

The causal direction in the association between respiratory syncytial virus hospitalization and asthma

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Background: Earlier studies have reported an increased risk of asthma after respiratory syncytial virus (RSV) hospitalization. Other studies found that asthmatic disposition and propensity to wheeze increase the risk of RSV hospitalization.

Objective: The current study examined the causal direction of the associations between RSV hospitalization and asthma in a population-based cohort of twins.

Methods: We conducted a prospective cohort study examining the associations between RSV hospitalization and asthma by using registry information on RSV hospitalization and asthma among 18,614 Danish twins born 1994 to 2003. The associations between RSV and asthma were examined in both directions: we examined the risk of asthma after RSV hospitalization, and the risk of RSV hospitalization in children with asthma in the same population-based cohort.

Results: Asthma hospitalization after RSV hospitalization was increased as much as 6-fold to 8-fold during the first 2 months after RSV hospitalization but was no longer increased 1 year later. Asthma increased the risk of RSV hospitalization by 3-fold, and the risk was not time-dependent. Analyzing these associations on the basis of asthma defined from use of inhaled corticosteroid did not materially change the risk estimates.

Conclusion: There is a bidirectional association between severe RSV infection and asthma. Severe RSV infection is associated with a short-term increase in the risk of subsequent asthma, suggesting that RSV induce bronchial hyperresponsiveness; and asthma is associated with a long-term increased susceptibility for severe RSV disease, suggesting a host factor being responsible for the severe response to RSV infection. This

suggests that severe RSV infection and asthma may share a common genetic predisposition and/or environmental exposure. (*J Allergy Clin Immunol* 2009;123:131-7.)

Key words: Asthma, child, epidemiology, respiratory syncytial virus, twins

Respiratory syncytial virus (RSV) is an important cause of viral lower respiratory tract disease in infants and children worldwide,¹⁻³ a very common cause of childhood hospitalization, and a major drain on public health resources.^{4,5}

The hospitalization rate for RSV infection in infants less than 6 months was 34 per 1000 in Denmark⁶ and seems to be increasing in the United States.⁷ The rehospitalization rate within the first year after RSV hospitalization is high, reportedly as high as 20%.⁸

Respiratory syncytial virus bronchiolitis has been associated with the development of abnormal pulmonary function, wheezing, and asthma in childhood.⁹⁻¹¹ One particular cohort reported an asthma rate by age 13 years of 43% versus 8% and sensitization to common allergens in 45% versus 26% in children with infant hospitalization for RSV bronchiolitis compared with a matched control group.^{12,13}

On the other hand, predisposition to asthma and atopy was associated with an increased risk of lower respiratory tract infection and RSV hospitalization,¹⁴⁻¹⁶ and early wheezy symptoms were found to be a strong risk factor for subsequent RSV hospitalization.¹⁷ Impaired pulmonary function at 1 month of age increased the risk of wheezing episodes and asthma¹⁸⁻²⁰ and has been suspected to increase the risk of severe reaction to viral infection.

Therefore, the direction of causality is unknown: does RSV increase risk of asthma, or is asthma constitution increasing the risk of severe response to RSV infection, or are they sharing common determinants such as a genetic predisposition or environmental exposure or both?

In a population-based study among Danish twins, we recently showed that risk of severe RSV infection was ascribable partly to genetic factors.²¹ In the current study, we examined the associations between RSV hospitalization and asthma in early childhood in this cohort of twins by testing the risk of subsequent asthma among twins hospitalized for RSV, and vice versa, by testing the risk of subsequent RSV hospitalization among twins with asthma.

METHODS

Registries

Personal identification number. A unique identification number is assigned to every Danish citizen and registered in the Danish Civil Registration System (CRS; <http://www.cpr.dk>). The personal identification number serves as key reference to the individual citizen in all registries and

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Supported by the Lundbeck Foundation, the Augustinus Foundation, and an unrestricted institutional grant from MedImmune.

Disclosure of potential conflict of interest: V. Backer receives grant support from AstraZeneca, Boehringer Ingelheim, ALK-Abelló, and Novartis. H. Bisgaard has been a consultant to, has been a paid lecturer for, and holds sponsored grants from Aerocrine, AstraZeneca, Altana, GlaxoSmithKline, Merck, MedImmune, NeoLab, and Pfizer; receives grant support from Aerocrine, AstraZeneca, GlaxoSmithKline, Merck, and MedImmune; and has provided legal consultation/expert witness testimony for NeoLab. The rest of the authors have declared that they have no conflict of interest.

