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Chest 2010;138:338-344; Prepublished online April 30, 2010;
DOI 10.1378/chest.10-0365

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ISSN:0012-3692





Causal Direction Between Respiratory Syncytial Virus Bronchiolitis and Asthma Studied in Monozygotic Twins

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Background: Respiratory syncytial virus (RSV) bronchiolitis has been associated with later development of asthma, wheezing, abnormal pulmonary function, and sensitization. Our aim was to determine the differential effect within monozygotic (MZ) twin pairs discordant for severe RSV bronchiolitis in infancy on the subsequent development of asthma, pulmonary function, and allergy.

Methods: Thirty-seven MZ twin pairs discordant for RSV hospitalization in infancy (mean age 10.6 months) were compared at the mean age of 7.6 years for lung function, bronchial responsiveness, fractional exhaled nitric oxide (FENO), asthma diagnosis, use of asthma medication, and skin prick test to common inhalant allergens.

Results: There were no differences within MZ twin pairs discordant for RSV hospitalization in infancy with respect to pulmonary function, FENO, asthma prevalence, asthma medication use, or sensitization ($P > .1$ for all comparisons).

Conclusions: We found no differential effect from severity of RSV infection on the development of asthma and allergy in MZ twin pairs discordant for RSV hospitalization in infancy. This argues against a specific effect of severe RSV infection in the development of asthma and allergy. Because of the small sample size, this study must be considered as a hypothesis-generating study.

CHEST 2010; 138(2):338–344

Abbreviations: FENO = fractional exhaled nitric oxide; MZ = monozygotic; PD20 = dose of methacholine producing a 20% fall in FEV₁; RSV = respiratory syncytial virus; sRaw = specific airway resistance

Respiratory syncytial virus (RSV) is a common cause of lower-respiratory-tract disease and hospitalization in infants and young children.^{1,2} Severe RSV bronchiolitis has been associated with later development of abnormal pulmonary function, wheezing, asthma, and allergic sensitization,^{3–7} but it is unclear whether severe

RSV bronchiolitis causes wheezing, or genetic predisposition or other environmental risk factors increase the propensity to such exaggerated response to RSV.

The aim of this study was to compare the long-term outcome of asthma, allergy, and pulmonary function in monozygotic (MZ) twin pairs discordant for hospitalization with verified RSV bronchiolitis in infancy as a surrogate marker of the RSV disease severity. Any differential long-term effect from RSV disease severity

Manuscript received February 8, 2010; revision accepted March 29, 2010.

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DOI: 10.1378/chest.10-0365

in these genetically identical twins would suggest a causal role of RSV.

MATERIALS AND METHODS

The study was approved by the ethics committee of Copenhagen (KA-20060022) and by the Danish Data Protection Agency (J.nr. 2005-41-5163 and J.nr. 2005-2311-0121). The children were enrolled after written consent was obtained from the parents or guardians.

Registries Used for Recruitment of the Study Population

The Danish Civil Registration System registers every Danish citizen by a unique personal identification number, providing a key for linking register information.⁸ The Danish Twin Registry contains information to enable complete ascertainment of all live-born twins since 1968. Zygosity information in the registry is determined from questions on similarity and mistaken identity in a postal questionnaire^{9,10} and was confirmed by DNA analysis with 10 highly polymorphic markers in our study population. The Danish National Patient Registry records all hospitalizations based on the *International Statistical Classification of Diseases and Related Health Problems, 10th revision*. A research database was established between January 1996 and May 2003, recording RSV tests from all hospitalizations in Denmark.¹¹

Study Population

The target population was identified by linking the personal identification number to (1) the twin status, (2) living address, and (3) hospitalizations resulting from diagnoses of RSV pneumonia (J12.1), RSV bronchitis (J20.5), RSV bronchiolitis (J21.0), and other diseases caused by RSV (B97.4) during the period from January 1, 1994 to December 31, 2003. The registry ensures that the control twin had never been hospitalized with RSV infection. Hospital records were retrieved to verify respiratory symptoms compatible with RSV bronchiolitis (severe cough, abnormal radiograph of the thorax, use of β_2 agonist, crackles or wheeze by auscultation of lungs)¹² and verified with an enzyme-linked immunosorbent assay or immunofluorescence assay test for RSV.

