

Perinatal risk factors for bronchial hyperresponsiveness and atopy after a follow-up of 20 years

Judith M. Vonk, MSc,^a H. Marike Boezen, PhD,^a Dirkje S. Postma, PhD,^b
Jan P. Schouten, MSc,^a Wim M.C. van Aalderen, PhD,^c and E. Rudy Boersma, PhD^d
Groningen and Amsterdam, The Netherlands

Background: Perinatal risk factors are associated with lung function and respiratory symptoms in adult life. Whether the same holds for distinctive asthma features, such as bronchial hyperresponsiveness (BHR) and atopy, has scarcely been studied.

Objective: We sought to identify the perinatal risk factors for the development of BHR and atopy.

Methods: BHR and atopy were measured after 20 years' follow-up in 597 of 3162 babies born from 1975 through 1978. Factors directly related to delivery of these children were studied in association with the presence of BHR and atopy. **Results:** Twenty-five percent had BHR, and 47% had atopy. Delivery duration of longer than 12 hours was associated with the development of atopy (odds ratio [OR], 2.24; 95% CI, 1.30-3.86), and severe respiratory infection in the first year of life was associated with the development of BHR (OR, 2.69; 95% CI, 1.41-5.16). Nonatopic subjects born after induced labor and current smokers were more likely to have BHR (ORs of 2.41 [95% CI, 1.07-5.41] and 2.50 [95% CI, 1.12-5.59], respectively). Prenatal smoke exposure and childhood pet keeping decreased the risk for atopy, especially in BHR-positive subjects (ORs of 0.51 [95% CI, 0.27-0.99] and 0.46 [95% CI, 0.24-0.88], respectively).

Conclusions: It has been shown that events before or during birth still have an effect on respiratory health 20 years later. We put forward that an extreme hormonal status during delivery primes the fetal immune system toward atopy development. Furthermore, a severe respiratory infection in the first year of life appears associated with BHR development, and prenatal smoke exposure might be protective for the development of atopy, yet explanatory mechanisms are lacking thus far. (*J Allergy Clin Immunol* 2004;114:270-6.)

Key words: Bronchial hyperresponsiveness, atopy, perinatal risk factors, prospective cohort study, children, adults

Abbreviations used

BHR: bronchial hyperresponsiveness

ECRHS: European Community Respiratory Health Survey

LRI: Lower respiratory tract infection

OR: Odds ratio

A number of longitudinal cohort studies have shown that some perinatal risk factors are associated with the achieved level of lung function and the development of respiratory symptoms later in life. Identified perinatal factors are low birth weight, prenatal smoke exposure, severe respiratory tract infection in the first year of life, and lack of breast-feeding.¹⁻⁶ To date, more distinctive features of asthma, such as bronchial hyperresponsiveness (BHR) and atopy, both core features of this disease, have scarcely been studied as outcome parameters with respect to their association with perinatal risk factors on asthma development.

BHR is present in the majority of patients with asthma and reflects the presence of airway inflammation.⁷ The few longitudinal studies identifying early risk factors for the development of BHR in later life have reported that repeated lower respiratory tract infections (LRIs) early in life⁸ increase the risk of BHR development. Repeated viral infections early in life⁸ and upbringing on a farm⁹ were associated with a lower risk of BHR development. Thus far, perinatal factors have not been investigated with regard to their association with the presence of BHR at young adult age.

The hygiene hypothesis of Strachan^{10,11} has triggered research to identify environmental exposures in early life that are associated both with the development of atopy and the occurrence of the T_H1/T_H2 shift of the immune system. This research mainly focused on postnatal exposures. The few studies investigating the potential role of perinatal exposures on atopy development reported that children born with a relatively large head circumference (indicating disproportionate fetal growth),^{12,13} children born to mothers using antibiotics during pregnancy,¹⁴ and children born after a pregnancy with uterus-related complications¹⁵ were at increased risk for the development of atopy. A lower gestational age at birth¹⁶ and breast-feeding^{3,17} appeared to be protective, whereas parental smoking, either before or immediately after birth, was not

From ^athe Department of Epidemiology and Statistics, University of Groningen; ^bthe Department of Pulmonology, University Hospital of Groningen; ^cPediatric Pulmonology, Academic Medical Centre, University of Amsterdam; and ^dthe Section of Perinatal Nutrition and Development, Department of Obstetrics and Gynecology/Pediatrics, University Hospital of Groningen.

Supported by The Netherlands Asthma Foundation (grant no. 96.28) and Stichting Astma Bestrijding, The Netherlands.

Received for publication October 30, 2003; revised March 12, 2004; accepted for publication March 16, 2004.

