

Palivizumab Prophylaxis in Preterm Infants and Subsequent Recurrent Wheezing Six-Year Follow-up Study

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Abstract

Rationale: Respiratory syncytial virus (RSV) induces not only infantile recurrent wheezing but also potentially atopic asthma.

Objectives: To test the effect of RSV infection on development of subsequent atopic asthma, we evaluated whether palivizumab, an anti-RSV monoclonal antibody, by preventing severe RSV disease in the first year of life, could impact subsequent recurrent wheezing and atopic asthma at 6 years of age.

Methods: During the 2007 to 2008 RSV season, the decision to administer palivizumab was made based on standard medical practice and an observational prospective multicenter (n = 52) case-control study in preterm infants with a gestational age between 33 and 35 weeks followed from 0 to 3 years (preceding Committee on Recurrent Wheezing study). The 52 investigators at hospitals then followed these subjects until 6 years of age, reported here (Effects of Preventive Treatment for Respiratory Syncytial [RS] Virus Infection During Infancy on Later Atopic Asthma in Preterm Infants; Scientific Committee for Elucidation of Infantile Asthma). Parents of study

subjects reported the infants' physicians' assessment of recurrent wheezing, using a report card and a novel mobile phone-based reporting system using the Internet. The primary endpoint was the incidence of atopic asthma.

Measurements and Main Results: Of 444 preterm infants enrolled, 349 received palivizumab during the first year of life. At 6 years, atopic asthma was not different in the groups: 15.3 and 18.2% of infants in the treated and untreated groups, respectively ($P = 0.57$). On the other hand, physician-diagnosed recurrent wheezing was observed in 15.3 and 31.6% in the treated and untreated groups, respectively ($P = 0.003$).

Conclusions: Palivizumab prophylaxis administered to preterm infants did not suppress the onset of atopic asthma but resulted in a significantly lower incidence of recurrent wheezing during the first 6 years.

Clinical trial registered with www.clinicaltrials.gov (NCT 01545245).

Keywords: asthma; respiratory infectious diseases; respiratory syncytial virus; monoclonal antibody; palivizumab

Respiratory syncytial virus (RSV)-related lower respiratory tract infection (LRI) in preterm infants has been associated with an increased prevalence of early childhood wheezing and asthma in later childhood (1–6). It has been proposed that RSV infection, by

influencing T-helper cell types 1/2 balance in early childhood, might induce an atopic state (7). In contrast, other studies suggest that the effect of RSV does not induce atopy but rather causes recurrent wheezing that might last up to 13 years

and is not associated with an atopic phenotype (4).

Palivizumab, a humanized anti-RSV monoclonal antibody that binds to the RSV fusion protein, neutralizes RSV and successfully inhibits viral replication (8).

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*A complete list of investigators in the Scientific Committee for Elucidation of Infantile Asthma (SCELIA) can be found before the References.

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At a Glance Commentary

Scientific Knowledge on the

Subject: An association between respiratory syncytial virus infection and subsequent asthma has been suggested by several studies but refuted by others.

Using passive prophylaxis that prevents severe respiratory syncytial virus disease in infancy, a few studies from Europe and North America have addressed this causal association. None have followed children for 6 years.

What This Study Adds to the

Field: In this prospective multicenter case-control study of 444 children, palivizumab prophylaxis was administered to preterm Japanese infants of 33- to 35-week gestational age in their first respiratory season. This did not reduce the incidence of atopic asthma but significantly reduced subsequent physician-diagnosed recurrent wheezing up to 6 years.

Monthly administration of palivizumab to preterm infants reduces the incidence of hospitalization due to RSV LRI (9) and recurrent wheezing, especially in nonatopic young children (10, 11).

We have previously reported the effectiveness of palivizumab prophylaxis in the first year of life on preventing recurrent wheezing in children aged 1–3 years (12). However, because the diagnosis of asthma is not entertained in this period, and the impact of palivizumab on the development of atopic asthma after RSV infection is still controversial, we followed the subjects of our previous trial, as reported here. Childhood wheezing has been classified into several phenotypes (infantile wheezing, nonatopic recurrent wheezing, and atopic wheezing) (4, 13–15), but the impact of RSV on the various wheezing phenotypes is mostly unsettled. Here, we use a controlled trial of palivizumab protection against RSV LRI to understand the impact of RSV on recurrent wheezing and asthma.

Methods

Study Design and Endpoints

The antecedent Committee on Recurrent Wheezing (CREW) study was a prospective, multicenter, observational cohort study to

compare the incidence of physician-diagnosed recurrent wheezing up to 3 years in preterm children of 33- to 35-week gestational age (wGA) who had and had not received palivizumab prophylaxis during their first RSV season (12). The primary endpoint of this 6-year follow-up study of the CREW study participants was the suppression of the onset of atopic asthma in palivizumab recipients. The secondary endpoints were as follows: the reduction in the rates of physician-diagnosed recurrent wheezing, the mean number of respiratory-related outpatient visits and hospitalizations, and growth of the children.

Follow-up of Children

The results of physician visits and monthly reports of illnesses followed procedures reported in the CREW study except that participants were followed up to 6 years of age (12). Briefly, all parents of enrolled children were advised to visit a hospital/clinic when their children showed cold-like symptoms. Physicians recorded the date of visit and presence or absence of wheeze, on a study card, with a Quick Response code. This was photographed by the parent/caregiver, with the mobile phone transmitting directly to the data center. Parents submitted monthly reports via a mobile phone-based automated answering system about the number of hospital/clinic visits and hospitalizations due to respiratory-related illness and diagnoses of allergic diseases. Allergic diseases were diagnosed by physicians and included atopic asthma, allergic rhinitis, allergic conjunctivitis, and food allergy. The parents were reached by telephone if they failed to submit the monthly mobile phone report. In addition, in the month of their sixth birthday, a history and growth parameters were noted and blood was obtained to measure serum total IgE level and specific IgE levels to *Dermatophagoides pteronyssinus*, using an *in vitro* diagnostic kit (Thermo Fisher Scientific Inc., Waltham, MA). Elevated total and specific IgE levels were greater than 30 IU/ml and greater than 0.35 IU/ml, respectively.