Clinical Examination

Twins and their parents were summoned to the Danish Pediatric Asthma Center's two centers in East and West Denmark for clinical examination, including interviews on the child's asthma according to the Global Initiative on Asthma guidelines¹³ and information about medical history and objective assessments. The interviews and clinical examinations were done by one physician (P. P.).

All lung function tests were performed the same day, starting with measurement of exhaled nitric oxide, followed by baseline FEV₁/specific airway resistance (sRaw) and hyperreactivity tests. The participants were informed not to use β_2 agonist 12 h before the lung function tests.

Lung Function Test

Children aged 7 years and older used a spirometer to measure FEV₁ (Spirotrac; Vitalograph Ltd; Buckingham, England) according to the criteria of the American Thoracic Society.¹⁴ Children younger than 7 years were tested using whole-body plethysmography to measure sRaw as previously detailed.¹⁵ We used the MasterScreen Body Unit Software JLAB (E. Jaeger GmbH; Wuerzburg, Germany).

Bronchial Responsiveness

Children aged 7 years and older were tested for responsiveness to methacholine chloride with FEV₁ measurements before and

3 min after each dose. Methacholine was delivered in successively increasing doses according to a protocol previously validated for school children¹⁶ by an automatic, inhalation-synchronized, dosimetric jet nebulizer (Spira Elektro 2; Respiratory Care Center; Hämeenlinna, Finland). The dose of methacholine producing a 20% fall in FEV₁ (PD₂₀; measured as μ mol) was calculated by linear interpolation between the dose points bracketing the 20% fall in FEV₁.¹⁷ Children younger than 7 years were tested with dry-air hyperventilation as previously described and validated in this age group.¹⁸

Fractional Exhaled Nitric Oxide

Fractional exhaled nitric oxide (FENO) was measured by the online single-breath method according to the European Respiratory Society/American Thoracic Society task force¹⁹ using the NIOX equipment (Nitric Oxide Monitoring System; Aerocrine AB; Stockholm, Sweden).

Sensitization

The skin prick test was done with standard inhalation allergens: birch, mugwort, grass, horse, dog, cat, dust mite, and mold (Soluprick, SQ; ALK-Abelló A/S; Hørsholm, Denmark).

Statistical Analysis

SAS version 9.1 (SAS Institute; Cary, NC) was used for statistical analyses. The continuous data were log transformed and presented as geometric means in the table. Odds ratios were calculated for the dichotomous data with 95% CIs. Data were analyzed with paired *t* tests for continuous outcome measures, Fisher exact test for dichotomous outcomes, and Wilcoxon (paired) test for dry-air hyperventilation outcome. All hypotheses tests were two-sided and used a significance level of 0.05.

RESULTS

During the period from January 1, 1994, to December 31, 2003, 12,349 twin pairs were born in Denmark. The proband-wise concordance rate of hospitalization for RSV bronchiolitis was significantly higher in MZ (0.66) than in dizygotic twin pairs (0.53), $P = .02$.²⁰ Fifty-seven MZ twin pairs (26 boys) were discordant for RSV hospitalization (Fig 1). Nine pairs were unavailable because of death or address protection. Five pairs were excluded based on their hospital records because the RSV infection was found incidentally during hospitalization for other reasons (eg, elective surgery) not associated with lower-respiratory symptoms. Forty-three pairs were invited, of which 37 pairs accepted to participate (14 male twins; mean age 7.6 years; interquartile range: 5.9-9.2). Twenty-two twin pairs were examined in Copenhagen, and 15 twin pairs in Aarhus. Fifty-four percent of parents answered retrospectively that the hospitalized RSV proband twin suffered more severe lung symptoms, 19% said it was the control twin, and 27% said both twins had comparable symptoms.