Received for publication July 6, 2008; revised October 11, 2008; accepted for publication October 14, 2008.

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doi:10.1016/j.jaci.2008.10.042

Abbreviations used

CRS: Danish Civil Registration System
 DNPR: Danish National Patient Registry
 RMPS: Register of Medicinal Product Statistics
 RSV: Respiratory syncytial virus

provides a simple method for linking registry information. The CRS keeps daily updated demographic information inclusive of deaths and migration on all residents in Denmark.²² To adjust the analysis, information on sex together with information on death and migration was obtained from the CRS.

Danish Twin Registry. The Danish Twin Registry (<http://www.dtr.sdu.dk>) consists of Danish twins born from 1870 to 2004. From 1968 there is complete ascertainment of all live-born twins. Zygosity was determined from 4 questions on similarity and mistaken identity in a mailed questionnaire. This method correctly assigns zygosity in more than 96% of the cases.²³

Danish National Patient Registry. The Danish National Patient Registry (DNPR)²⁴ contains information on all hospitalizations in the Danish population. The diagnoses are based on the International Classification of Diseases, Tenth Revision. The diagnoses used to define RSV hospitalization, asthma hospitalization, and chronic diseases are specified in this article's Online Repository at www.jacionline.org.

Danish National Birth Registry. The Danish National Birth Registry is part of the DNPR and contains information on all births and newborns in Denmark. To adjust the analysis, information on the type of birth, gestational age, birth weight, parents' ages, maternal smoking, and single parenthood was obtained from the Danish National Birth Registry.

RSV database. A database was assembled from the Danish laboratories testing hospitalized patients for RSV in Denmark between January 1996 and May 2003. The information gathered includes date and result of the RSV test and the patient's personal identification number. The database has been validated by using information from DNPR, which registers all inpatient hospitalizations in Denmark; it was found to cover 96% of RSV hospitalizations.²⁵ The validation study furthermore found that 73% of infants with proven RSV infection were registered in DNPR with RSV diagnoses. No data were available regarding outpatient RSV illness.

Statistics Denmark. Statistics Denmark (<http://www.dst.dk>) contains detailed statistical information on Danish society—for example, on demography, social parameters, economics, and business—and supplies many research projects with data.²⁶ To adjust the analysis, information on siblings, maternal education, job, and income was obtained from Statistics Denmark.

Register of Medicinal Product Statistics. The Register of Medicinal Product Statistics (RMPS; http://www.dkma.dk/1024/visUKLS_Artikel.asp?artikelID=743) is a database that contains figures on the total sale of medicinal products in Denmark. The information is collected from Danish pharmacies, which register every dispatch or delivery of medicinal products in Denmark. The RMPS is administered by Statistics Denmark.

Study base

All Danish live-born twin pairs, a total of 24,718 infants born from January 1, 1994, to December 31, 2003, were retrieved from the Danish Twin Registry. Among them, 21,952 children had information on exposure, outcome, and covariables. A total of 3338 (15.2%) children with chronic disease were excluded from the analysis. A total of 18,614 infants were included from birth and followed prospectively for 5 years in a cohort study design.

Exposure and outcome

RSV hospitalization. RSV hospitalization was defined by a registration in the RSV database or in the DNPR with a RSV-specific diagnosis, and the date of admission was used in the analyses.

Asthma. Three different asthma outcomes were studied:

1. Asthma diagnosis in the DNPR—that is, the date of admission of the child's first asthma hospitalization ("asthma hospitalization").
2. Filling of at least 1 prescription of inhaled corticosteroids for the child (RMPS) and the date of the first prescription ("asthma medication").
3. Filling of 2 or more prescriptions of inhaled corticosteroids within a year for the child (RMPS) and the date of the first prescription ("asthma medication twice").