Respiratory Assessment

An episode of expiratory wheezing was defined as bronchial obstruction lasting for at least 24 hours preceded by at least a 1-week nonwheezing healthy period, as defined by a physician. Recurrent wheezing was defined as the occurrence of three or more episodes of expiratory wheezing

diagnosed by a physician in a 12-month period (10, 11). Children with a high serum total or specific IgE level were deemed atopic. Atopy and recurrent expiratory wheezing defined atopic asthma. We also examined these outcomes in those with and without a family history of allergy (11). Although these outcomes were prospectively defined in our study, subsequent to the end of our study, the Global Initiative for Asthma (GINA) consortium suggests a probabilistic approach to defining asthma in this age group (16). They suggest that several phenotypes, described in various studies (1, 2, 13, 14, 17–19), lack clinical utility in predicting the need for asthma treatment and are not stable over time. They suggest a broader definition that includes atopy or a family history of asthma and suggests these children are more likely to be given a diagnosis of asthma or respond to regular controller treatment than children with episodes two to three times a year. Hence, we did a secondary analysis on the basis of this definition and defined probable asthma as “recurrent wheezing with a high serum total or specific IgE level or a family history of allergy.”

Statistical Methods

Target sample sizes of 300 infants for the palivizumab-treated group and 150 infants for the untreated group for the CREW study were as described earlier (12). Student's *t* test or Wilcoxon sign-rank test were used to test for significance of differences in groups for quantitative variables and the chi-square test or Fisher's exact test for categorical variables. Possible confounders (gestational age, smokers in the home, and a family history of allergy), on the basis of their potential association with recurrent wheezing and significant background differences in groups, were used for adjusting background risks in a logistic regression model. For time-to-event analyses, a Kaplan-Meier test with the log-rank test and an adjusted Cox regression model were used. Differences between the groups in numbers of hospital/clinic visits and hospitalizations due to respiratory-related diseases were compared using an adjusted Poisson regression model.

Ethical Approval

The institutional review board at each center and the central institutional review board at Tokai University Hospital (No. 10R-133) approved the study, and written informed

consent was obtained from each infant's parent or legal guardian before enrollment.

Results

Participants and Follow-up

In 2007 to 2008, 349 infants who received at least three doses of palivizumab and 95 infants who did not receive palivizumab were enrolled in the CREW study (12). The number of the control infants was less than the target sample size because of more widespread use of palivizumab among preterm infants in Japan than expected. Of the 440 children enrolled in the study (intention-to-treat [ITT] population), 328 children (75%) completed the 6-year follow-up ending December 2013 (per-protocol [PP] population), 268 of whom were consented for the blood examination at 6 years of age (atopic asthma substudy population) (Figure 1).

Demographics and Baseline Characteristics

Although there were statistically significant differences between the groups in

gestational age ($P=0.008$), smokers in home ($P=0.011$), and family history of allergy ($P=0.005$) in the ITT population, there were no significant differences in the PP or atopy substudy populations (Table 1). In those who consented to have a blood examination at 6 years, the mean total IgE was 258.8 and 258.6 IU/ml in the palivizumab recipient and control groups, respectively ($P=0.997$), and the mean specific IgE was 21.7 and 16.3 IU/ml ($P=0.245$). Also, there was no difference in allergic diseases between the palivizumab recipient and control groups (40.1 and 44.3%, respectively; $P=0.997$).

Primary Outcome

The prevalence of atopic asthma was similar, 31 of 202 (15.3%) in the palivizumab-treated group and 12 of 66 (18.2%) in the untreated group (relative risk [RR], 0.82; 95% confidence interval [CI], 0.39–1.70; $P=0.57$; Table 2). There was no difference in this outcome in those with and without a family history of allergy. The univariate time-to-event analysis (Figure 2) and the multivariable logistic regression and Cox

regression analyses (Table 3) confirmed this finding. A sensitivity analysis using the revised GINA definition above of probable asthma in later life showed no difference either (34 of 205 [15%] vs. 16 of 66 [18.2%]; RR, 0.91; 95% CI, 0.50–1.66; $P=0.85$ for the treated and untreated groups, respectively).

Secondary Outcomes

Physician-diagnosed recurrent wheezing.

On the other hand, there were significant differences in rates of physician-diagnosed recurrent wheezing between two groups. On univariate analysis, there was a 2.64-fold relative reduction in the rate of recurrent wheezing in the palivizumab-treated group compared with the palivizumab-untreated group ($P<0.001$) in the ITT population. There was a 2.1-fold relative reduction in the PP population ($P<0.001$). Even in the smaller atopic population, there was a significant reduction in recurrent wheezing ($P=0.022$) (Table 2). These significant differences were confirmed in the time-to-event analyses for all three populations examined (Figure 2).

Multivariable logistic regression analysis and Cox regression analyses showed significant differences for physician-diagnosed recurrent wheezing in the ITT, PP, and atopic populations in both analyses (Table 3).

These differences were demonstrated only in the subgroups of children with a family history of allergy but not in those without. These results were consistent in univariate (Table 2) time-to-event (Figure 3) and multivariate analyses (Table 3) for all three populations (ITT, PP, and atopic subgroups).

Respiratory outpatient visits and hospitalizations. In the ITT analysis, children who received palivizumab prophylaxis in infancy had a significant reduction in outpatient respiratory visits (19.0 vs. 23.9 visits/person for the palivizumab recipients and the control infants, respectively; $P=0.018$, Wilcoxon test), whereas there was no difference in the number of hospitalizations due to respiratory disease (0.24 and 0.34 hospitalizations/person for the palivizumab recipients and the control infants, respectively; $P=0.46$). In the PP analysis, there were no differences in outpatient visits (21.8 and 28.1 visits/person for the palivizumab recipients and the control

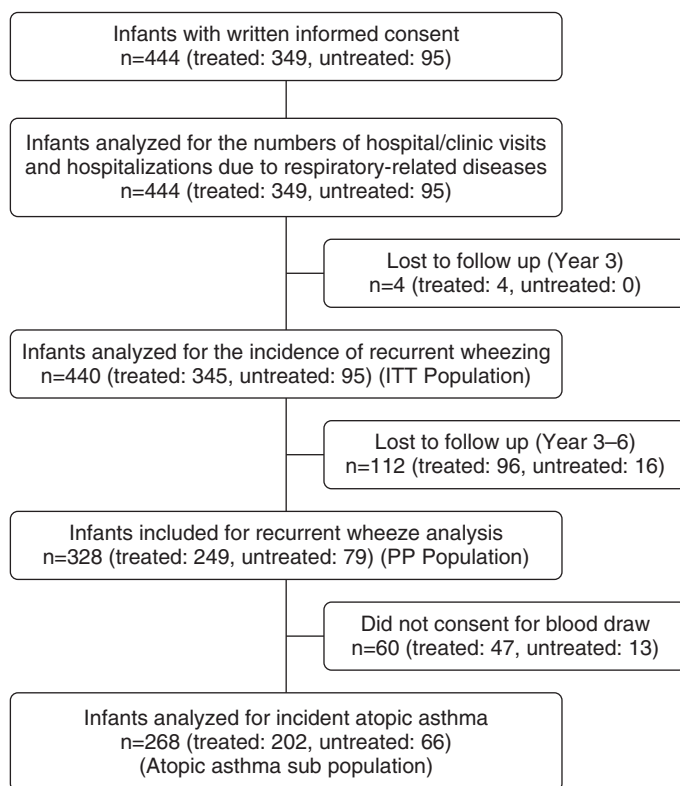


Figure 1. Flowchart of registration and outcome evaluation. Infants were enrolled from July 1 to December 31, 2007. ITT = intention-to-treat; PP = per protocol.