Reprint requests: Judith M. Vonk, MSc, Department of Epidemiology and Statistics, University of Groningen, PO Box 196, 9700 AD Groningen, The Netherlands. E-mail: j.m.vonk@med.rug.nl.

0091-6749/\$30.00

© 2004 American Academy of Allergy, Asthma and Immunology
doi:10.1016/j.jaci.2004.03.051

associated with atopy development.¹⁸ Information on factors directly related to the delivery of the child, such as duration and mode of delivery, was lacking in most of these studies, although some investigators reported no effect of cesarean section on the development of atopy.^{15,19-21}

A well-defined cohort of babies followed for 18 to 22 years was studied to identify perinatal risk factors for the development of BHR, atopy, or both. This cohort gave us the unique opportunity to investigate the effect of variables related directly to the delivery of the child and to assess their effect on the subsequent development of distinct asthma phenotypes.

METHODS

Sample selection

From 1975 through 1978, all 3162 newborn babies in the Department of Obstetrics of the University Hospital in Groningen were included in a prospective cohort study.²² Detailed information was collected about perinatal conditions, such as age of the mother, parity, prenatal smoke exposure, delivery-related variables (ie, mode and duration of the delivery, induction of labor with medication, and position of the fetus), gestational age at birth, Apgar scores at 1 and 3 minutes after birth, and birth weight. In 1997, European Community Respiratory Health Survey (ECRHS)²³ questionnaires were mailed to all mothers and their children, now young adults, originally born in this cohort. In 1998, all responders were invited for further medical characterization (ie, testing of lung function, BHR, and atopy). The medical ethics committee of the University Hospital of Groningen approved the study, and subjects provided written informed consent before lung function testing.

Perinatal factors

Prenatal smoke exposure was defined as having a mother who had smoked at any time during pregnancy. Birth weight was measured directly after birth, with low birth weight being defined as less than 2500 g. The total duration of the delivery (ie, the time between the start of the dilation phase and the birth of the baby) was divided into 3 categories: less than 8, 8 to 12, and greater than 12 hours. Mode of delivery was taken from the records (ie, delivery by means of cesarean section, with the aid of a forceps, or by means of vacuum extraction, spontaneous, or induced labor). The fetus was considered to be in malposition for delivery when it was not in the vertex position, with the face facing the mother's back. An Apgar score of less than 7 was considered abnormal.²⁴

Questionnaire

The standardized questionnaire of the ECRHS²³ was used to determine current smoking habits of the now young adults, a positive family history for asthma or allergy (having at least one parent with asthma or allergy), severe respiratory tract infection in the first year of life (mothers' positive answers to both questions: "Did your child have a severe respiratory tract infection in the first year of life?" and "Has the infection been treated by a doctor?"), and pets in the home in childhood.

Lung function and methacholine responsiveness

The ECRHS protocol was used for lung function and methacholine responsiveness measurements.^{23,25} FEV₁ was recorded from at least 2 and up to 5 technically satisfactory maneuvers, with the highest values being used in the analyses. Subjects were considered to have BHR if they had a 20% or greater decrease in FEV₁ from the best

postdiluent FEV₁ at any cumulative dose of methacholine during the provocation test.²⁵

Skin tests

Skin prick tests with house dust mite, cat, dog, birch, timothy grass, and molds were performed. Subjects were considered atopic if they had at least one positive skin prick test response (mean of the widest and perpendicular diameter of the wheal ≥ 2 mm).

Statistical analysis

Subjects were classified into 4 groups (ie, phenotypes) according to the absence or presence of BHR and atopy. Differences in perinatal factors and other potential risk factors were tested by using χ^2 tests. A *t* test was used to test differences in age and lung function levels between the groups. The independent association between perinatal and other risk factors and the presence of BHR, atopy, or both was investigated by means of binary and multinomial logistic regression. The following perinatal factors were investigated simultaneously: prenatal smoke exposure, induction of labor, duration of delivery, breast-feeding for at least 2 weeks, and having had a severe respiratory tract infection in the first year of life. All regressions were performed, taking other risk factors (sex, current smoking at young adult age, having a parent with asthma or allergy, being firstborn, having had pets in childhood, and current age) into account. Additional analyses were performed to check whether mode of delivery, malposition of the fetus during delivery, and low birth weight were additional risk factors. *P* values of less than .05 were considered to be significant. Analyses were performed with SPSS 11.0.1 software.