Statistics

To study the association between RSV hospitalization and asthma, the cohort was examined in 2 directions:

1. RSV hospitalization as exposure and asthma as outcome.
2. Asthma as exposure and RSV hospitalization as outcome.

Separate Cox proportional hazard models were used to investigate the risk factors for RSV and asthma using the SAS proc phreg procedure (Statistical Analysis System; SAS Institute Inc, Cary, NC). Age was used as the underlying time. Children were censored at time of their 5-year birthday, migration, death, or time of follow-up, whatever came first. To investigate the association between RSV and asthma, the risk of asthma was allowed to depend on whether the child had a previous RSV infection and the time since the RSV infection. A similar analysis was performed with asthma as the exposure and RSV as outcome. The models were adjusted for possible confounders and other factors that significantly improved the model fit. To adjust for the dependencies between twins, the covariance matrix was estimated with the robust sandwich estimator aggregated on twin pair. When studying the risk of asthma, the risk was allowed to depend on whether 1 twin had a recent asthma diagnosis and, if so, how long ago, and the same was done with RSV as outcome. This dependency was further allowed to depend on whether the twins were monozygotic or dizygotic. The risk of asthma was considered continuously dependent of the time since onset of RSV hospitalization, and vice versa. The risk curves presented were estimated by using the cubic-splines technique.

Confounders

To adjust the estimates of the associations between RSV hospitalization and asthma, confounders were included in the final multivariable model: sex, whether the cotwin had the outcome, type of birth (normal vs cesarean section), gestational age (immature birth <196 days, premature birth 196-259 days, and mature birth >259 days of gestation), birth weight (grouped in intervals of 500 g), siblings (0, 1, 2+ [the cotwin not inclusive]), maternal age at birth (<20, 20-25, 25-30, 30-35, 40-45, >45 years), maternal level of education (short, intermediate, long), maternal yearly income (0-100,000, 100,000-200,000, 200,000-300,000, 300,000-400,000, 400,000-500,000, >500,000 Danish Kroner), maternal smoking during pregnancy (yes/no/stopped during pregnancy), whether the parents were living together when the twin pair was born (yes/no), and seasonality defined as a Fourier function.²⁷

Furthermore, variables describing zygosity (monozygotic/dizygotic), maternal job, and paternal age were tested in the multivariable model but found not to change the estimates significantly.

Ethics

The study was registry-based. The ethical foundation was the World Medical Association Declaration of Helsinki (<http://www.wma.net/e/policy/b3.htm>). The Danish Data Protection Board (J. No.: 2005-41-51632005-41-5163 and J. No. 2005-2311-0121) and the Ethical Committee for Greater Copenhagen (KA-20060022) approved the study.

RESULTS

Among the included infants, 4.6% (848/18,614) had an RSV-associated hospitalization within their first 5 years of life. Of the

TABLE I. Occurrence of child cases of RSV hospitalization and asthma defined as asthma hospitalization or use of inhaled corticosteroids by sex, zygosity, and age in Danish twins born 1994 to 2004

	N	RSV hospitalization	Asthma hospitalization	Asthma medication*	Asthma medication* twice within 1 year
Total	18,614	848	1,014	2,307	1,273
Sex					
Boys	9,519	456	650	1,429	798
Girls	9,095	392	364	878	475
Zygosity					
Dizygotic	11,428	554	638	1,401	819
Monozygotic	1,705	101	131	221	130
Unknown	5,481	193	245	685	324
Age (y)					
0	—	693	406	717	448
1	—	134	361	852	515
2	—	10	120	367	196
3	—	9	71	215	114
4	—	2	56	156	—†

*Corticosteroids for inhalation.

†Follow-up was stopped at 5 years of age, and the second use of inhaled corticosteroid had to be within 1 year of the first.

infants, 5.9% (1014/18,614) were hospitalized with asthma, 13.2% (2307/18,614) used inhaled corticosteroids at least once, and in a subgroup of these, 7.3% (1273/18,608) used inhaled corticosteroids twice during any 1 year of their first 5 years of life. The occurrence in the cohort of RSV hospitalization and asthma by sex, zygosity, and age is presented in Table I.