Mean gestational age was 35.5 weeks. There was no significant difference between RSV hospitalized and nonhospitalized twins with respect to birth weight (mean 2,369 g), neonatal treatment of lung

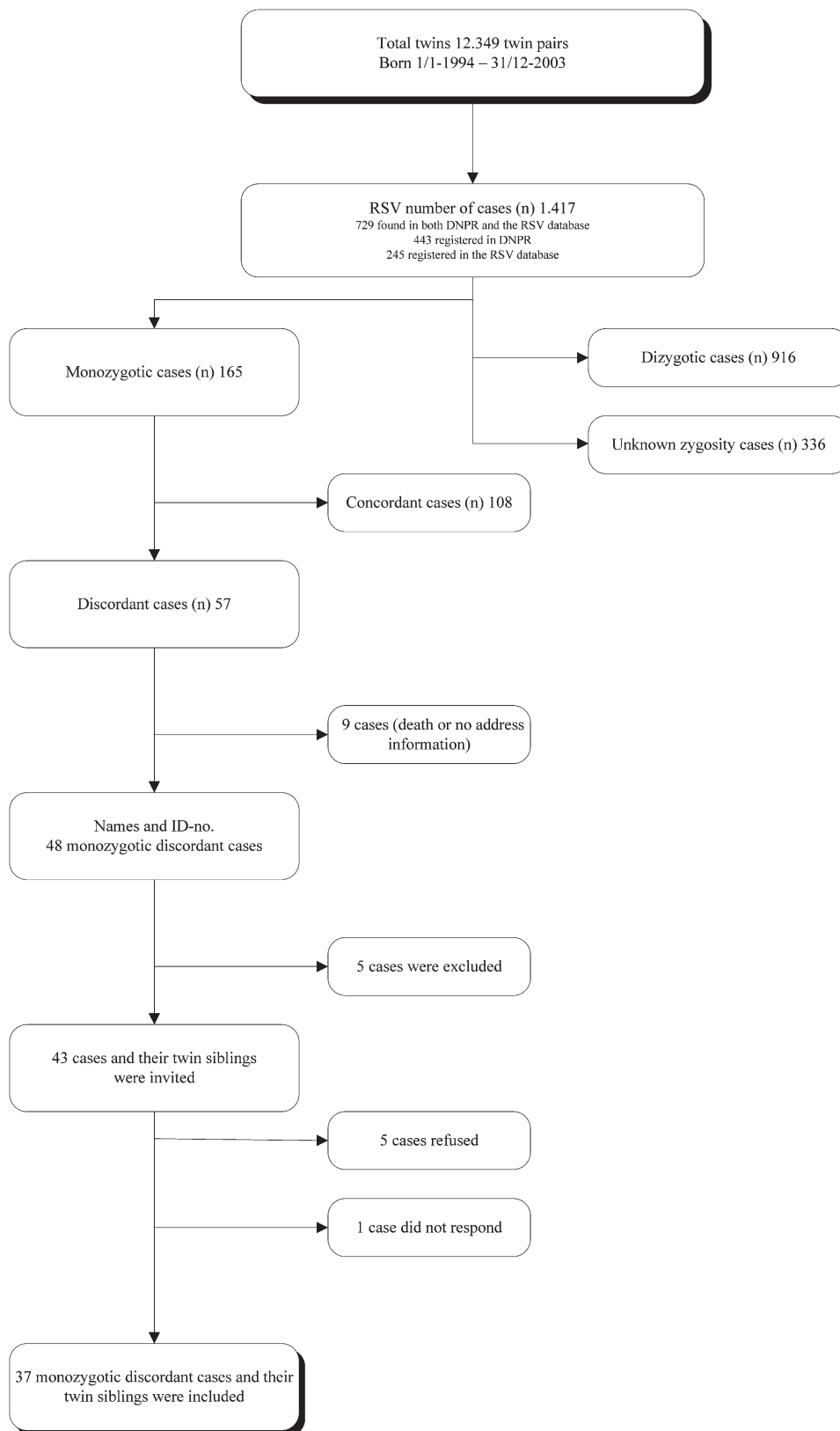


FIGURE 1. Flow chart. ID = identification; RSV = respiratory syncytial virus.

complications (continuous positive airway pressure, surfactant, or pneumothorax), and birth order (22/37 probands were first born).

Forty-nine percent of the twin pairs had parental atopic predispositions. The average age when hospitalized for severe RSV bronchiolitis was 10.6 months

(interquartile range, 5.1-13.3), the median age was 8.4 months. Mean duration of hospitalization was 4.3 days.