RESULTS

Study population

Of the 3162 mother-child pairs in the original cohort, the addresses of 397 pairs were not available, and in 66 pairs the mother or the child had died. The questionnaire response rate of the remaining pairs was 58% (1568 of the 2699 eligible pairs). The mean age of the responding children was 20.4 years (range, 19-22 years), with 51.7% being female. Of these questionnaire responders, 597 (38%) came to the hospital for further medical characterization at a mean age of 20.9 years (range, 19-23 years). Comparing the subjects who performed medical characterization with all subjects of the original cohort who were not medically characterized showed a higher percentage of female subjects (55% vs 47%) and a lower prevalence of prenatal smoke exposure (51% vs 57%) in the subjects who performed further medical characterization. There were no other significant differences in the prevalence of perinatal and other risk factors between these groups.

The characteristics by current status of BHR and atopy are shown in Table I. One hundred thirty-three (24.9%) of the 534 subjects who underwent a BHR test were hyperresponsive, and 46.7% (*n* = 265) of the 568 subjects who underwent skin testing were atopic. Female subjects tended to have BHR more frequently than male subjects, whereas they were less frequently atopic. Subjects with BHR tended to have a higher prevalence of being born by means of induced labor and cesarean section, a severe respiratory infection in the first year of life, and current smoking compared with the subjects who were not hyperresponsive. Current FEV₁ percent predicted and

TABLE I. Prevalence of risk factors by current status of BHR and atopy

	No BHR (n = 401)	BHR (n = 133)	No atopy (n = 303)	Atopy (n = 265)
Perinatal risk factors				
Prenatal smoke exposure	50.5	45.2	53.8	46.0†
Induction of labor	22.8	30.8†	24.1	25.6
Delivery duration				
<8 h	55.5	49.2	59.5	47.8*
8-12 h	24.6	26.3	24.1	24.5*
>12 h	19.9	24.6	16.4	27.8*
Apgar score 1 min <7	10.8	11.4	10.6	12.0
Breast-feeding ≥2 wk	31.9	34.6	33.1	28.1
Malposition of the fetus	9.8	9.8	8.3	10.2
Cesarean section	6.2	10.5†	7.9	6.0
Forceps-vacuum extraction	10.8	9.2	7.3	12.5*
Gestational age <38 wk	13.0	12.0	11.8	13.9
Gestational age >42 wk	20.9	15.8	20.4	19.5
Birth weight <2500 g	7.0	6.8	6.3	8.6
Respiratory infection in first year‡	10.9	17.3†	10.3	15.1†
Other risk factors				
Female sex	53.9	62.4†	58.1	50.6†
Current smoking	31.6	40.5†	35.0	33.0
Family history of atopy	56.8	56.1	50.2	58.7*
Family history of asthma	17.0	18.9	14.8	19.7
Firstborn	53.6	50.4	49.7	52.3
Pets in childhood	74.6	69.0	78.7	68.5*
Age, y (mean [SD])	20.8 (1.0)	21.0 (1.0)	20.9 (1.0)	20.9 (0.9)
FEV ₁ % predicted (mean [SD])	105.2 (10.4)	99.0 (12.0)*	103.2 (10.6)	103.9 (12.1)
FEV ₁ % FVC (mean [SD])	87.8 (6.4)	85.6 (8.0)*	87.3 (6.8)	87.3 (7.1)

FVC, Forced vital capacity.

* $P < .05$.† $P < .10$.

‡Respiratory infection in the first year is defined as severe respiratory tract infection in the first year of life.

FEV₁ percent vital capacity were lower in the hyper-responsive subjects. Other (perinatal) risk factors did not differ between the subjects with and without BHR.

Atopic subjects had a significantly longer duration of delivery, more often a family history of atopy, and less often pets in their home in childhood, and they were more often born with the aid of a forceps or a vacuum pump than nonatopic subjects. There was a trend toward lower prevalence of prenatal smoke exposure and higher prevalence of severe respiratory infection in the first year of life in atopic subjects.

Fig 1 shows the prevalences of perinatal and other risk factors for the development of BHR, atopy, or their combination. Subjects with BHR and without atopy differed in many respects from the other 3 groups. They had a higher prevalence of being born by means of induced labor, female sex, current smoking, and pets in childhood, whereas the prevalence of a low Apgar score at 1 minute after birth, malposition of the fetus, being born with the aid of a forceps or by means of vacuum extraction, low birth weight, family history of atopy, and being firstborn was lowest in this group.

The 2 groups with atopy (with or without BHR) only differed from each other in the prevalence of being born by means of a cesarean section; this occurred more frequently in the atopic group with BHR. The atopic groups differed from the groups without atopy in that the prevalence of

prenatal smoke exposure and pets in childhood was lower and the prevalence of duration of the delivery longer than 12 hours, birth in malposition, aid of a forceps or a vacuum pump, and family history of atopy was higher. Finally, the groups with BHR (with or without atopy) more frequently had a severe respiratory infection in the first year of life compared with the groups without BHR, with the prevalence being highest in the BHR group with concomitant atopy.