RSV hospitalization and subsequent asthma

The adjusted relative risk of asthma hospitalization after RSV hospitalization was time-dependent (test of no time dependency, $P < .0001$), decreasing from a relative risk of 6.2 (95% CI, 4.1-9.4) the first 2 months after the RSV hospitalization, to 1.9 (1.2-3.2) from 3 to 5 months, and 2.2 (1.5-3.3) from 6 to 11 months after the RSV hospitalization (Fig 1). From 1 year after the RSV hospitalization, the risk of asthma hospitalization was no longer significantly increased. The risk of asthma after more than 1 RSV hospitalization did not significantly differ from the risk of asthma after 1 RSV hospitalization ($P = .54$). When asthma was defined as use of inhaled corticosteroids, the risk of asthma was increased and time-dependent (test of no time dependency, $P < .0001$): 7.5-fold (5.5-10.3) the first 2 months, 4.2 (3.1-5.6) from 3 to 5 months, 2.1 (1.6-2.9) from 6 to 11 months, 1.9 (1.4-2.6) from 1 to 2 years, and 1.7 (1.1-2.5) >2 years after the RSV hospitalization (Fig 2).

Likewise, the risk of asthma was time-dependent (test of no time dependency, $P < .0001$) and remained increased >2 years after the RSV hospitalization when asthma was defined as use of inhaled corticosteroids twice during 1 year (6.1 [3.9-9.4] the first 2 months, 4.1 [2.8-6.0] from 3 to 5 months, 1.9 [1.3-2.7] from 6 to 11 months, 2.2 [1.5-3.2] from 1 to 2 years, and 1.9 [1.1-3.3] >2 years after; Fig 3).

These estimated effects were primarily based on observations in infants below 1 year of age (Table I). The risk of asthma tended to be higher in infancy; however, the number of cases beyond the age of 1 year was limited, and there was no significant age dependency: if asthma was defined by asthma hospitalization, the test of no age dependency resulted in a P value of .161, and if asthma was defined by use of inhaled corticosteroids, the P value was .118.

Asthma and subsequent risk of RSV hospitalization

The adjusted relative risk of RSV hospitalization after asthma hospitalization was 3.0 (2.0 to 4.7) and did not depend on time since the child's first asthma episode (test of no time dependency, $P = .292$). Furthermore, the risk did not depend on the age of the children (test of no age effect, $P = 1.0$). The risk of RSV hospitalization depended on days of asthma hospitalizations. Children with 1 day of asthma hospitalization did not have an increased risk of subsequent RSV hospitalization (1.1 [0.26-4.5]). The increased risk was significant only among individuals with 2 or more days of hospitalization, with their adjusted relative risk of RSV hospitalization 4.7 (2.8-7.8), and the test of equal risk of RSV hospitalization compared with individuals with no asthma hospitalization yielded a P value of .002.

The risk of RSV hospitalization was essentially the same, 3.9 (2.9-5.5), not time-dependent ($P = .413$), and not dependent on age ($P = .544$) when asthma was defined as use of inhaled corticosteroids, and 4.3 (3.0-6.3), not time-dependent ($P = .483$) and not dependent on age ($P = .637$) when asthma was defined as use of inhaled corticosteroids twice during 1 year.

DISCUSSION

We examined the risk of asthma after RSV hospitalization and the risk of RSV hospitalization after asthma in a cohort of all Danish twins born alive between 1994 and 2004 and followed from birth to 5 years of age. We found an increased risk of asthma after RSV hospitalization, in agreement with previous studies.^{8-13,28} The risk of asthma depended on the time since the RSV hospitalization, with a 6-fold to 8-fold increase the first few months but only a slight increase after 1 year. Complementary to this, we found the risk of RSV hospitalization was increased 3-fold to 4-fold in twins with asthma, independent of the time since the debut of asthma. This is in accordance with recent studies showing that asthmatic disposition and early wheezing increased the risk of severe lower respiratory tract infections and RSV hospitalization,¹⁴⁻¹⁷ probably because of airway hyperresponsiveness.