According to the interviews (Global Initiative on Asthma guidelines), the prevalence of asthma was 18% in our twin sample. The twins did not differ with respect to current asthma, use of inhaled corticosteroid or β_2 agonist ever, atopic dermatitis ever, FENO, baseline lung function, bronchial responsiveness, or sensitization (Table 1, Table 2). Only four children were in present use of inhaled corticosteroids (Table 2); one twin pair and two control twins.

We tried to dichotomize both the dry-air hyperventilation test and the methacholine test. Dry-air hyperventilation response is positive with $>20\%$ sRaw change. Currently, there is no cutoff value for methacholine challenge for children. We arbitrarily chose the second dose in the challenge of $PD_{20} < 0.18 \mu\text{mol}$ as the cutoff value. There were no significant differences between hospitalized twin and control twin when pooling the two airway responsiveness challenges (Table 2).

DISCUSSION

We found no difference within cohabiting MZ twin pairs discordant for hospitalization for RSV bronchiolitis in infancy on asthma prevalence, baseline lung function, bronchial responsiveness, biomarker of airway inflammation (FENO), and sensitization 7 years after such severe RSV bronchiolitis. Though a number of criticisms may be raised, including the small study population, it is noteworthy that no trends suggested a differential effect from severe RSV infection. Therefore a strong effect from this virus seems unlikely.

Limitations and Strengths of the Study Design

MZ twins are useful for investigating the role of genetic and environmental factors on asthma because of their identical genetic backgrounds and similar childhood environmental exposures.²¹ However, comparison of MZ twin pairs discordant to hospitalization for RSV bronchiolitis is prone to a number of biases.

The underlying assumption was that RSV sequelae were proportional to the severity of the RSV infection. We have no evidence to prove the twin serving as control was actually infected with RSV (no serologic data), but rely on the very high virulence of RSV among cohabiting twins, previously estimated at 93% to 96%,²⁰ though this could not be verified.

We do not have positive evidence that this twin had milder symptoms, but rely on the fact that one was hospitalized while the other was not. Danish children are generally only admitted if they need support with a feeding tube, suction of upper airways, mask inhalations, or nasal continuous positive airway pressure. Yet, this could be biased from registration practice. Indeed, 19% of parents recalled the control twin being most severely affected. However, there is a significant risk for recall bias, and the MZ pairs could be mixed up since the hospitalization was on average 7 years ago and parents were generally most unsure of the details. We could have restricted the analysis to the 20 pairs who recalled the proband twin to have been the most severely affected, but this was limited by the low numbers in the resulting analysis. Instead, we relied on the Danish registration practice and included all 37 pairs.

The distinction between possible “wheezers” and “bronchiolitis” may be inaccurate in this as in other studies. The distinction between wheezers and bronchiolitis is normally related to severity of wheeze and

Table 1—Comparison of Clinical End Points at Follow-up Between Monozygotic Twin Pairs Discordant for Hospitalization for Severe RSV Bronchiolitis

End Points	Units of Measure	Hospitalized vs Nonhospitalized	P Value
Asthma	OR (95% CI)	1.21 (0.36-4.00)	1.00 ^a
History of atopic dermatitis	OR (95% CI)	1.14 (0.41-3.14)	1.00 ^a
Use of inhalation steroid ever	OR (95% CI)	1.26 (0.49-3.22)	.81 ^a
Use of β_2 agonist ever	OR (95% CI)	1.38 (0.55-3.46)	.64 ^a
logFENO (n = 30)	ppb mean (SD)	2.05 (0.66); 2.17 (0.69)	.16 ^b
logBaseline FEV ₁ (n = 25)	L mean (SD)	0.42 (0.26); 0.46 (0.23)	.12 ^b
logMethacholine PD ₂₀ (n = 24)	μmol mean (SD)	0.74 (1.83); 0.41 (1.71)	.27 ^b
logsRaw baseline (n = 12)	kPa*s mean (SD)	0.18 (0.26); 0.19 (0.30)	.79 ^b
sRaw after dry air hyperventilation (n = 5)	Percent increase (median)	27; 18	.40 ^c
Positive skin prick test	OR (95% CI)	0.36 (0.07-2.08)	.43 ^a

FENO = fractional exhaled nitric oxide; MZ = monozygotic; n = number of twin pairs that completed a specific test; OR = odds ratio; ppb = parts per billion; PD₂₀ = dose of methacholine producing a 20% fall in FEV₁; sRaw = specific airway resistance.