Table II shows the results of binary logistic regression analyses on the development of BHR and atopy. A risk factor for the development of BHR was a severe respiratory infection in the first year of life. The development of atopy was associated with a delivery duration of longer than 12 hours, whereas prenatal smoke exposure was associated with a lower risk of atopy development. Pet keeping in childhood was almost significantly associated with a lower risk of development of atopy ($P = .06$).

The results of the multinomial logistic regression on the combined presence of BHR and atopy are shown in Table III. A severe respiratory infection in the first year of life was associated with the development of BHR, irrespective of atopic status. A total time of delivery longer than 12 hours was a risk factor for the development of atopy, irrespective of BHR status. The decreased risk for development of atopy if the mother smoked during pregnancy and of pet keeping in childhood was only

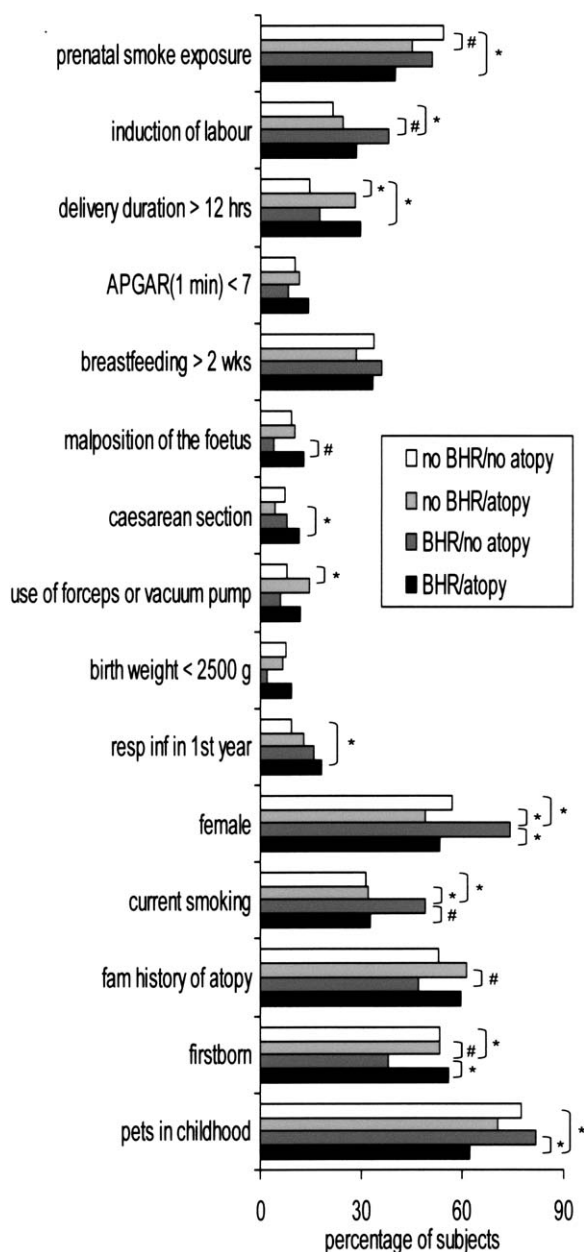


FIG 1. Prevalences of perinatal and other risk factors for the development of BHR or atopy. Subjects are classified into 4 groups: no BHR/no atopy, n = 229; no BHR/atopy, n = 163; BHR/no atopy, n = 50; BHR/atopy, n = 77. #*P* < .10, **P* < .05.

significant when BHR was present. Finally, being born by means of induced labor and current smoking at young adult age were associated with the presence of BHR only in the nonatopic subjects. Being breast-fed for at least 2 weeks, sex, having a parent with asthma or allergy, and being firstborn did not show a statistically significant estimate for any of the outcome groups.

Additional analyses with mode of delivery, malposition of the fetus, and low birth weight did not show a significant association for these risk factors, and the

estimates for the other factors did not change. Because maternal asthma is a known risk factor for adverse pregnancy outcomes,²⁶ the analyses were repeated with adjustment for maternal asthma rather than asthma or allergy in either parent. This did not change the results. Because only 6 mothers reported corticosteroid use during pregnancy, we were not able to assess its effect on BHR development, atopy development, or both. Furthermore, inclusion of longer periods of being breast-fed (>6 or >12 weeks) did not result in a significant estimate for breast-feeding. The occupational status of the father at time of birth was included in the model to control for possible confounding by socioeconomic status. Occupational status did not significantly contribute to the model nor did it affect the estimates of the other variables in the model.