Our study design is unique in that we examined the associations between RSV and asthma in both directions in the same

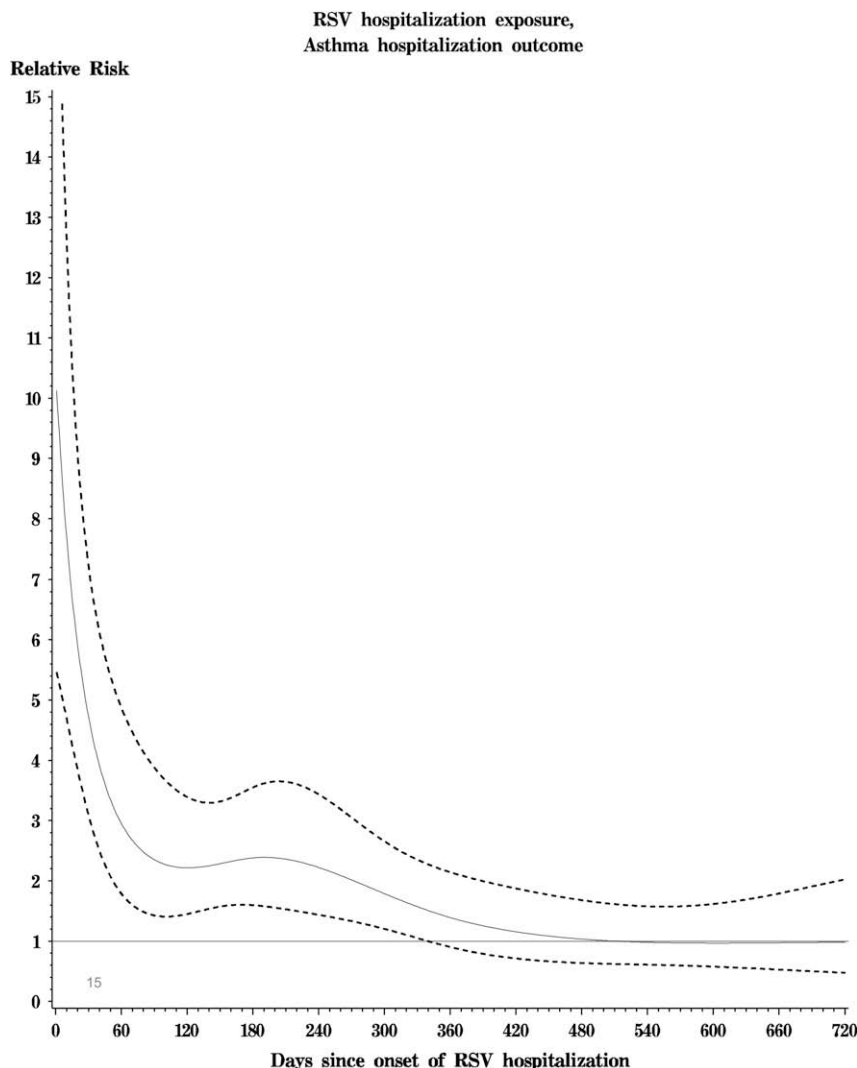


FIG 1. Adjusted risk of asthma defined as an asthma hospitalization by time since RSV hospitalization in Danish twins born 1994 to 2004. *Dotted lines* present the 95% CIs. Adjusted for age, sex, whether the cotwin had the outcome, type of birth, gestational age, birth weight, siblings, maternal age, maternal education, maternal yearly income, maternal smoking, whether the parents were living together when the twin pair was born, and seasonality.

population-based cohort of twins. Thus, we examined the risk of asthma after RSV hospitalization, and the risk of RSV hospitalization in children with an asthma diagnosis in the same cohort.

Because the symptomatology, the need for treatment, and the establishment of the asthma diagnosis in patients with asthma are highly observer-dependent,²⁹ we defined asthma in 2 different ways: (1) hospitalization-requiring asthma, or (2) use of inhaled corticosteroids. When asthma was defined as asthma hospitalization, the risk of asthma after RSV hospitalization was increased for 1 year. However, when asthma was defined by the use of asthma medication (inhaled corticosteroids ever, or twice within a year), the risk remained increased >2 years after the RSV hospitalization. This observation might be explained by asthma medication being a more sensitive measure of asthma. However, the increased risk of use of asthma medication might also be a result of confounding by indication—that is, increased alertness among parents and physicians concerning the twins

might lower and maintain the level for asthma medication, or the medication continues routinely.

Asthma is a poorly understood disease, probably covering many entities.³⁰ Although we used more than 1 asthma definition, probably many children did not have persistent asthma but transient early wheeze.³¹ However, the increased risk of RSV hospitalization after asthma hospitalization was present only in individuals with 2 or more days of asthma hospitalization. Hence, individuals who erroneously received an asthma diagnosis based on, for example, 1 day of hospitalization-requiring wheezing had no increased risk of RSV hospitalization. Furthermore, we observed a clear difference in the pattern of asthma after RSV hospitalization compared with the pattern of RSV hospitalization after asthma in this child population.