Table 1. Demographics of Study Populations

Demographic and Risk Factors	Recurrent Wheezing Population: ITT			Recurrent Wheezing Population: PP			Atopic Asthma Population		
	Treated (n = 345)	Untreated (n = 95)	P Value	Treated (n = 249)	Untreated (n = 79)	P Value	Treated (n = 202)	Untreated (n = 66)	P Value
Birth weight, kg, mean $\pm$ SD	2.11 $\pm$ 0.34	2.19 $\pm$ 0.32	0.058*	2.12 $\pm$ 0.34	2.18 $\pm$ 0.32	0.17	2.11 $\pm$ 0.32	2.19 $\pm$ 0.34	0.074*
Gestational age, wk, mean $\pm$ SD	34.2 $\pm$ 0.80	34.5 $\pm$ 0.65 [†]	0.008 [‡]	34.3 $\pm$ 0.8	34.4 $\pm$ 0.7	0.08	34.3 $\pm$ 0.78	34.5 $\pm$ 0.66	0.14 [†]
Female sex, %	42.1	49.5	0.20 [§]	50.6	41.3	0.15	42.4	50	0.32 [‡]
Birthday July through September, %	47	50.5	0.56 [§]	45.6	51.9	0.37	45.4	53	0.32 [‡]
No. of siblings, mean $\pm$ SD	0.9 $\pm$ 0.99	1.0 $\pm$ 0.97	0.40 [¶]	1.0 $\pm$ 1.0	0.9 $\pm$ 0.9	0.92	1.0 $\pm$ 1.04	0.8 $\pm$ 0.81	0.54
Subject in daycare, %	12.3	6.3	0.14 [§]	14.6	13.1	0.62	11.7	3	0.052 [‡]
Smokers in home, %	48.4	63.2**	0.011 [§]	48.4	58.2	0.16	49.3	57.6	0.26 [‡]
Pets in home, %	23.2	22.1	0.89 [§]	22.2	26.6	0.45	22	27.3	0.40 [‡]
Parental history of asthma, %	17.2	23.2	0.18 [§]	20.6	25.3	0.44	21	28.8	0.24 [‡]
Parental history of allergy, %	53	69.5 [†]	0.005 [§]	58.3	68.4	0.12	61	71.2	0.14 [‡]

Definition of abbreviations: ITT = intention-to-treat; PP = per protocol.

*Student's *t* test.

[†]*P* < 0.01 (significant differences between groups).

[‡] χ^2 test.

[§]Fisher's exact test.

^{||}Birthday of all patients in the study is between July and December.

[¶]Wilcoxon rank-sum test.

***P* < 0.05 (significant differences between groups).

infants, respectively; *P* = 0.10, Wilcoxon test) or in the number of respiratory hospitalizations (0.27 and 0.35 hospitalizations/person for the palivizumab recipients and the control infants, respectively; *P* = 0.76). In the atopic substudy population, there were no differences in outpatient visits, (25.5 and 23.7 visits/person for the palivizumab recipients and the control infants, respectively; *P* = 0.67,

Wilcoxon test) or in the number of respiratory hospitalizations (0.21 and 0.23 hospitalizations/person for the palivizumab recipients and the control infants, respectively; *P* = 0.217).

Growth. At age 6 years, there were no significant differences in weight (mean $\pm$ SD) (19.4 $\pm$ 3.46 kg vs. 19.5 $\pm$ 2.66 kg; *P* = 0.83), height (112.0 $\pm$ 4.40 cm vs. 112.7 $\pm$ 5.76 cm; *P* = 0.33), or body mass

index (15.4 $\pm$ 1.85 vs. 15.3 $\pm$ 1.26; *P* = 0.75) in palivizumab recipients compared with control subjects, respectively.

Discussion

RSV is a leading cause of serious LRI in infants and induces persistent airway damage and bronchial hyperresponsiveness (20).

Table 2. Univariate Comparison of Outcomes in the Study Populations

	Treated [n/N (%)]	Untreated [n/N (%)]	Comparison [RR (95% CI)]	P Value
Intention-to-treat population				
Recurrent wheezing, n = 440	44/345 (12.8)	27/95 (28.4)	0.45 (0.29–0.68)	<0.001
Recurrent wheezing: family history of allergy, n = 250	22/184 (12.0)	21/66 (31.6)	0.38 (0.22–0.64)	<0.001
Recurrent wheezing: no family history of allergy, n = 190	22/161 (13.7)	6/29 (20.7)	0.66 (0.29–1.49)	0.39
Per-protocol population				
Recurrent wheezing, n = 328	38/249 (15.3)	25/79 (31.6)	0.48 (0.31–0.75)	<0.001
Recurrent wheezing: family history of allergy, n = 200	21/146 (14.4)	19/54 (35.2)	0.41 (0.24–0.70)	0.002
Recurrent wheezing: no family history of allergy, n = 128	17/103 (16.5)	6/25 (24.0)	0.69 (0.30–1.56)	0.39
Atopic asthma population				
Recurrent wheezing, n = 268	34/202 (16.8)	20/66 (30.3)	0.47 (0.25–0.88)	0.022
Recurrent wheezing: family history of allergy, n = 171	19/124 (15.3)	18/47 (38.3)	0.40 (0.23–0.69)	0.002
Recurrent wheezing: no family history of allergy, n = 97	15/78 (19.2)	2/19 (10.5)	2.02 (0.42–9.72)	0.51
Atopic asthma, n = 268	31/202 (15.3)	12/66 (18.2)	0.82 (0.39–1.70)	0.57
Atopic asthma: family history of allergy, n = 171	20/124 (16.1)	10/47 (21.3)	0.71 (0.31–1.11)	0.51
Atopic asthma: no family history of allergy, n = 97	11/78 (14.1)	2/19 (10.5)	1.40 (0.28–6.90)	1

Definition of abbreviations: CI = confidence interval; RR = relative risk.