Because a severe respiratory infection in young childhood could be the result of perinatal factors, the analyses were repeated without the variable, indicating a severe respiratory infection in the first year of life. The results of these analyses were not different. Finally, it was investigated whether the relationship between duration of delivery and the development of atopy was linear by introducing quintiles of delivery duration into the model. The results indicated nonlinearity; there was no increased risk of atopy development in the lowest 3 quintiles, and this risk increased slightly in the fourth quintile and was highly increased in the highest quintile (duration of delivery >12.2 hours).

DISCUSSION

Twenty-five percent of this large birth cohort followed up to a mean age of 20.9 years (range, 19-23 years) had BHR, and almost 50% had atopy. A long duration of delivery was associated with the development of atopy, and a severe respiratory infection in the first year of life was associated with the development of BHR. In nonatopic subjects, being born by means of induced labor and current smoking constituted risk factors for the presence of BHR. Finally, prenatal smoke exposure and pet keeping in childhood were associated with a decreased risk for the development of atopy, especially in subjects with BHR.

To our knowledge, this is the first study investigating the effect of the duration of delivery on the development of BHR and atopy. A remarkable finding was that children who were born after a delivery taking longer than 12 hours were at increased risk of atopy at young adult age. This association was not due to confounding risk factors associated with prolonged labor, such as older age and nulliparity of the mother, big head circumference, and high birth weight of the baby. We hypothesize that the association between prolonged labor and increased risk for atopy might be explained by hormonal changes during pregnancy and delivery. In normal pregnancy there is a progressive increase in maternal plasma concentrations of stress hormones, including cortisol, with a peak at

TABLE II. Binary logistic regression analyses on the current status of BHR and on the current status of atopy

	BHR, OR (95% CI)	Atopy, OR (95% CI)
Perinatal risk factors		
Prenatal smoke exposure	0.74 (0.45-1.21)	0.64 (0.42-0.98)
Induction of labor	1.27 (0.74-2.19)	1.09 (0.69-1.74)
Delivery duration		
< 8 h	1.00	1.00
8-12 h	1.30 (0.72-2.37)	1.25 (0.76-2.06)
>12 h	1.50 (0.80-2.81)	2.24 (1.30-3.86)
Breast-feeding $\geq$ 2 wk	1.24 (0.75-2.06)	0.71 (0.47-1.09)
Respiratory infection in first year*	2.69 (1.41-5.16)	1.67 (0.91-3.09)
Other risk factors		
Female sex	1.62 (0.99-2.64)	0.72 (0.48-1.07)
Current smoking	1.41 (0.83-2.39)	1.18 (0.75-1.85)
Family history of atopy	0.93 (0.57-1.52)	1.29 (0.86-1.94)
Family history of asthma	1.19 (0.65-2.20)	1.02 (0.60-1.73)
Firstborn	0.79 (0.48-1.30)	0.97 (0.64-1.48)
Pets in childhood	0.71 (0.42-1.19)	0.65 (0.41-1.02)
Age, y	1.40 (1.09-1.80)	0.95 (0.76-1.17)

OR, Odds ratio.

*Respiratory infection in the first year is defined as severe respiratory tract infection in the first year of life.

TABLE III. Multinomial logistic regression analysis on the current status of BHR and atopy

	No BHR/atopy, OR (95% CI)	BHR/no atopy, OR (95% CI)	BHR/atopy, OR (95% CI)
Perinatal risk factors			
Prenatal smoke exposure	0.68 (0.43-1.10)	0.84 (0.38-1.83)	0.51 (0.27-0.99)
Induction of labor	1.40 (0.82-2.38)	2.41 (1.07-5.41)	1.03 (0.49-2.17)
Delivery duration			
< 8 h	1.00	1.00	1.00
8-12 h	1.30 (0.73-2.30)	1.56 (0.61-3.97)	1.46 (0.67-3.14)
>12 h	2.40 (1.29-4.47)	1.52 (0.51-4.53)	2.67 (1.18-6.04)
Breast-feeding $\geq$ 2 wk	0.63 (0.38-1.02)	0.95 (0.43-2.10)	0.97 (0.50-1.86)
Respiratory infection in first year*	1.82 (0.85-3.88)	3.95 (1.38-11.34)	3.64 (1.52-8.76)
Other risk factors			
Female sex	0.73 (0.46-1.15)	2.13 (0.94-4.82)	1.12 (0.60-2.10)
Current smoking	1.46 (0.87-2.44)	2.50 (1.12-5.59)	1.25 (0.61-2.54)
Family history of atopy	1.28 (0.80-2.04)	0.86 (0.40-1.85)	1.19 (0.63-2.24)
Family history of asthma	0.80 (0.43-1.49)	0.67 (0.23-1.98)	1.36 (0.64-2.89)
Firstborn	0.84 (0.52-1.37)	0.54 (0.24-1.20)	0.89 (0.46-1.72)
Pets in childhood	0.82 (0.49-1.38)	1.49 (0.55-4.04)	0.46 (0.24-0.88)
Age, y	0.85 (0.66-1.09)	1.18 (0.79-1.76)	1.37 (0.99-1.88)