^aFisher exact test.

^bPaired *t* test.

^cWilcoxon test (paired).

Table 2—Prevalence of Atopic Outcomes in the Proband and Control Twin Groups

Atopic Outcome	Hospitalized Twin (%)	Nonhospitalized Twin (%)
Asthma	19	16
Wheeze the first 5 y of life	44	39
History of atopic dermatitis	30	27
Use of inhalation steroid ever	41	35
Present use of inhalation steroid	3	8
Use of β_2 agonist ever	51	43
Positive airway responsiveness	17	14
Positive skin prick test	6	14

concurrent clinical signs of lower-airway infection. Our samples included the latter, that is, first hospitalization for severe wheeze with concomitant signs of lower-airway infection.

It is known that male sex could be a risk factor for RSV hospitalization.^{22,23} In the whole twin cohort there were more boys than girls in all outcomes,²⁰ but there was a random overrepresentation of girls in our study.

The discordant MZ twins in our study were born slightly earlier (mean gestational age 35.5 weeks and mean birth weight 2,369 g) than the MZ twins in the overall twin cohort (mean gestational age 36.1 weeks [SD 2.5] and birth weight 2,498 g (SD 549)).²⁰ The differences were small and not significant; therefore, it seems that the discordant twins were representative of MZ twins in general.

The highest prevalence of hospitalization for RSV bronchiolitis is often reported in children ≤ 1 year old.^{24,25} However, the reported mean age may be biased from excluding older children from such analyses. Sigurs et al⁶ reported the mean age of RSV hospitalization to be 3.5 months excluding infants older than 12 months. Fjaerli et al²³ reported the admission age median to be 6 months in children under 2 years old in their study. One study included children up to 2 years and showed the median age of hospitalization was 10 months of age, similar to our findings.²⁶

Most importantly, the power of our study is limited by the low number of 37 paired cases, and the 95% CI is correspondingly wide, particularly for the clinical end point, though less so for the objective surrogate markers of asthma such as lung function and FENO. However, our study was based on the complete national database and not power calculations.

Mean age at the clinical examination was 7.6 years. A difference in asthma prevalence later in life cannot be excluded, but the possibility seems low inasmuch as those studies showing higher asthma prevalence after severe RSV found this mainly in early childhood⁴ and most cases of asthma debut before school age.

Interpretation of the Study

We studied the direction of the causal relationship between severe RSV bronchiolitis and asthma. RSV bronchiolitis has been associated with wheezing, asthma, and abnormal pulmonary function in childhood.³⁻⁶ One particular cohort study reported an asthma rate of 43% vs 8% and sensitization to common allergens of 45% vs 26% by age 13 years in children with infant hospitalization for RSV bronchiolitis compared with a matched control group.⁶ A review of pooled data from 10 controlled studies concluded that wheezing (but not recurrent wheezing) is more common after severe RSV bronchiolitis up to 5 years of follow-up.²⁷ Approximately 42% of the twins in this study had wheezing the first 5 years of life, and the prevalence of current asthma was 18%, but with non-significant differences between the hospitalized vs the control twin (Table 2). Two Finnish studies reported only marginal increase in the prevalence of asthma after RSV bronchiolitis in infancy.^{26,28} However, predisposition to asthma and atopy was associated with increased risk of lower-respiratory-tract infection and hospitalization for RSV infection,^{25,29} and early wheezy symptoms were found to be a strong risk factor for subsequent hospitalization for RSV.²⁴ Therefore, the direction of causality is unknown: Does RSV increase the risk of asthma, is asthma constitution increasing the risk of severe response to RSV infection, or are both sharing a common, undisclosed environmental exposure?