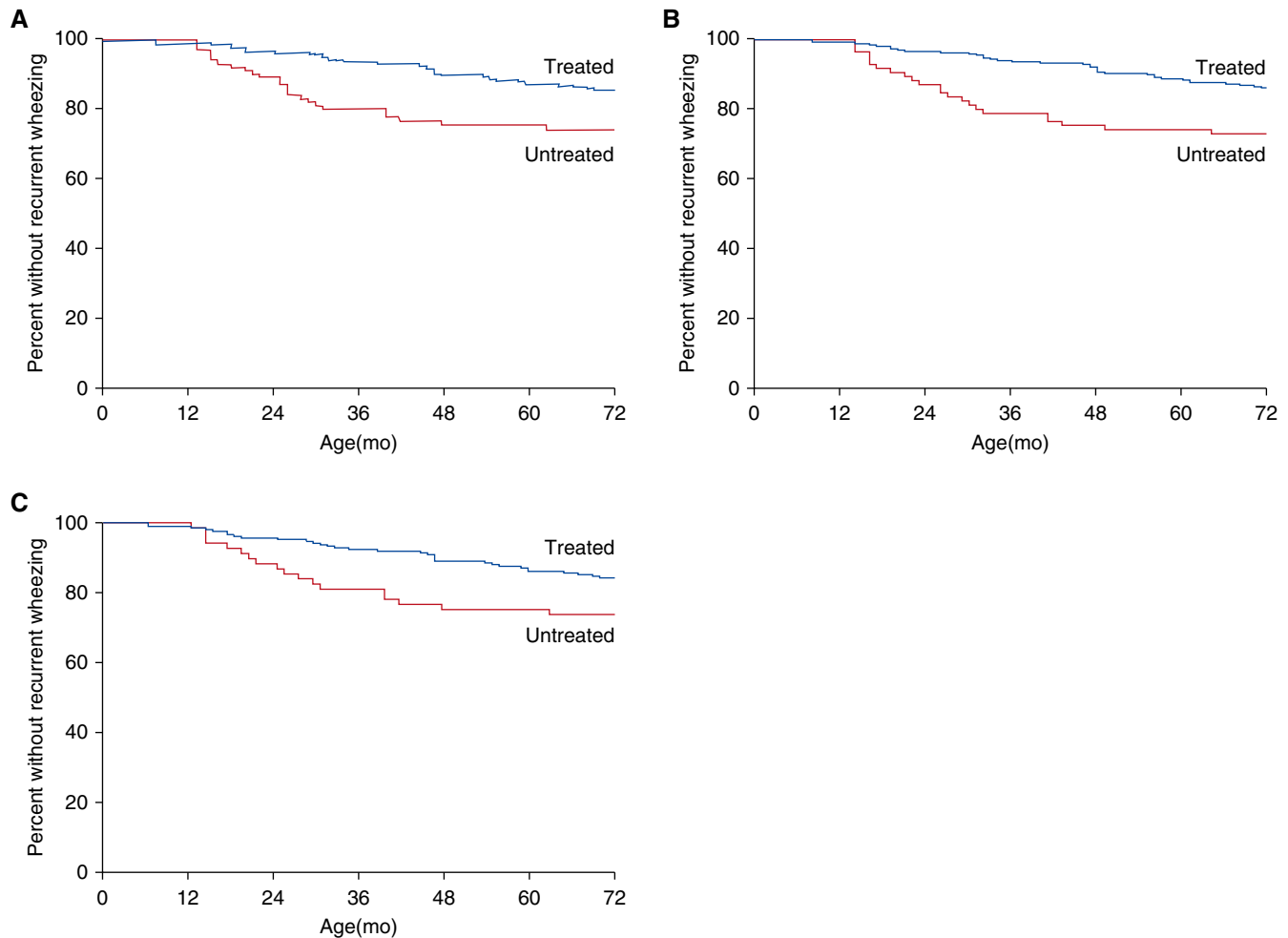


Figure 2. Kaplan-Meier plot of time to the onset of physician-diagnosed recurrent wheezing. Infants' age (in months) is indicated on the x-axis. The study infants were followed up until 6 years of age. (A) Intention-to-treat analysis: Percentage without recurrent wheezing shown for the treated group ($n = 345$) and the untreated group ($n = 95$). Analysis of the time to onset using a log-rank test showed a significant reduction of recurrent wheezing in the treated group ($P < 0.001$). (B) Per-protocol analysis: Percentage without recurrent wheezing shown for the treated group ($n = 249$) and the untreated group ($n = 79$). Analysis of the time to onset using a log-rank test showed a significant reduction of recurrent wheezing in the treated group ($P < 0.001$). (C) Atopic asthma population analysis: Percentage without recurrent wheezing shown for the treated group ($n = 202$) and the untreated group ($n = 66$). Analysis of the time to onset using a log-rank test showed a significant reduction of recurrent wheezing in the treated group ($P = 0.014$).

It has been suggested that RSV infection not only exacerbates asthma attacks but also is involved in the inception of asthma (13, 21). The observation that infantile RSV infection induces a predominantly Th2 response to airway allergens supports this suggestion (7, 22). However, the relationship between early RSV infection and allergic sensitization in the development of asthma at a later age is still hotly debated. Palivizumab, an anti-RSV fusion protein monoclonal antibody, is used to prevent serious RSV disease in preterm infants and those with congenital heart disease (23). Premature infants have airway prematurity,

which induces persistent bronchial hyperresponsiveness (24). A metaanalysis of the relationship between wheezing disorders and gestational age suggests that preterm birth, particularly very preterm birth, results in higher rates of wheezing than term infants (25). Compared with infants born at full term, early preterm infants have the highest odds of developing later asthma, but late preterm infants have the second highest odds (26). Using palivizumab as a probe to identify its protective effect against later respiratory outcomes in preterm infants, previous studies have demonstrated a significant relationship between preventing RSV

infection and preventing subsequent recurrent wheezing (10–12, 27). However, the precise diagnosis of asthma and other allergic diseases is difficult to establish in infants. Thus, we planned a continuous investigation of late preterm infants recruited in the previous CREW study (12), now followed up to 6 years of age to investigate the impact of preventing RSV LRI on the development of atopic asthma.

