

Hospital admission with neonatal sepsis and development of atopic disease: Is there a link?

Kopp MV, Semmler S, Ihorst G, Berner R, Forster J. Hospital admission with neonatal sepsis and development of atopic disease: Is there a link?

Pediatr Allergy Immunol 2005; 16: 630–636. © 2005 Blackwell Munksgaard

The role of suspected or confirmed neonatal sepsis in modifying the risk of atopic disease during childhood was assessed. Children with early-onset neonatal sepsis were identified from a cohort of neonates, hospitalized between 1990 and 1995. Of 196 individuals, 140 were recruited (71.4%). Pre- and postnatal history was ascertained from neonatal medical records. Based on clinical symptoms and a positive blood culture or at least three of initially defined laboratory or bacteriological criteria, they were stratified in either confirmed neonatal sepsis (CS) or suspected sepsis (SS) group. A control group (C) comprised children who were never hospitalized during infancy ($n = 696$). Primary end-point was the development of atopic dermatitis, bronchial asthma or allergic rhinitis during childhood (mean age 8.4 yr, range 5.7–12.4). CS and SS children had a higher prevalence of atopic dermatitis (CS 15.7%, SS 21.4%) compared with controls (C 5.2%, $p < 0.001$). Similarly, children with SS (7.1%), but not with CS (4.3%) had significantly more often a doctor's diagnosis of bronchial asthma compared to controls (1.9%, $p = 0.02$). No difference in the prevalence of allergic rhinitis was observed (CS 4.3%, SS 10%, C 8.3%). After adjusting for parental history of atopic disease and demographic factors, no significant difference for the risk to develop atopic dermatitis, asthma or allergic rhinitis among the groups was calculated in children with normal birth weight (> 2500 g). Our data failed to show a possible link between hospital admission with SS and development of atopic disease.

Matthias Volkmar Kopp¹, Steffi Semmler¹, Gabriele Ihorst¹, Reinhard Berner¹ and Johannes Forster²

¹University Children's Hospital, Freiburg, Germany,

²St. Josefs-Hospital, Freiburg, Germany

Key words: allergy; allergic rhinitis; atopic dermatitis; bronchial asthma; neonatal sepsis; sensitization

Priv Doz Dr Matthias V. Kopp, University Children's Hospital, Mathildenstraße 1, D-79106 Freiburg, Germany

Tel.: +49 761 270 4450

Fax: +49 761 270 4301

E-mail: matthias.kopp@uniklinik-freiburg.de

Accepted 16 August 2005

The 'hygiene hypothesis' postulates that multiple infections in infancy transmitted by older siblings or day care classmates may protect against atopic disease and allergic sensitization (1). According to the hygiene hypothesis, viral and/or bacterial infections inhibit the T-helper (Th)-2 immune response associated with atopic reactions while stimulating a Th-1 response involved in defence of bacterial infections (2). The prenatal period and early childhood are particularly considered to be critical for the establishment and maintenance of a normal Th-1/Th-2 balance.

However, although other factors associated with microbial exposure, such as early day care, domestic animal keeping and living conditions

on a farm have analogously been associated with decreased risk of allergic diseases, the inverse association between infectious diseases and allergic diseases has not been consistent (3–8). Moreover, it is largely unknown, which factors of infectious diseases might be protective against atopy, i.e. if the number, the severity or mode of infection (respiratory or gastrointestinal), the kind of infectious agent, the exposure time or a combination of these factors might be decisive.

The pathogen of neonatal sepsis is the first stimulus leading to the earliest anti-infective immune response in infancy. The definition of early-onset sepsis comprise a beginning of symptoms in the first 7 days of life in contrast to those

with onset after the seventh day of life (late-onset group). The most frequently encountered pathogens in the early-onset group are group B streptococci (GBS) and *Escherichia coli*, while in the late-onset group, the organisms are coagulase-negative staphylococci and Enterobacteriaceae, including *E. coli*, *Klebsiella pneumoniae* (9).