Reference category is no BHR/no atopy.

OR, Odds ratio.

*Respiratory infection in the first year is defined as severe respiratory tract infection in the first year of life.

delivery. An increasing body of evidence shows that corticosteroids, such as cortisol, drive the T_H1/T_H2 balance of the immune system toward a T_H2 cytokine profile.^{27,28} Because maternal cortisol concentrations are linearly related to fetal concentrations during pregnancy,²⁹ maternal cortisol concentrations might have a major effect on the early differentiation of the T_H cell phenotypes and the development of T_H2 -type immunity in the fetus. Furthermore, neonatal plasma levels of cortisol have been shown to be significantly higher after completion of normal labor than after elective cesarean section, indicating the so-called cortisol surge described to occur during vaginal delivery.³⁰ We speculate that a long

duration of labor implies that the fetus is exposed to very high maternal cortisol levels for a relatively long period, and this directs the newborn to a T_H2 -type skewing that contributes to the later development of atopy.

The occurrence of a respiratory infection in the first year of life severe enough to require treatment by a doctor was associated with BHR at young adult age. A previous study on the same birth cohort reported an association between a severe respiratory infection and the presence of asthma symptoms and a lower level of lung function at young adult age.³¹ Although a low lung function is associated with the presence of BHR,³² the observed association was independent of the level of lung function. Only one other

study has investigated the association between LRIs in early childhood and the presence of BHR at follow-up⁸ and reported a dose-response relationship between the number of LRIs in the first 3 years of life and the presence of BHR at age 7 years. Our study is unique with respect to the long period of follow-up. It is a new and remarkable observation that the association between an LRI in the first year and the presence of BHR is still present after 20 years. Although it cannot be excluded that recall bias partially accounts for the association we observed, other studies have also shown that LRIs early in life constitute a risk factor for the presence of asthma symptoms or a low lung function.^{1,33} A causal relationship between LRIs early in life and the later development of asthmatic features cannot be ruled out, yet another plausible explanation for this relationship is reverse causation. Children who are predisposed to asthma might more likely have LRIs. Recently, several studies have supported this explanation.^{8,34,35}

Classification of subjects into 4 groups on the basis of the presence of BHR, atopy, or both indicated that subjects with BHR but without atopy differ in many respects from the other groups. The perinatal factors of babies later having BHR without atopy indicate a relatively uncomplicated delivery (ie, they had the lowest prevalence of a low Apgar score at 1 minute after birth, malposition, forceps or vacuum extraction delivery, and a low birth weight). However, drug-induced labor was more prevalent in this group compared with that in the other groups. The indication for labor induction was not registered but was likely associated with a high maternal blood pressure: in induced deliveries a diastolic maternal blood pressure of greater than 100 mm Hg occurred significantly more often than in those not induced (36% vs 9%, respectively; $P < .001$). There were no differences between induced and spontaneous deliveries in all other stress factors during pregnancy and delivery, as analyzed in our study. High maternal blood pressure was, however, not predictive of later development of BHR, whereas the association between induction of labor and BHR development remained unchanged in the analysis, suggesting a direct effect of labor induction on BHR in adult life in nonatopic subjects. The pharmacologic agent used for labor induction from 1975 through 1978 was intravenous oxytocin. The effects of oxytocin during labor induction on mother and child are not well established, although a causal effect on later development of BHR in the child seems unlikely. Thus it remains to be established which factor links labor induction to the later development of BHR in nonatopic individuals.