The results of our 6-year follow-up study, that atopic asthma was not significantly reduced in preterm palivizumab recipients, suggests the possibility that preventing RSV LRI has

Table 3. Multivariate Comparison of Outcomes in the Study Populations

	Adjusted OR (95%CI)	P Value	Adjusted HR (95% CI)	P Value
Intention-to-treat population				
Recurrent wheezing, n = 440	0.34 (0.19–0.60)	<0.001	0.38 (0.23–0.62)	<0.001
Recurrent wheezing: family history of allergy, n = 250	0.48 (0.26–0.90)	0.023	0.52 (0.31–0.87)	0.012
Recurrent wheezing: no family history of allergy, n = 190	0.55 (0.20–1.55)	0.26	0.59 (0.23–1.53)	0.28
Per-protocol population				
Recurrent wheezing, n = 328	0.36 (0.20–0.67)	0.001	0.38 (0.23–0.65)	<0.001
Recurrent wheezing: family history of allergy, n = 200	0.28 (0.13–0.60)	0.001	0.31 (0.16–0.60)	<0.001
Recurrent wheezing: no family history of allergy, n = 128	0.55 (0.18–1.63)	0.278	0.52 (0.20–1.37)	0.187
Atopic asthma population				
Recurrent wheezing, n = 268	2.35 (1.12–4.56)	0.012	0.46 (0.26–0.81)	0.007
Recurrent wheezing: family history of allergy, n = 171	0.54 (0.11–0.27)	0.001	0.30 (0.16–0.59)	<0.001
Recurrent wheezing: no family history of allergy, n = 97	3.99 (1.79–8.87)	0.45	1.81 (0.40–8.12)	0.44
Atopic asthma, n = 268	1.27 (0.60–2.70)	0.53	N/A	
Atopic asthma: family history of allergy, n = 171	0.68 (0.13–3.47)	0.24	N/A	
Atopic asthma: no family history of allergy, n = 97	1.71 (0.70–4.18)	0.64	N/A	

Definition of abbreviations: CI = confidence interval; HR = hazard ratio; N/A = not applicable: HR could not be calculated because the assessment was made only at 6 yr of age; OR = odds ratio.

Treatment effects adjusted for gestational age, smokers in the home, and a family history of allergy.

no impact on the development of an atopic state. Supporting this observation, we found no significant differences between the two groups in total serum IgE value, specific IgE antibody, and the onset of other allergy diseases.

Sigurs and colleagues reported that RSV bronchiolitis in infancy is an important risk factor for the later development of asthma and allergy (2), whereas Simões and colleagues (11) reported that RSV prevention by palivizumab prophylaxis in nonatopic children decreased the relative risk of recurrent wheezing. They suggested that RSV predisposes to recurrent wheezing in an atopy-independent manner. The results of our investigation further this hypothesis, because we found no impact on atopic asthma.

On the other hand, the secondary endpoints of physician-diagnosed recurrent wheezing in the ITT and PP analyses as well as in the atopy substudy were significantly reduced in the palivizumab recipient group. These results are consistent with that of our earlier CREW study (12) as well as the earlier European studies (10, 11, 27) and strongly suggest a reduction of recurrent wheezing by RSV prophylaxis that persists up to at least 6 years.

A recent placebo-controlled trial of motavizumab (an efficacious anti-RSV monoclonal antibody) in North American aboriginal peoples failed to demonstrate any impact on medically attended recurrent wheezing (28). However, this impact should

be interpreted with caution, because it was underpowered to show any impact on this outcome. Thus, the rate of medically attended recurrent wheeze in the motavizumab study (28) was approximately 20- to 30-fold lower than in the other palivizumab studies (10–12, 27).

Considering the phenotypes of childhood asthma, Stein and colleagues have suggested three types on the basis of a time trend classification (4): transient wheeze (ending before 3 yr), persistent wheeze (starting before 3 yr, persisting beyond 6 yr), and late-onset wheeze (starting after 3 yr). Persistent wheeze is induced by virus infection, and late-onset wheeze is classic atopic asthma. In our study, palivizumab suppressed about half of the recurrent wheezing seen: 12.8% in palivizumab-treated group versus 28.4% in the palivizumab-untreated group. The ratio of virus-related nonatopic wheeze/asthma and atopic wheeze/asthma might be close to 50:50, as in previous reports (10, 21, 29). The European Respiratory Society task force has proposed a symptom-based classification that defines episodic wheezing and multitrigger wheeze (30). Finally, the GINA consortium has proposed a probability-based approach to diagnosis of wheezing children, suggesting that in preschool children with symptoms for more than 10 days during viral infections; severe or frequent episodes; interval symptoms during play, laughing, or crying; and with atopy or a family history of asthma are much more likely to be given a

diagnosis of asthma later on (16). We chose to use this recommendation to explore our population. Whether we used our definition or the GINA approach, we did not find that preventing RSV prevented current or probable future atopic asthma.

Different from our earlier study of palivizumab prophylaxis on wheeze outcomes in Europe/Canada (11), the impact seen in our study was primarily in those with a family history of allergy/asthma. In contrast, in the European/Canadian study the impact was primarily in those without this family history. The rates of the family history of allergy/atopy in the European/Canadian study, 220 of 421 (52%), were not dissimilar to our study in Japan, 250 of 440 (57%). The European/Canadian study followed children up to 3 years of age, and ours followed them to 6 years. However, a review of the Kaplan-Meier curves in our study (Figures 2 and 3) shows that the differences in the atopic subgroup started before 3 years, suggesting a fundamental difference in the two study populations, related either to genetic makeup or the environment.