Early-onset group B streptococcal disease is the most frequent serious infection in the neonatal period. In developed countries, the incidence varies from 0.3 to 1 /1000 live births (10).

There are no studies in the literature investigating a possible link between neonatal sepsis and the development of allergic sensitization or atopic disease, i.e. atopic dermatitis, bronchial asthma or allergic rhinitis. Neonatal sepsis may have bidirectional effects on the development of allergy. An early contact with bacterial products might be protective, whereas, the antibiotic therapy and the 'hygienic' conditions in the hospital might favour the development of atopic disease. Therefore, we conducted a follow-up exploration of neonates with suspected early-onset sepsis and compared the prevalence of allergic disease with an age-matched control group of children without postnatal sepsis or hospital treatment.

Methods

Subjects and study design

Between 1990 and 1995, 339 neonates had been hospitalized with the diagnosis of 'sepsis' or 'suspected sepsis' in the University Children's Hospital in Freiburg, Germany. In 2002, we were able to contact 196 families, who received a questionnaire. Of these 196 families, 145 (73.9%) replied and 140 (71.4%) returned a duly completed and evaluable questionnaire. Only 75 children (54.5%) of our analysable study population responded to our invitation and participated in a skin prick test (SPT).

The control group (C) had been enrolled as pupils in 1998 in a large population-based epidemiological study investigating possible health effects of ozone in south-west Germany. This group comprised 696 children. Based on information obtained by a questionnaire, these children were never hospitalized. We used the identical questions in both populations to identify children with a doctor's diagnosis of atopic disease.

Definition of neonatal sepsis

Sepsis was defined as a tentative diagnosis made within the first 96 h of life based on symptoms of

poor peripheral circulation, respiratory distress, cyanosis, lethargy, irritability, apnoeic spells, tachypnea, fever, bradycardia, tachycardia and poor feeding. The diagnosis was finally based on (a) a positive blood culture or (b) when at least three of the following criteria were met: (i) C-reactive protein (CRP) > 2 mg/100 ml within 48 h after onset of clinical suspected sepsis, (ii) tracheal or gastric or urine aspirate with microscopic or cultural evidence of bacterial infection or positive latex agglutination test in urine for GBS, (iii) proportion of immature (bands and less mature forms) to total neutrophils >0.2 documented in any blood sample within 48 h after clinically suspected sepsis or (iv) maternal fever or antibiotic treatment within 48 h of delivery or pre-mature (> 48 h) rupture of membranes before delivery (11). We obtained the data of our study population analysing the medical records of each patient. According to this evaluation patients were classified into the following groups:

Group CS: children, who had a neonatal early-onset sepsis according to the criteria (a) or (b).

Group SS: children, who were suspected to have a neonatal sepsis but did not meet the criteria (a) or (b).

Questionnaire

A standardized questionnaire was filled by the parents. For atopic disease the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire was used. A doctor's diagnosis of asthma, allergic rhinitis and atopic dermatitis were recorded as lifetime doctor's diagnosis. The family history of atopy was ascertained as well as current tobacco smoke exposure at home. Such exposure was recorded if smoking of at least one cigarette per day was reported.

Skin prick test

The SPT was performed on the volar surface of the forearm using extracts from hazel, birch and grass pollens, dog and cat dander and dust mites (*Dermatophagoides farinae*, *D. pteronyssinus*) with histamine hydrochloride (10 mg/ml) and sodium chloride (9 g/l) as control solutions. The allergens (ALK-Scherax, Hamburg, Germany) corresponded to a concentration of 10 histamine equivalent potency. All skin reactions were evaluated after 15 min. A mean wheal diameter ≥ 2 mm together with a ratio of the allergen wheal to the histamine wheal >0.5 was considered to be a positive reaction (12).