We speculate that the short-term increased risk in asthma hospitalization after hospitalization for severe RSV infection reflects viral induced bronchial hyperresponsiveness, whereas the long-term increased risk of hospitalization for severe RSV

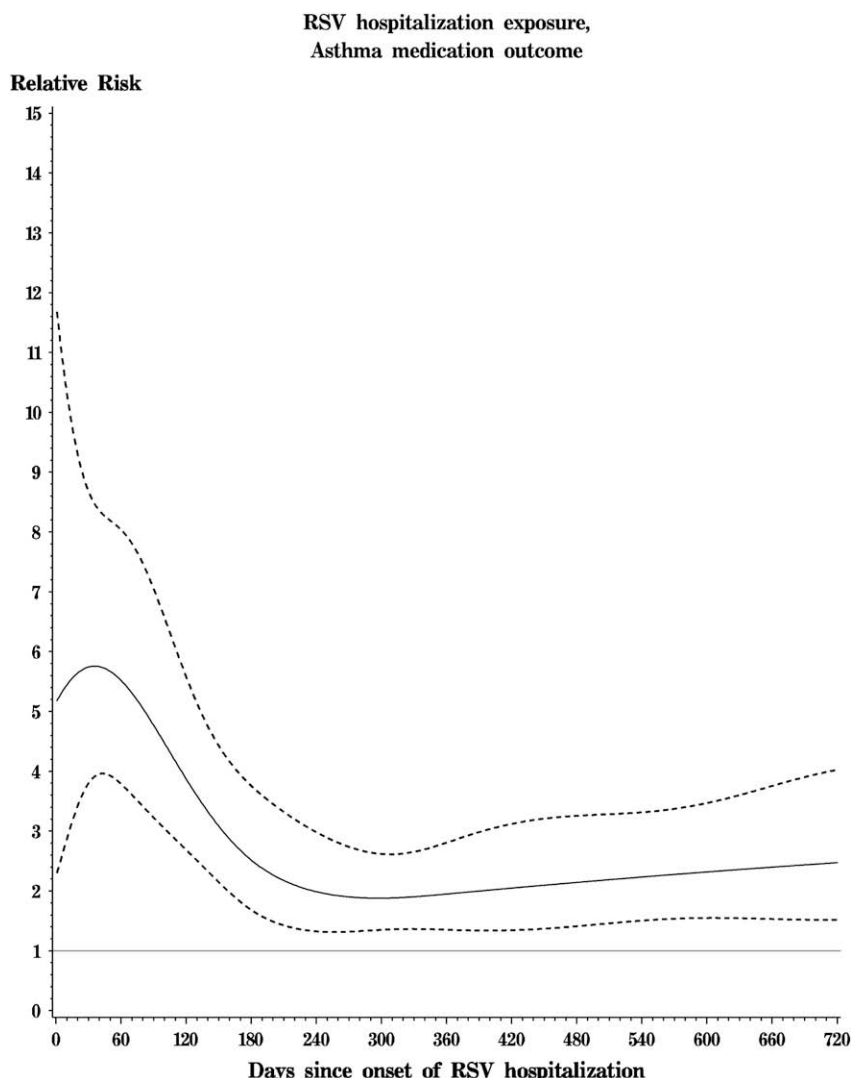


FIG 2. Adjusted risk of asthma defined as use of inhaled corticosteroids by time since RSV hospitalization in Danish twins born 1994 to 2004. *Dotted lines* present the 95% CIs. Adjusted for age, sex, whether the cotwin had the outcome, type of birth, gestational age, birth weight, siblings, maternal age, maternal education, maternal yearly income, maternal smoking, whether the parents were living together when the twin pair was born, and seasonality.

infection after asthma hospitalization reflects a host factor. Thus, the increased risk of hyperresponsive airways, asthma, and sensitization after RSV hospitalization found in earlier studies might be a combination of a predisposition in some of the children to atopy and asthma discovered at the time of the severe viral infection, and a transient increase in airway hyperresponsiveness among individuals without atopic disposition.²¹

The study was strengthened by the large sample size of twins. Although twins do not represent the general child population and the size of the effect cannot be generalized to singletons, the direction of the associations would probably be the same in other children.