Maternal asthma confers a five- to sixfold higher risk for RSV hospitalization in Danish infants up to 18 months of age (31). Although this risk is not as carefully studied in Japan (32), other factors, including environmental, daycare, and other sociodemographic factors, might play a larger role in Japan on severe RSV disease, which might indirectly impact the role of

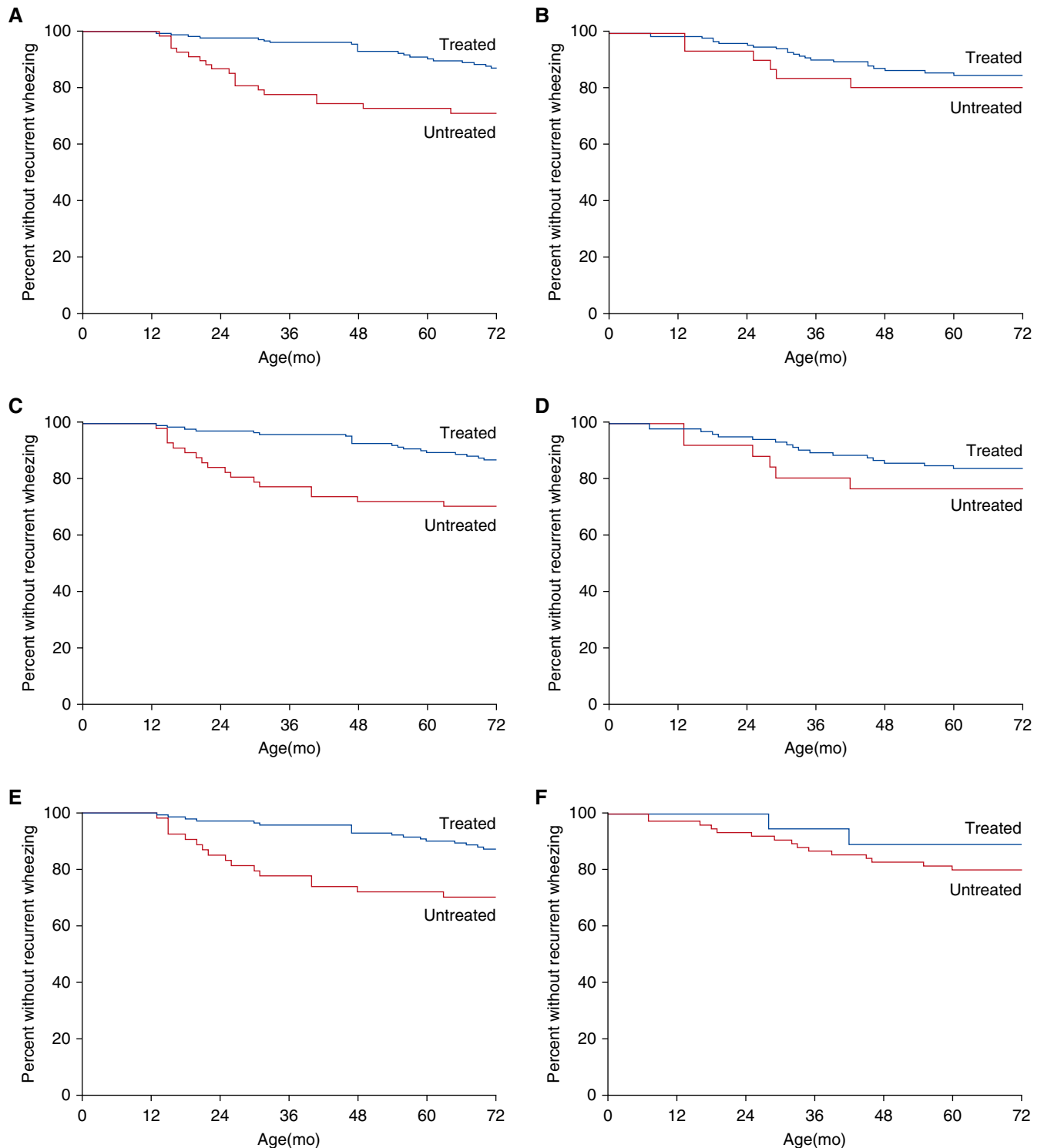


Figure 3. Kaplan-Meier plot of time to the onset of physician-diagnosed recurrent wheezing, by family history of allergy. Infants' age (in months) is indicated on the x-axis. The study infants were followed up until 6 years of age. (A) Intention-to-treat analysis (with a family history of allergy): Percentage without recurrent wheezing shown for the treated group ($n = 184$) and the untreated group ($n = 66$). Analysis of the time to onset using a log-rank test showed a significant reduction of recurrent wheezing in the treated group ($P < 0.001$). (B) Intention-to-treat analysis (without a family history of allergy): Percentage without recurrent wheezing shown for the treated group ($n = 161$) and the untreated group ($n = 29$). Analysis of the time to onset using a log-rank test showed no significant reduction of recurrent wheezing in the treated group ($P = 0.440$). (C) Per-protocol analysis (with a family history of allergy): Percentage without recurrent wheezing shown for the treated group ($n = 146$) and the untreated group ($n = 54$). Analysis of the time to onset using a log-rank test showed a significant reduction of recurrent wheezing in the treated group ($P < 0.001$). (D) Per-protocol analysis (without a family history of

RSV on subsequent recurrent wheezing. Currently ongoing studies in Holland (27) might throw some more light on this issue.

The limitations of our study include the potential biases due to the nonrandomized study design. The differences in demographics and baseline characteristics make interpretation of the results more complex. Although the differences in family history of asthma, birth weight, and gestational age were minimal, smokers in the home and family members with a history of allergy were significantly more frequent in the untreated group in the ITT population, but there were no differences in the PP population and the atopic substudy populations. Bias in the enrollment process was minimized, because notification of this study to investigators and parents of eligible infants was purposefully started after the end of the infant's first RSV season, so that the decision for prophylaxis was already made before enrollment (12). The medical expenses related to the use of palivizumab for this infant population are completely reimbursed in Japan, which minimizes bias due to access to palivizumab. In Japan, RSV prophylaxis in preterm infants between 33 and 35 wGA is generally accepted as a standard of care, as reflected in our cohort, and was the reason for substantially fewer than expected infants in the untreated group (33). Because an interventional study with a placebo control group was considered unethical, we used a prospective observational study design. Given the differences in palivizumab in the two groups studied, it is possible that usage patterns of erythromycin-like drugs and steroids, which could impact the recurrent wheezing phenotype, might have been different in the two study groups. We did not collect this information. However, given the government-subsidized free availability of these drugs, this usage is unlikely to have been different in the two groups.

We chose a limited definition of atopy on pragmatic grounds, which could potentially influence the interpretation of

our results. House dust mite allergy is strongly implicated in the pathogenesis of respiratory allergic diseases, a large proportion of patients with allergic rhinitis or allergic asthma being sensitized to *D. pteronyssinus* or *Dermatophagoides farinae* (34). Thus, a cohort of children with atopy to house dust mite had lower lung function than those who were unsensitized (35). In a recent study from Japan, levels of serum IgE to *D. pteronyssinus* were highly predictive of an immediate allergic response to bronchoprovocation (36). Several studies assessing the association between atopy, viruses, and subsequent asthma have used varying definitions for atopy. These range from single tests for IgE to *D. pteronyssinus* (37), to the inclusion of three measures of IgE sensitization (38), to those that include skin prick tests and very comprehensive measures, including up to 14 specific IgE tests (1, 4, 13, 35, 39–43). We could not do skin prick tests in a standardized manner at 52 pediatric offices; however, we do acknowledge that, although *D. pteronyssinus* might be the predominant aeroallergen, testing to a wider range of aeroallergens could have increased the number of children with an atopic diagnosis.