Subjects with pets in childhood had a lower risk of having atopy. This has been reported before, but there is some controversy about the explanatory mechanism for this association. In accordance with the hygiene hypothesis, early exposure to furred animals and the endotoxins they carry with them might trigger the immune system toward a T_H1 -type immunity that diverts from atopic sensitization.³⁶ On the other hand, another plausible explanation is that (parents of) those subjects who had

allergic symptoms when exposed to animals did not have pets.³⁷

We found a protective effect of prenatal smoke exposure on the presence of atopy after 20 years, especially in subjects with BHR. Other studies generally report no effect of maternal smoking during pregnancy on the development of atopy,¹⁸ although there is one study reporting the same protective effect as we found.³⁸ A recent study on the effect of tobacco smoke exposure in adults (16-49 years) and their children (3-15 years) showed a low risk for atopic disorders in the smokers themselves and a similar tendency in their children.³⁹ Further research is clearly needed to answer the question of causality in this matter.

In conclusion, in this 20-year-old cohort, events that took place before or during birth appeared to have a large effect on the current status of BHR and atopy. Although more research is necessary to confirm our findings, we put forward that the extreme hormonal status during a relatively long delivery can prime the fetal immune system toward atopy development. Furthermore, having had a severe respiratory infection in the first year of life is associated with the presence of BHR at young adult age, and prenatal smoke exposure might be protective for the development of atopy.

REFERENCES

1. Barker DJP, Godfrey KM, Fall C, Osmond C, Winter PD, Shaheen SO. Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. *BMJ* 1991; 303:671-5.
2. Shaheen SO, Sterne JAC, Montgomery SM, Azima H. Birth weight, body mass index and asthma in young adults. *Thorax* 1999;54:396-402.
3. Oddy WH, Holt PG, Sly PD, Read AW, Landau LI, Stanley FJ, et al. Association between breast feeding and asthma in 6 year old children: findings of a prospective birth cohort study. *BMJ* 1999;319:815-9.
4. Stick SM, Burton PR, Gurrin L, Sly PD, LeSouëf PN. Effects of maternal smoking during pregnancy and a family history of asthma on respiratory function in newborn infants. *Lancet* 1996;348:1060-4.
5. Haby MM, Peat JK, Marks GB, Woolcock AJ, Leeder SR. Asthma in preschool children: prevalence and risk factors. *Thorax* 2001;56:589-95.
6. Lewis S, Richards D, Bynner J, Butler N, Britton J. Prospective study of risk factors for early and persistent wheezing in childhood. *Eur Respir J* 1995;8:349-56.
7. Sterk PJ, Fabbri LM, Quanjer PhH, Cockcroft DW, O'Byrne PM, Anderson SD, et al. Airway responsiveness. Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. Report working party standardization of lung function tests. European community for steel and coal. Official statement of the European Respiratory Society. *Eur Respir J* 1993;6(suppl 16):53-83.
8. Illi S, von Mutius E, Bergmann R, Lau S, Niggemann B, Wahn U, et al. Early childhood infectious diseases and the development of asthma up to school age. *BMJ* 2001;322:390-5.
9. Ernst P, Cormier Y. Relative scarcity of asthma and atopy among rural adolescents raised on a farm. *Am J Respir Crit Care Med* 2000;161: 1563-6.
10. Strachan DP. Hay fever, hygiene and household size. *BMJ* 1989;299: 1259-60.
11. Strachan DP. Family size, infection and atopy: the first decade of the "hygiene hypothesis." *Thorax* 2000;55(suppl):S2-10.
12. Godfrey KM, Barker DJ, Osmond C. Disproportionate fetal growth and raised IgE concentration in adult life. *Clin Exp Allergy* 1994;24:641-8.
13. Gregory A, Doull I, Pearce N, Cheng S, Leadbitter P, Holgate S, et al. The relationship between anthropometric measurements at birth: asthma and atopy in childhood. *Clin Exp Allergy* 1999;29:330-3.