The model we used adjusted for genetic variation by analyzing long-term outcome in MZ twin pairs in which one infant had been hospitalized for severe lung symptoms in response to verified RSV bronchiolitis, whereas the twin sibling had not been hospitalized at any time for RSV bronchiolitis. This allowed a comparison of severe vs milder response to RSV infection, genetic factors, and environmental exposures during follow-up years, with other factors being equal between the cohabiting MZ twin proband and control pairs.

Our recent publication based on 8,280 twin pairs showed that a model in which asthma “causes” RSV hospitalization fit significantly better than a model in which RSV hospitalization “causes” asthma.³⁰ On the other hand, Wu and colleagues³¹ concluded in another recent paper that they have shown strong evidence for a causal relationship of winter viruses and early childhood asthma.

A genetic contribution to asthma and severe RSV bronchiolitis is suggested from the high prevalence of asthma in our twin sample compared with the current asthma prevalence in our region,³² as well as the high prevalence of parental atopic predisposition in the present study. Likewise, such a genetic component

was reflected by our previous finding of a higher concordance for hospitalization for RSV bronchiolitis in MZ than dizygotic twin pairs.²⁰

We found no differential effect from severity of RSV infection on asthma and allergy 7 years after infection. This may suggest that some undisclosed environmental factor instead could be responsible for the different severities of RSV infection. The nature of such exposure is unknown and surprising in MZ twins. Studies suggest that phenotypic discordance between MZ twins is to some extent due to epigenetic factors. Acute environmental factors are directly associated with epigenetic-dependent disease phenotype.³³

Speculations may consider differing coinfections with an agent of less virulence, including bacterial colonization³⁴ or other viral infections. There is increasing evidence that rhinoviruses are able to cause lower-airway infections and to induce wheezing in young children, and they may be as common as RSV as a cause of bronchiolitis.³⁵ However, the long-term effect of this and other viral agents on lung function and symptoms later in childhood is not yet fully investigated.

In conclusion, we found no differential effect from severity of RSV infection on the development of asthma and allergy in MZ twin pairs discordant for RSV hospitalization in infancy. This argues against a specific effect of severe RSV infection in the development of asthma and allergy, and may suggest an undisclosed environmental factor interacting in these genetically similar twins, leading to different severity of their response to RSV infection. Because of the small sample size, this study must be considered as a hypothesis-generating study.

ACKNOWLEDGMENTS

Author contributions: Dr Poorisrisak: contributed to the planning of the visits, performed the experimental work, and contributed to the presentation, interpretation, and discussion of the obtained data.

Dr Halkjaer: contributed to the planning of the visits, was involved in the experimental work, and contributed to the discussion of the obtained data.

Dr Thomsen: contributed to the formulation of the scientific problem, the methodology design, and discussion of the obtained data.

Dr Stensballe: contributed to the formulation of the scientific problem, the methodology design, and the discussion of the obtained data.

Dr Kyvik: contributed to the formulation of the scientific problem, the methodology design, and the discussion of the obtained data.

Dr Skytthe: contributed to the formulation of the scientific problem, the methodology design, and the discussion of the obtained data.

Dr Schioetz: contributed to the formulation of the scientific problem, the methodology design, and the discussion of the obtained data.

Dr Bisgaard: contributed to the formulation of the scientific problem, the methodology design, and the interpretation and discussion of the obtained data.

Financial/nonfinancial disclosures: The authors have reported to CHEST the following conflicts of interest: Dr Stensballe is a consultant to Abbott Laboratories. Dr Bisgaard has been a consultant to and paid lecturer for AstraZeneca, Altana, GlaxoSmithKline, Merck, MedImmune, NeoLab, and Pfizer. Drs Poorisrisak, Halkjaer, Thomsen, Kyvik, Skytthe, and Schioetz have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Other contributions: We thank all the children and parents for participating in the study. We also thank S. V. Thorsen (Danish Pediatric Asthma Center, Copenhagen University Hospital, Copenhagen, Denmark) for statistical advice; and J. Henriksen, H. Niekrenz, L. Johnsen, and E. M. Raaby (Department of Pediatrics, Aarhus University Hospital, Skejby, Denmark) for practical help.

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Chest 2010;138; 338-344; Prepublished online April 30, 2010;
DOI 10.1378/chest.10-0365

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