In conclusion, among twins, the risk of asthma after RSV hospitalization was time-dependent, with a 6-fold to 8-fold increase for the first 2 months after the RSV hospitalization. One year after RSV hospitalization, there was no longer an

increased risk of asthma hospitalization, and after 2 years, there was only a minor increased risk of asthma medication use, suggesting short-term bronchial hyperresponsiveness induced by the viral infection. The risk of RSV hospitalization after asthma was 3-fold increased and did not depend on time since asthma or on the definition of asthma, suggesting a host factor. A common genetic constitution and/or environmental exposure may underlie the propensity to both disorders.

Key messages

- Respiratory syncytial virus hospitalization in early childhood is associated with short-term bronchial hyperresponsiveness.
- Childhood asthma is associated with a long-term 3-fold increased risk of severe RSV infection, reflecting a host factor.

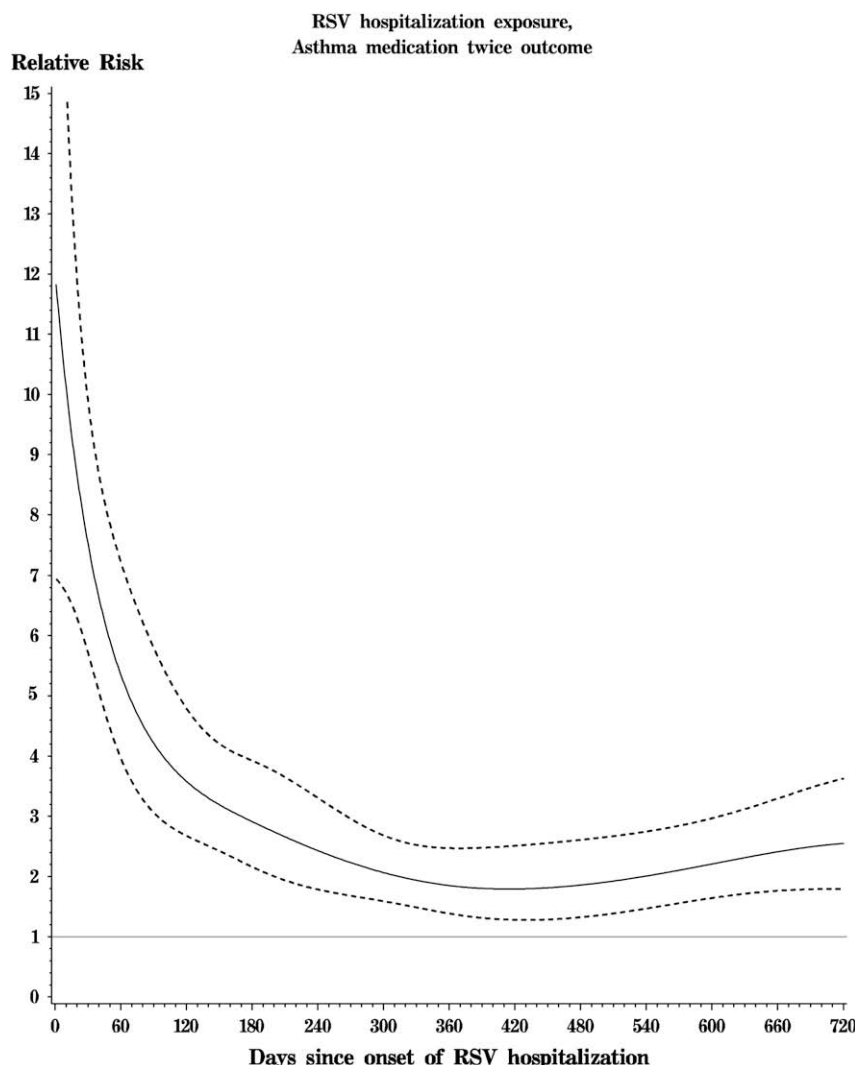


FIG 3. Adjusted risk of asthma defined as use of inhaled corticosteroids twice during 1 year by time since RSV hospitalization in Danish twins born 1994 to 2004. Dotted lines present the 95% CIs. Adjusted for age, sex, whether the cotwin had the outcome, type of birth, gestational age, birth weight, siblings, maternal age, maternal education, maternal yearly income, maternal smoking, whether the parents were living together when the twin pair was born, and seasonality.