Statistical analysis

The analysis was carried out using the Statistical Analysis System, version 8.2 (SAS Institute Inc, Cary, NC, USA). Groups were compared by employing Fisher's exact test for binary variables and Wilcoxon's two sample test or the Kruskal–Wallis test for continuous variables. Group comparisons with respect to the occurrence of diagnoses of an atopic disease were conducted within logistic regression models, where gender (age < 8 yr), parental atopy and passive smoke exposure were incorporated as independent variables. The results are expressed in terms of odds ratios (OR) with corresponding 95% confidence interval (CI).

Results

Study population

We were able to contact 196 families whose children had been hospitalized in Freiburg as neonates for suspected sepsis. Of these, 145 families returned a questionnaire (73.9%) and 140 (71.4%) were completely evaluable. Based on clinical and laboratory criteria (11), 70 were defined as children with CS (group CS), 70 must be regarded as children with SS (group SS) and 696 children without hospital stay served as control (group C). The relevant characteristics of the study population are summarized in Table 1.

We observed no statistical significant differences between children (CS + SS/C) with respect to gestational age, birth weight, gender or way of delivery (Table 1). Based on the definition of 'neonatal sepsis' CRP was significantly higher and the duration of intravenous (i.v.) antibiotic therapy was significantly longer in the sepsis group (Wilcoxon test, $p < 0.001$).

The parental history of atopy was similar among the three groups. The family history of atopic dermatitis was negative in 84.3% (group CS), 82.9% (SS) and 80.2% (C) respectively. With respect to allergic rhinitis 75.7% (group CS), 54.3% (SS) and 68.7% (C) and with respect to bronchial asthma 87% (group CS), 87.1% (SS) and 78.4% (C) reported a negative family history respectively.

Prevalence of atopic dermatitis, bronchial asthma and allergic rhinitis

Lifetime prevalence of atopic dermatitis was similar in CS children (15.7%) and SS children (21.4%, $p > 0.5$). In the C group, the prevalence of atopic dermatitis was 5.2%, which was

Table 1. Study population

	Group CS (n = 70)	Group SS (n = 70)	Group C (n = 696)
Age (yr)			
Median	8.1	7.6	8.4
Mean	8.4	8	8.4
5th–95th percentile	5.7–12.4	5.7–12.5	7.4–9.6
Gender (%)			
Male	62.9	61.4	48.3
Female	37.1	38.6	51.7
Time of delivery (gestational weeks)			
Median	38	39	40
Mean	37.1	38.3	39.4
5th–95th percentile	30–42	31–42	36–42
Way of delivery (%)			
Spontaneous delivery	55.7	54.3	No data
Caesarean section	35.7	22.9	
Birth weight (g)			
Median	3065	3265	3400
Mean	2871.9	3090.8	3381.2
5th–95th percentile	1050–4250	1440–4150	2500–4200
C-reactive protein (mg/l)			
Median	36.4*	12	–
Mean	53.4*	23.9	–
5th–95th percentile	6–170*	6–86	–
Antibiotic therapy (days)			
Median	7*	4	–
Mean	8.3*	4.8	–
5th–95th percentile	3–18*	2–10	–

Median, mean and 5th–95th percentile are presented. With regard to way of delivery, no data are available on the control group. *Within the neonatal sepsis group, C-reactive protein was significantly higher and the duration of intravenous antibiotic therapy was significantly longer in the confirmed sepsis group (Wilcoxon test; $p < 0.001$ respectively).

CS, children with confirmed neonatal sepsis; SS, children with suspected neonatal sepsis; C, control group.

significantly lower when compared with group CS and SS ($p < 0.001$ respectively; Fisher's exact test, Fig. 1).

Doctor's diagnosed asthma was statistically significantly higher only in SS children (7.1%) compared with the C group (1.9%; $p = 0.02$). No difference was observed between CS children (4.3%) and the C group ($p = 0.72$) and between CS and SS children ($p = 0.5$) respectively (Fig. 2).

We observed no statistical difference in the prevalence of allergic rhinitis among the three groups (CS 4.3%, SS 10% and C 8.3%).