The strength of our study is the high follow-up rate, which was achieved with our original method with the convenient mobile phone answering and photo submission system (12). The most important advantages of this system include (1) parental follow-up reporting, especially mothers; (2) minimum physician involvement in reporting findings during clinic visits; and (3) conveniently efficient data transfer directly to the research center, which seemingly attracted and motivated mothers.

Palivizumab prophylaxis in preterm infants 33 to 35 wGA appears to have no impact on preventing subsequent atopic asthma but effectively prevents recurrent wheezing up to 6 years. This study suggests two independent phenotypes of recurrent wheezing in young children: RSV LRI-dependent recurrent wheeze and RSV

LRI-independent recurrent wheeze. Whether RSV impacts lung function in later life remains to be answered by this and other ongoing studies. ■

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Figure 3. (Continued). allergy): Percentage without recurrent wheezing shown for the treated group ($n = 103$) and the untreated group ($n = 25$). Analysis of the time to onset using a log-rank test showed no significant reduction of recurrent wheezing in the treated group ($P = 0.337$). (E) Atopic asthma population analysis (with a family history of allergy): Percentage without recurrent wheezing shown for the treated group ($n = 124$) and the untreated group ($n = 47$). Analysis of the time to onset using a log-rank test showed a significant reduction of recurrent wheezing in the treated group ($P < 0.001$). (F) Atopic asthma population analysis (without a family history of allergy): Percentage without recurrent wheezing shown for the treated group ($n = 80$) and the untreated group ($n = 19$). Analysis of the time to onset using a log-rank test showed no significant reduction of recurrent wheezing in the treated group ($P = 0.383$).

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References

1. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. *Am J Respir Crit Care Med* 2000;161:1501–1507.
2. Sigurs N, Aljassim F, Kjellman B, Robinson PD, Sigurbergsson F, Bjarnason R, Gustafsson PM. Asthma and allergy patterns over 18 years after severe RSV bronchiolitis in the first year of life. *Thorax* 2010;65:1045–1052.
3. Sigurs N, Gustafsson PM, Bjarnason R, Lundberg F, Schmidt S, Sigurbergsson F, Kjellman B. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *Am J Respir Crit Care Med* 2005;171:137–141.
4. Stein RT, Sherrill D, Morgan WJ, Holberg CJ, Halonen M, Taussig LM, Wright AL, Martinez FD. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999;354:541–545.
5. Bont L, Steijn M, van Aalderen WM, Kimpen JL. Impact of wheezing after respiratory syncytial virus infection on health-related quality of life. *Pediatr Infect Dis J* 2004;23:414–417.
6. Henderson J, Hilliard TN, Sherriff A, Stalker D, Al Shammari N, Thomas HM. Hospitalization for RSV bronchiolitis before 12 months of age and subsequent asthma, atopy and wheeze: a longitudinal birth cohort study. *Pediatr Allergy Immunol* 2005;16:386–392.
7. Román M, Calhoun WJ, Hinton KL, Avendaño LF, Simon V, Escobar AM, Gaggero A, Diaz PV. Respiratory syncytial virus infection in infants is associated with predominant Th-2-like response. *Am J Respir Crit Care Med* 1997;156:190–195.
8. Johnson S, Oliver C, Prince GA, Hemming VG, Pfarr DS, Wang SC, Dormitzer M, O'Grady J, Koenig S, Tamura JK, et al. Development of a humanized monoclonal antibody (MEDI-493) with potent in vitro and in vivo activity against respiratory syncytial virus. *J Infect Dis* 1997;176:1215–1224.
9. Impact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics* 1998;102:531–537.
10. Simões EA, Groothuis JR, Carbonell-Estrany X, Rieger CH, Mitchell I, Fredrick LM, Kimpen JL. Palivizumab prophylaxis, respiratory syncytial virus, and subsequent recurrent wheezing. *J Pediatr* 2007;151:34–42, 42.e1.
11. Simões EA, Carbonell-Estrany X, Rieger CH, Mitchell I, Fredrick L, Groothuis JR; Palivizumab Long-Term Respiratory Outcomes Study Group. The effect of respiratory syncytial virus on subsequent recurrent wheezing in atopic and nonatopic children. *J Allergy Clin Immunol* 2010;126:256–262.
12. Yoshihara S, Kusuda S, Mochizuki H, Okada K, Nishima S, Simões EA; C-CREW Investigators. Effect of palivizumab prophylaxis on subsequent recurrent wheezing in preterm infants. *Pediatrics* 2013;132:811–818.
13. Henderson J, Granell R, Heron J, Sherriff A, Simpson A, Woodcock A, Strachan DP, Shaheen SO, Sterne JA. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax* 2008;63:974–980.
14. Savenije OE, Granell R, Caudri D, Koppelman GH, Smit HA, Wijga A, de Jongste JC, Brunekreef B, Sterne JA, Postma DS, et al. Comparison of childhood wheezing phenotypes in 2 birth cohorts: ALSPAC and PIAMA. *J Allergy Clin Immunol* 2011;127:1505–1512.e14.
15. Savenije OE, Mahachie John JM, Granell R, Kerkhof M, Dijk FN, de Jongste JC, Smit HA, Brunekreef B, Postma DS, Van Steen K, et al. Association of IL33-IL-1 receptor-like 1 (IL1RL1) pathway polymorphisms with wheezing phenotypes and asthma in childhood. *J Allergy Clin Immunol* 2014;134:170–177.
16. Reddel HK, Bateman ED, Becker A, Boulet LP, Cruz AA, Drazen JM, Haahtela T, Hurd SS, Inoue H, de Jongste JC, et al. A summary of the new GINA strategy: a roadmap to asthma control. *Eur Respir J* 2015;46:622–639.
17. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ; The Group Health Medical Associates. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995;332:133–138.
18. Spycher BD, Silverman M, Brooke AM, Minder CE, Kuehni CE. Distinguishing phenotypes of childhood wheeze and cough using latent class analysis. *Eur Respir J* 2008;31:974–981.
19. Schultz A, Devadason SG, Savenije OE, Sly PD, Le Souëf PN, Brand PL. The transient value of classifying preschool wheeze into episodic viral wheeze and multiple trigger wheeze. *Acta Paediatr* 2010;99:56–60.
20. Jafri HS, Chavez-Bueno S, Mejias A, Gomez AM, Rios AM, Nassi SS, Yusuf M, Kapur P, Hardy RD, Hatfield J, et al. Respiratory syncytial virus induces pneumonia, cytokine response, airway obstruction, and chronic inflammatory infiltrates associated with long-term airway hyperresponsiveness in mice. *J Infect Dis* 2004;189:1856–1865.
21. Lemanske RF Jr. The childhood origins of asthma (COAST) study. *Pediatr Allergy Immunol* 2002;13:38–43.
22. Caballero MT, Serra ME, Acosta PL, Marzec J, Gibbons L, Salim M, Rodriguez A, Reynaldi A, Garcia A, Bado D, et al. TLR4 genotype and environmental LPS mediate RSV bronchiolitis through Th2 polarization. *J Clin Invest* 2015;125:571–582.
23. Hall CB, Simões EA, Anderson LJ. Clinical and epidemiologic features of respiratory syncytial virus. *Curr Top Microbiol Immunol* 2013;372:39–57.
24. Bertrand JM, Riley SP, Popkin J, Coates AL. The long-term pulmonary sequelae of prematurity: the role of familial airway hyperreactivity and the respiratory distress syndrome. *N Engl J Med* 1985;312:742–745.
25. Been JV, Lugtenberg MJ, Smets E, van Schayck CP, Kramer BW, Mommers M, Sheikh A. Preterm birth and childhood wheezing disorders: a systematic review and meta-analysis. *PLoS Med* 2014;11:e1001596.
26. He H, Butz A, Keet CA, Minkovitz CS, Hong X, Caruso DM, Pearson C, Cohen RT, Wills-Karp M, Zuckerman BS, et al. Preterm birth with childhood asthma: the role of degree of prematurity and asthma definitions. *Am J Respir Crit Care Med* 2015;192:520–523.
27. Blanken MO, Rovers MM, Molenaar JM, Winkler-Seinstra PL, Meijer A, Kimpen JL, Bont L; Dutch RSV Neonatal Network. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. *N Engl J Med* 2013;368:1791–1799.
28. O'Brien KL, Chandran A, Weatherholtz R, Jafri HS, Griffin MP, Bellamy T, Millar EV, Jensen KM, Harris BS, Reid R, et al.; Respiratory Syncytial Virus (RSV) Prevention study group. Efficacy of motavizumab for the prevention of respiratory syncytial virus disease in healthy Native American infants: a phase 3 randomised double-blind placebo-controlled trial. *Lancet Infect Dis* 2015;15:1398–1408.
29. Pullan CR, Hey EN. Wheezing, asthma, and pulmonary dysfunction 10 years after infection with respiratory syncytial virus in infancy. *Br Med J (Clin Res Ed)* 1982;284:1665–1669.
30. Brand PL, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A, de Blic J, de Jongste JC, Eber E, Everard ML, et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Respir J* 2008;32:1096–1110.