14. McKeever TM, Lewis SA, Smith C, Hubbard R. The importance of prenatal exposures on the development of allergic disease. A birth cohort study using the West Midlands general practice database. *Am J Respir Crit Care Med* 2002;166:827-32.
15. Nafstad P, Magnus P, Jaakkola JJK. Risk of childhood asthma and allergic rhinitis in relation to pregnancy complications. *J Allergy Clin Immunol* 2000;106:867-73.
16. Pekkanen J, Xu B, Jarvelin MR. Gestational age and occurrence of atopy at age 31—a prospective birth cohort study in Finland. *Clin Exp Allergy* 2001;31:95-102.
17. Saarinen UM, Kajosaari M. Breastfeeding as prophylaxis against atopic disease: prospective follow-up study until 17 years old. *Lancet* 1995;346:1065-9.
18. Strachan DP, Cook DG. Health effects of passive smoking. 5. Parental smoking and allergic sensitization in children. *Thorax* 1998;53:117-23.
19. Xu B, Pekkanen J, Hartikainen A-L, Jarvelin MR. Caesarean section and risk of asthma and allergy in adulthood. *J Allergy Clin Immunol* 2001;107:732-3.
20. McKeever TM, Lewis SA, Smith C, Hubbard R. Mode of delivery and risk of developing allergic disease. *J Allergy Clin Immunol* 2002;109:800-2.
21. Bager P, Melbye M, Rostgaard K, Stabell Benn C, Westergaard T. Mode of delivery and risk of allergic rhinitis and asthma. *J Allergy Clin Immunol* 2003;111:51-6.
22. Touwen BC, Huisjes HJ, Jurgens-van der Zee AD, Bierman-van Eendenburg ME, Smyrkovsky M, Olinga AA. Obstetrical condition and neonatal neurological morbidity. *Early Hum Dev* 1980;4:207-28.
23. Burney PGJ, Luczynska C, Chinn S, Jarvis D. The European community respiratory health survey. *Eur Respir J* 1994;7:954-60.
24. Apgar V. A proposal for a new method of evaluation of the newborn infant. *Curr Res Anesth Analg* 1953;32:260-7.
25. Chinn S, Burney P, Jarvis D, Luczynska C. European Community Respiratory Health Survey. Variation in bronchial responsiveness in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1997;10:2495-501.
26. Demissie K, Breckenridge MB, Rhoads GG. Infant and maternal outcomes in the pregnancies of asthmatic women. *Am J Respir Crit Care Med* 1998;158:1091-5.
27. Wilckens T, de Rijk R. Glucocorticoids and immune function: unknown dimensions and new frontiers. *Immunol Today* 1997;18:418-24.
28. DeKruyff RH, Fang Y, Umetsu DT. Corticosteroids enhance the capacity of macrophages to induce Th2 cytokine synthesis in CD4+ lymphocytes by inhibiting IL-12 production. *J Immunol* 1998;160:2231-7.
29. Gitau R, Cameron A, Fisk NM, Glover V. Fetal exposure to maternal cortisol. *Lancet* 1998;352:707-8.
30. Power LL, Popplewell EJ, Holloway JA, Diaper ND, Warner JO, Jones CA. Immunoregulatory molecules during pregnancy and at birth. *J Reprod Immunol* 2002;56:19-28.
31. Boezen HM, Vonk JM, van Aalderen WMC, Brand PLP, Gerritsen J, Schouten JP, et al. Perinatal predictors of respiratory symptoms and lung function at a young adult age. *Eur Respir J* 2002;20:383-90.
32. Rijcken B, Schouten JP, Weiss ST, Speizer FE, van der Lende R. The relationship between airways responsiveness to histamine and pulmonary function level in a random population sample. *Am Rev Respir Dis* 1988;137:826-32.
33. Castro-Rodriguez JA, Holberg CJ, Wright AL, Halonen M, Taussig LM, Morgan WJ, et al. Association of radiologically ascertained pneumonia before age 3 yr with asthmalike symptoms and pulmonary function during childhood. *Am J Respir Crit Care Med* 1999;159:1891-7.
34. Martinez FD. What have we learned from the Tucson children's respiratory study. *Pediatr Respir Rev* 2002;3:193-7.
35. Koopman LP, Smit HA, Heijnen ML, Wijga A, van Strien RT, Kerkhof M, et al. Respiratory infections in infants: interaction of parental allergy, child care, and siblings—The PIAMA study. *Pediatrics* 2001;108:943-8.
36. Liu AH, Szefer SJ. Advances in childhood asthma: hygiene hypothesis, natural history, and management. *J Allergy Clin Immunol* 2003;111(suppl):S785-92.
37. Jaakkola JJK, Jaakkola N, Piipari R, Jaakkola MS. Pets, parental atopy, and asthma in adults. *J Allergy Clin Immunol* 2002;109:784-8.
38. Soyseth V, Kongerud J, Boe J. Postnatal maternal smoking increases the prevalence of asthma but not of bronchial hyperresponsiveness or atopy in their children. *Chest* 1995;107:389-94.
39. Hjelm A, Hedberg A, Haglund B, Rosén M. Does tobacco smoke prevent atopic disorders? A study of two generations of Swedish residents. *Clin Exp Allergy* 2001;31:908-14.

Availability of Journal back issues

As a service to our subscribers, copies of back issues of *The Journal of Allergy and Clinical Immunology* for the preceding 5 years are maintained and are available for purchase until inventory is depleted. Please write to Elsevier Inc, Subscription Customer Service, 6277 Sea Harbor Dr, Orlando, FL 32887, or call (800) 654-2452 or (407) 345-4000 for information on availability of particular issues and prices.