, 0.10 and 0.15).

level lost significance after inclusion of smoking and lack of breastfeeding. The risk profiles identified were virtually identical in boys and girls and subgroups according to different level of parental education.

DISCUSSION

This prospective population-based study identified a number of significant risk predictors for hospitalizations because of atopic childhood asthma (Tables 1 and 2). Some of the associations have been described in previous birth cohorts focusing on asthma manifestation or hospitalization (9,11,15–18), whereas others like a farming environment have not yet been addressed in prospective studies. Notably, the bulk of risk predictors were neonatal characteristics indicating that early life is crucial for the determination of childhood asthma. The positive association with postnatal smoking and urban living environment indicates a detrimental effect of in- and outdoor air pollution on asthma manifestation and course, while the strong inverse association with the number of siblings (surrogate for microbiological burden) and living on a farm and in a rural environment may be considered further support for the hygiene hypothesis (8,10).

In more detail, hospitalization for atopic asthma was strongly associated with male sex, lack of breastfeeding, low birth weight and neonatal admission to hospital. Sex differences in asthma and atopy with a preponderance of boys before puberty are well established (6,7,17). Notably, the sex ratio switches after puberty, presumably due to the proinflammatory capacity of female sex steroids (6). Protective effects of breastfeeding against asthma have been suggested in some but not all (19) of the few previous reports and may operate by several mechanisms (15,16). Breastfeeding

reduces the risk of infection-induced airway obstruction (19) and has profound effects on the infant's intestinal microflora, and anti-inflammatory as well as immunomodulatory properties (20). The higher risk for asthma among low birth weight infants is in accordance with previous studies (4,21) and probably results from irreversible constraints in airway development (21) and subsequent small airway size (22). The majority (80%) of the neonatal hospital admissions in our cohort were due to respiratory distress, and this was especially true for preterm infants. Therefore, the increased risk for severe asthma with subsequent hospitalization in this group might be explained by chronic lung disease, as commonly observed in premature neonates, and/or by lung injury after mechanical ventilation. There is evidence that infants who survive a respiratory distress syndrome and those with a lower than normal lung function are at greater risk for developing respiratory disease in later life (23). Vice versa, a family history of asthma (genetic predisposition) was shown to increase the risk for severe neonatal respiratory distress leading to hospital admission (24).

As anticipated, environmental exposure early in life may interfere in the maturing immune system and play a crucial role in the development and course of atopy and asthma. An effective innate immune system (involving its signalling pathways), induction of a profound shift in the TH1/TH2 balance towards TH1 preponderance and more complex changes in immune responsiveness like the development of immune tolerance and subtle modifications in TH2 response are considered protective against atopy and asthma (11–13). The type and amount of allergens, window of allergen contact and associated circumstances (e.g. level of airway inflammation) may determine whether exposure causes sensitization or immune tolerance. Early exposure to infections transmitted by contact with older siblings has repeatedly been related to a decreased risk for atopic disease (8,11). This theory, first postulated by Strachan in the 1980s, was termed the hygiene hypothesis (10). Lifestyle changes in western society, especially the decreasing number of children in a family, may well have contributed to the increase in allergic diseases. The current study provides further evidence that a larger number of siblings may afford protection against the development of severe asthma leading to hospitalization, but this finding does not extend to families with four and more children. Observation of a protective effect of farming in our study is in accordance with a few cross-sectional evaluations (12,13).

Early-life contact with microbial compounds that are highly prevalent on farms may account for this phenomenon and trigger development of immune tolerance to these and various other components of the natural environment (12,13). Similar mechanisms may account in part for our finding of a lesser risk for asthma among children growing up in a rural or semi-urban environment characterized by a more pronounced exposure to microbial components, pollen and other airborne natural allergens. On the other hand, living in an urban environment is associated with an enhanced burden of outdoor air pollution (mainly particulate matter and nitrogen dioxides). Outdoor air pollution per

se facilitates the development of respiratory illness (25) and promotes sensitization to environmental allergens and may trigger severe asthma attacks. Analogue effects have to be assumed for indoor exposure to tobacco smoke. Actually, the results of the current study support the notion that parental smoking is an important determinant of atopic asthma in children (16,26).

Apart from inducing airway inflammation and priming sensitization (27), smoking impairs lung development and function in utero and in the postnatal period (28).

Merits and limitations The main merits of our study are its prospective design and size ($n = 33\,808$). Size clearly exceeds that of comparable birth-cohort studies focusing on neonatal characteristics, most of which included a few thousand infants (9,11,15–18). Furthermore, ascertainment of asthma did not rely on the parents' responses to the questionnaire or the patient's self-report but on a thorough in-hospital examination by a specialist in paediatric pulmonology. In each case the diagnosis was confirmed by proof of atopy (positive skin-prick test reaction to common aeroallergens and/or increased specific IgE levels). There are limitations as well. Firstly, this study was primarily designed to assess risk factors for sudden infant death syndrome (SIDS) and apparent life-threatening event (29,30) and later extended to childhood asthma. Accordingly, some variables meaningful for the current analysis like family history of asthma and pet contact were not systematically assessed. Secondly, the focus on asthma hospitalization does ultimately not allow to differentiate whether risk predictors are related to asthma manifestation or exacerbation. In this context it should also be mentioned that in Tyrol health care is free of charge and easily accessible throughout the survey area and does not differ between sociodemographic groups, making confounding by selective hospital admission unlikely. Finally, a minor proportion of families moved out of the survey area during the study period (1.2% per year). Because these families do no longer contribute to the population of hospitalized asthmatics relative risks in Table 2 may be modestly underestimated.

In conclusion, our study identifies a broad array of neonatal and environmental risk predictors for hospitalization for atopic asthma in childhood, suggesting that disease manifestation and expression is in part determined early in life, and provides further indirect support to the hygiene hypothesis.

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