31. Stensballe LG, Ravn H, Kristensen K, Agerskov K, Meakins T, Aaby P, Simões EA. Respiratory syncytial virus neutralizing antibodies in cord blood, respiratory syncytial virus hospitalization, and recurrent wheeze. *J Allergy Clin Immunol* 2009;123:398–403.
32. Kaneko M, Watanabe J, Ueno E, Hida M, Sone T. Risk factors for severe respiratory syncytial virus-associated lower respiratory tract infection in children. *Pediatr Int* 2001;43:489–492.
33. Çalışkan M, Bochkov YA, Kreiner-Møller E, Bønnelykke K, Stein MM, Du G, Bisgaard H, Jackson DJ, Gern JE, Lemanske RF Jr, et al. Rhinovirus wheezing illness and genetic risk of childhood-onset asthma. *N Engl J Med* 2013;368:1398–1407.
34. Calderón MA, Linneberg A, Kleine-Tebbe J, De Blay F, Hernandez Fernandez de Rojas D, Virchow JC, Demoly P. Respiratory allergy caused by house dust mites: what do we really know? *J Allergy Clin Immunol* 2015;136:38–48.
35. Ulrik CS, Backer V. Markers of impaired growth of pulmonary function in children and adolescents. *Am J Respir Crit Care Med* 1999;160:40–44.
36. Minami T, Fukutomi Y, Lidholm J, Yasueda H, Saito A, Sekiya K, Tsuburai T, Maeda Y, Mori A, Taniguchi M, et al. IgE Abs to Der p 1 and Der p 2 as diagnostic markers of house dust mite allergy as defined by a bronchoprovocation test. *Allergol Int* 2015;64:90–95.
37. Tovey ER, Almqvist C, Li Q, Crisafulli D, Marks GB. Nonlinear relationship of mite allergen exposure to mite sensitization and asthma in a birth cohort. *J Allergy Clin Immunol* 2008;122:114–118, 118.e1–5.
38. Celedón JC, Milton DK, Ramsey CD, Litonjua AA, Ryan L, Platts-Mills TA, Gold DR. Exposure to dust mite allergen and endotoxin in early life and asthma and atopy in childhood. *J Allergy Clin Immunol* 2007;120:144–149.
39. Rhodes HL, Thomas P, Sporik R, Holgate ST, Cogswell JJ. A birth cohort study of subjects at risk of atopy: twenty-two-year follow-up of wheeze and atopic status. *Am J Respir Crit Care Med* 2002;165:176–180.
40. Oddy WH, de Klerk NH, Sly PD, Holt PG. The effects of respiratory infections, atopy, and breastfeeding on childhood asthma. *Eur Respir J* 2002;19:899–905.
41. Illi S, von Mutius E, Lau S, Niggemann B, Grüber C, Wahn U; Multicentre Allergy Study (MAS) group. Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study. *Lancet* 2006;368:763–770.
42. Kusel MM, de Klerk NH, Kebabdz T, Vohma V, Holt PG, Johnston SL, Sly PD. Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma. *J Allergy Clin Immunol* 2007;119:1105–1110.
43. Sly PD, Boner AL, Björkstén B, Bush A, Custovic A, Eigenmann PA, Gern JE, Gerritsen J, Hamelmann E, Helms PJ, et al. Early identification of atopy in the prediction of persistent asthma in children. *Lancet* 2008;372:1100–1106.

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