Prevalence of allergic sensitization

The prevalence of allergic sensitization was determined by SPT. Only 75 of 140 children (54.5%) with SS or CS were responsive to our invitation and participated in SPT. In group CS, 11 of 37 children (29.7%) showed at least one positive reaction to one of the tested allergens

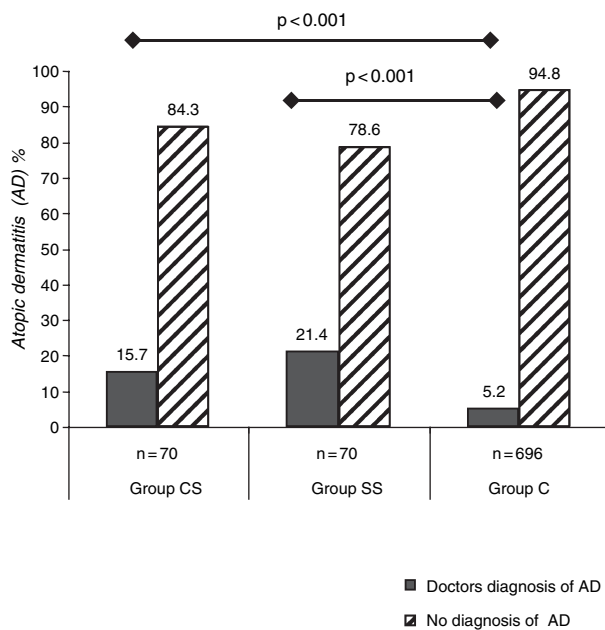


Fig. 1. Prevalence of doctor's diagnosis of atopic dermatitis (black bars) in children with confirmed (CS), suspected (SS) neonatal sepsis and external controls (C). In order to determine the statistical significance of differences between the different groups the Fisher's exact test was employed and p-values were calculated.

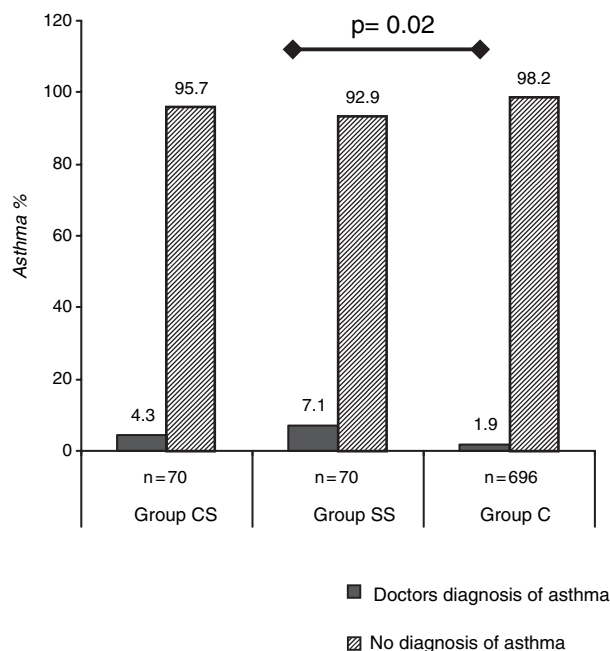


Fig. 2. Prevalence of doctor's diagnosis of bronchial asthma (black bars) in children with confirmed (CS), suspected (SS) neonatal sepsis and external controls (C). In order to determine the statistical significance of differences between the different groups the Fisher's exact test was employed and p-values were calculated.

compared with 15 of 38 children (39.5%) and 184 of 696 children (26.4%) in group SS and C respectively. The differences in the prevalence of allergic sensitization between the groups were statistically not significant. However, the high number of dropouts in group CS and SS need a cautious interpretation of the data.

Intravenous antibiotic therapy and development of atopic dermatitis, bronchial asthma and allergic rhinitis

Besides the classification to the group with SS or CS, we analysed the effect of an applied i.v. antibiotic therapy in both groups (CS + SS, n = 140) on the development of atopic dermatitis, bronchial asthma and allergic rhinitis. The administration of antibiotics was not associated with the prevalence of any disorder. For doctor's diagnosed atopic dermatitis (n = 26), 20 children received i.v. antibiotics compared with six without i.v. antibiotics (p = 0.2; Fisher's exact test).