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DIAGNOSES USED IN THE DEFINITION OF RSV HOSPITALIZATION

Four RSV-specific diagnosis codes: RSV pneumonia (diagnosis code J12.1), RSV bronchitis (J20.5), RSV bronchiolitis (J21.0), and other diseases caused by RSV (B97.4).

DIAGNOSES USED IN THE DEFINITION OF ASTHMA HOSPITALIZATION

Five diagnosis codes for asthma: allergic asthma (J45.0), nonallergic asthma (J45.1), unspecified asthma (J45.8, J45.9), and asthmatic status (J46.0) were used in the definitions of exposure and outcome.

DIAGNOSES USED IN THE DEFINITION OF INDIVIDUALS WITH CHRONIC DISEASE

The infants and children with chronic disease who were excluded from the analysis were defined by the following diseases and diagnosis codes:

Intrauterine growth retardation (P05.0, P05.1, P05.2, P05.9)
Cystic fibrosis (E84.0, E84.1, E84.8, E84.9)
Chronic lung disease (P27.0, P27.1, P27.8, P27)
Heart disease (Q20.0, Q20.1, Q20.2, Q20.3, Q20.4, Q20.5, Q20.6, Q20.8, Q20.9, Q21.0, Q21.1, Q21.2, Q21.3, Q21.4, Q21.8, Q21.9, Q22.0, Q22.1, Q22.2, Q22.3, Q22.4, Q22.5, Q22.6, Q22.8, Q22.9, Q23.0, Q23.1, Q23.2, Q23.4, Q23.8,

Q23.9, Q24.0, Q24.1, Q24.2, Q24.3, Q24.4, Q24.5, Q24.6, Q24.8, Q24.9, Q25.0, Q25.1, Q25.2, Q25.3, Q25.4, Q25.5, Q25.6, Q25.7, Q25.8, Q25.9, Q26.0, Q26.1, Q26.2, Q26.3, Q26.4, Q26.5, Q26.8, Q26.9, Q27.0, Q27.1, Q27.2, Q27.3, Q27.4, Q27.8, Q27.9, Q28.0, Q28.1, Q28.2, Q28.3, Q28.8, Q28.9, Q29.0, Q29.1, Q29.2, Q29.3, Q29.4, Q29.8, Q29.9)
Immune deficiency (D80.0, D80.1, D80.2, D80.3, D80.4, D80.5, D80.6, D80.7, D80.9, D81.0, D81.1, D81.2, D81.3, D81.4, D81.5, D81.6, D81.7, D81.8, D81.9, Q82.0, D82.1, D82.2, D82.3, D82.4, D82.8, D82.9, Q83.0, Q83.1, Q83.2, Q83.8, Q83.9, Q84.0, Q84.1, Q84.8, Q84.9, Q89.0, Q89.1, Q89.2, Q89.8, Q89.9)
Down syndrome (Q90.0, Q90.1, Q90.2, Q90.9)
Cerebral palsy (G80.0, G80.1, G80.2, G80.3, G80.4, G80.8, G80.9)
Neuromuscular disease (G10.9, G11.0, G11.1, G11.2, G11.8, G12.0, G12.1, G12.2, G12.8, G12.9, G13.0, G13.1, G13.2, G13.8)
Emphysema (J43.0, J43.1, J43.2, J43.8, J43.9)
Atelectasis (P28.0, P28.1, J98.1)
Alveolitis (J84.0, J84.1, J84.8, J84.9)
Congenital airway disease (Q31.0, Q31.1, Q31.2, Q31.3, Q31.4, Q31.8, Q31.9, Q32.0, Q32.1, Q32.2, Q32.3, Q32.4, Q33.0, Q33.1, Q33.2, Q33.3, Q33.4, Q33.5, Q33.6, Q33.8, Q33.9, Q34.0, Q34.1, Q34.8, Q34.9)
Other airway disease (J98.0, J98.1, J98.2, J98.3, J98.4, J98.5, J98.6, J98.8, J98.9, J81.9, J82.9, J84.0, J84.1, J84.8, J84.9)