Similarly, for bronchial asthma (n = 8) and allergic rhinitis (n = 10), six children (allergic rhinitis nine) received i.v. antibiotics compared with two (n = 1) without i.v. administration of antibiotics (p = 0.42 and p = 0.64 respectively).

Logistic regression model

To describe a possible effect of the hospital admission during infancy on the development of atopic disease we set up logistic regression models.

Besides the attribution to the different groups (CS, SS and C), the model include gender, age, parental history of atopy and passive smoke exposure as independent variables. The regression model gives parameter estimates for the differences between the groups as a description of possible effect of a SS or CS.

Our model revealed no significant difference for the risk to develop atopic dermatitis and allergic rhinitis between the groups. However, a family history of atopic disorder was found to be a significant risk factor for the development of atopic dermatitis (OR 1.9, 95% CI 1.3–2.8, p = 0.0006) and allergic rhinitis (OR 2.2, 95% CI 1.4–3.6, p = 0.009), but not for asthma (OR 1.2, 95% CI 0.6–2.8, p = 0.53).

With respect to the development of bronchial asthma, we calculated for children with SS at birth an OR of 2.8 (95% CI 0.95–8.3), which marginal failed to reach statistical significance. No difference was observed between children with CS and children without hospitalization during infancy (OR 1.6, 95% CI 0.4–5.8, p = 0.46).

However, five of eight children with doctor's diagnosed asthma had a low gestational age (< 36 wk). Therefore, we re-evaluated the model for children with birth weight of > 2500 g. We included 48 (CS), 54 (SS) and 641 (C) children in this model. Analysing these children, no difference between CS (OR 0.7, 95% CI 0.1–5.7) or SS (OR 1.7, 95% CI 0.4–7.7) and controls with respect to asthma development was detectable. Only for passive smoke exposure an OR of 2.3 (95% CI 0.9–5.5) was calculated, which marginal failed to reach statistical significance.

The analysis of children with birth weight of > 2500 g did not change the parameter estimates analysing the effect of CS or SS on the development of atopic eczema or allergic rhinitis.

Discussion

A germ-free or germ-depleted environment during infancy is accused to be at least partially responsible for the increasing prevalence of atopic disease. On the contrary, an early contact with multiple microbes or their products, i.e. endotoxins, is assumed to be protective (1). Therefore, we performed this study to elucidate the role of neonatal sepsis on the development of atopic disease during childhood.

We identified a positive family history of atopy as a significant risk factor for the development of allergic rhinitis and atopic dermatitis. These data obtained from our study population are in accordance with numerous reports, which consistently indicate that family history of atopy remains the most important risk factor for atopy in children (13–15).

Moreover, we also observed a marginal statistically significant association between bronchial asthma and environmental tobacco smoke exposure. Again, an extensive body of evidence indicates that tobacco smoke exposure increases the prevalence of wheezing, cough and phlegm and cause exacerbations in asthma (16, 17).

These two observations give us some confidence that the data on the primary outcome of the study are reliable. Here, we were able to demonstrate that children with SS or CS developed significantly more often an atopic dermatitis during childhood compared with individuals without a history of hospitalization during infancy. Similarly, children with SS had significantly more often a doctor's diagnosis of bronchial asthma compared with our control group. However, performing a multivariate analysis in children with normal birth weight (> 2500 g), no significant difference for the risk to develop

atopic dermatitis, asthma or allergic rhinitis between the groups was calculated.

We also tested the hypothesis, if a hospitalization *per se* increased the risk for atopy. Therefore, we pooled our data from the CS and SS group and compared these children with our controls. However, this did not change the calculated parameter estimates.

For children with SS, a tendency for an elevated risk to develop asthma was calculated in all neonates (OR 2.8, 95% CI 0.95–8.3), which marginal failed to reach statistical significance. However looking at the data in detail, we observed that five of eight children with doctors diagnosed asthma were pre-mature infants with an gestational age of < 36 wk. Therefore, we only included children with normal birth weight (> 2500 g) in our analysis. With respect to these children, no association was evident between CS or SS and asthma development.

Similar to these findings, von Mutius et al. (18) reported that pre-mature girls had significantly more current asthma and recurrent wheezing than term girls, especially if they required mechanical ventilation after birth. Von Mutius also observed that more pre-maturely born children who required mechanical ventilation had a family history of asthma than children born at term and concluded that a family history of asthma may pre-dispose pre-mature children to more severe respiratory disease.

In accordance with von Mutius, 50% of a cohort with very low birth weight infants in New Zealand had been diagnosed with asthma before age 7 yr, compared with 27% of an international cohort study in New Zealand (19). Taken together, rates of childhood asthma are high in this very low birth weight neonates.

There are no data reported in the literature analysing a possible link between neonatal sepsis and the development of atopic disease in term infants.

Grishkan et al. (20) reported that pre-term children who were septic post-birth were less likely to have asthma. However, our cohort of asthmatic children is too small to study the influence of pre-term maturity in detail.

Very recently, in a large population-based sample, the history of viral infection was shown to be consistently positively associated with allergic rhinitis and sensitization to aeroallergens (21). In contrast, bacterial disease was a negative predictor for atopy development in the subgroup of patients with atopic eczema sensitized to nutritional allergens. However, these results were based on a retrospective personal interview with 25–74 yr old adults and scores for bacterial and

viral infections were established. These differences in populations hamper a direct comparison with our data.

Alm et al. (22) reported that children at anthroposophic school had lower prevalence of atopy than children of the same age at neighbouring schools. The authors concluded that lifestyle factors associated with anthroposophy may lower the risk of atopy in childhood, i.e. people who follow an anthroposophic way of life use antibiotics restrictively and only 52% of these children had had antibiotics in the past, compared with 90% in the control schools. We found no difference comparing children with suspected or confirmed sepsis with regard to the treatment with i.v. antibiotics. This might suggest that the use of antibiotics is merely one factor in a more complex interaction of the environmental conditions in a hospital and the affected individual.

In general, because of the retrospective case-control study design, the results must be interpreted with caution. One limitation of our study design is that we did not include a concurrent control group of children born at term in the University Children's Hospital but contemporary data on children of the same age available from an environmental study to assess health effects of ozone. These data are from a population-based cohort and may therefore accurately reflect the prevalence of atopic disease among school-aged children. Children with SS or CS had been excluded with the item of the questionnaire 'Was your child ever hospitalized during the first years of their life?'

Moreover, we relied on parental recall for the history of atopic disease in the past, honesty with regard to passive smoke exposure, a doctor's diagnosis as a basis of our classification and we did not measure lung function testing. However, the questionnaire was identical and derived from the ISAAC standard questions (23).

In conclusion, there are no data in the literature that have reported a long-term outcome in children with neonatal sepsis with regard to atopic disease. This pilot study does not suggest a possible link between hospital admission for SS and development of atopic disease. However, prospectively performed studies are clearly needed to confirm our findings.

References

- STRACHAN DP. Hay fever, hygiene, and household size. *BMJ* 1989; 299: 1259–60.
- ROMAGNANI S. The increased prevalence of allergy and the hygiene hypothesis: missing immune deviation, reduced immune suppression, or both? *Immunology* 2004; 112: 352–63.
- WILLIAMS LK, PETERSON EL, OWNBY DR, JOHNSON CC. The relationship between early fever and allergic sensitization at age 6 to 7 years. *J Allergy Clin Immunol* 2004; 113: 291–6.
- KRAMER MS, GUO T, PLATT RW, et al. Does previous infection protect against atopic eczema and recurrent wheeze in infancy? *Clin Exp Allergy* 2004; 34: 753–6.
- NAFSTAD P, MAGNUS P, JAAKKOLA JJ. Early respiratory infections and childhood asthma. *Pediatrics* 2000; 106: E38.
- WICKENS KL, CRANE J, KEMP TJ, et al. Family size, infections, and asthma prevalence in New Zealand children. *Epidemiology* 1999; 10: 699–705.
- PONSONBY AL, COUPER D, DWYER T, CARMICHAEL A, KEMP A. Relationship between early life respiratory illness, family size over time, and the development of asthma and hay fever: a seven year follow up study. *Thorax* 1999; 54: 664–9.
- BODNER C, GODDEN D, SEATON A. Family size, childhood infections and atopic diseases. The Aberdeen WHEASE Group. *Thorax* 1998; 53: 28–32.
- JIANG JH, CHIU NC, HUANG FY, et al. Neonatal sepsis in the neonatal intensive care unit: characteristics of early versus late onset. *J Microbiol Immunol Infect* 2004; 37: 301–6.
- Centers for Disease Control, Prevention. Early-onset group B streptococcal disease – United States, 1998–1999. *MMWR. Morb Mortal Wkly Rep* 2002; 49: 793–6.
- BERNER R, NIEMEYER CM, LEITITIS JU, et al. Plasma levels and gene expression of granulocyte colony-stimulating factor, tumor necrosis factor- α , interleukin (IL)-1 β , IL-6, IL-8, and soluble intercellular adhesion molecule-1 in neonatal early onset sepsis. *Pediatr Res* 1998; 44: 469–77.
- MEINERT R, FRISCHER T, KARMAUS W, KUEHR J. Influence of skin prick test criteria on estimation of prevalence and incidence of allergic sensitization in children. *Allergy* 1994; 49: 526–32.
- JAAKKOLA JJ, NAFSTAD P, MAGNUS P. Environmental tobacco smoke, parental atopy, and childhood asthma. *Environ Health Perspect* 2001; 109: 579–82.
- SEARS MR, HOLDAWAY MD, FLANNERY EM, HERBISON GP, SILVA PA. Parental and neonatal risk factors for atopy, airway hyper-responsiveness, and asthma. *Arch Dis Child* 1996; 75: 392–8.
- TARIQ SM, MATTHEWS SM, HAKIM EA, STEVENS M, ARSHAD SH, HIDE DW. The prevalence of and risk factors for atopy in early childhood: a whole population birth cohort study. *J Allergy Clin Immunol* 1998; 101: 587–93.
- GILLILAND FD, LI YF, PETERS JM. Effects of maternal smoking during pregnancy and environmental tobacco smoke on asthma and wheezing in children. *Am J Respir Crit Care Med* 2001; 163: 429–36.
- GERGEN PJ, FOWLER JA, MAURER KR, DAVIS WW, OVERPECK MD. The burden of environmental tobacco smoke exposure on the respiratory health of children 2 months through 5 years of age in the United States: Third National Health and Nutrition Examination Survey, 1988 to 1994. *Pediatrics* 1998; 101: E8.
- VON MUTIUS E, NICOLAI T, MARTINEZ FD. Prematurity as a risk factor for asthma in preadolescent children. *J Pediatr* 1993; 123: 223–9.
- DARLOW BA, HORWOOD LJ, MOGRIDGE N. Very low birth weight and asthma by age seven years in a national cohort. *Pediatr Pulmonol* 2000; 30: 291–6.

20. GRISCHKAN J, STORFER-ISSER A, ROSEN CL, et al. Variation in childhood asthma among former preterm infants. *J Pediatr* 2004; 144: 321–6.
21. RESCH A, SCHLIPKOTER U, CRISPIN A, et al. Atopic disease and its determinants – a focus on the potential role of childhood infection. *Clin Exp Allergy* 2004; 34: 1184–91.
22. ALM JS, SWARTZ J, LILJA G, SCHEYNIUS A, PERSHAGEN G. Atopy in children of families with an anthroposophic lifestyle. *Lancet* 1999; 353: 1485–8.
23. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinokonjunctivitis and atopic eczema: ISAAC. *Lancet* 1998; 351: 1225–32.