

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Principal investigators at the 17 participating sites in MARC-35

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eTable 2. Characteristics and clinical presentation of 716 infants hospitalized for bronchiolitis by recurrent wheeze by age 3 years

	No recurrent wheeze	Recurrent wheeze	P-value
Variables	n=485	n=231	
Characteristics			
Age (mo), median, (IQR)	2.7 (1.4-5.0)	3.6 (2.1-5.9)	<0.01
Male sex	290 (60)	140 (61)	0.90
Race/ethnicity			0.54
Non-Hispanic white	214 (44)	107 (46)	
Non-Hispanic black	106 (22)	57 (25)	
Hispanic	144 (30)	60 (26)	
Other	21 (4)	7 (3)	
Parental history of asthma	149 (31)	88 (38)	0.12
Parental history of eczema	67 (14)	64 (28)	<0.01
Maternal smoking during pregnancy	61 (13)	37 (16)	0.24
Mode of birth (c-section)	170 (35)	81 (35)	0.59
Prematurity (32-37 weeks)	96 (20)	42 (18)	0.68
History of eczema	59 (12)	40 (17)	0.08
Previous breathing problems before index hospitalization	60 (12.4)	62 (26.8)	<0.01
Ever attended daycare	93 (19)	58 (25)	0.09
Household sibling	383 (79)	184 (80)	0.91
Breastfed	210 (43)	110 (48)	0.05
Smoke exposure at home	77 (16)	29 (13)	0.29
Presentation and course at hospitalization for bronchiolitis			
Weight at presentation (kg), median (IQR)	5.6 (4.5-7.3)	6.4 (5.0-7.8)	<0.01
Oxygen saturation at presentation			0.85
<90%	45 (9)	21 (9)	
90%-93%	72 (15)	32 (14)	
≥94%	354 (73)	173 (75)	
Received corticosteroids during pre-hospitalization visit	28 (6)	30 (13)	<0.01
Laboratory testing			
Virology ^a			0.14
RSV-only	378 (89)	163 (71)	
Rhinovirus-A	54 (11)	31 (13)	
Rhinovirus-B	8 (2)	4 (2)	
Rhinovirus-C	45 (9)	33 (14)	
Rhinovirus cycle threshold value ^b	31 (27-35)	28 (25-31)	<0.01

Nasopharyngeal CCL5 (pg/ml), median (IQR)	37 (15-88)	42 (22-115)	0.11
	No recurrent wheeze	Recurrent wheeze	P-value
Variables	n=485	n=231	
Blood eosinophilia ($\geq 4\%$)	48 (10)	20 (9)	0.25
Serum total 25OHD (ng/ml), median (IQR)	46 (34-58)	46 (33-64)	0.40
Serum LL-37 (ng/ml), median (IQR)	26 (17-32)	27 (18-35)	0.07
sIgE sensitization ^c	94 (19)	44 (19)	0.99
Food sensitization	87 (18)	41 (18)	0.99
Aeroallergen sensitization	9 (2)	4 (2)	0.99
Clinical course			
Intensive care use ^d	67 (14)	40 (17)	0.26
Use of mechanical ventilation	21 (4)	14 (6)	0.41
Hospital length-of-stay (day), median (IQR)	2 (1-3)]	2 (1-3)	0.13
Data are no. (%) of children unless otherwise indicated. Percentages may not equal 100, because of rounding and missingness			
Abbreviations: IQR, interquartile range; RSV, respiratory syncytial virus; sIgE, specific immunoglobulin E; 25OHD, 25-hydroxyvitamin D			
^a Excluded 5 infants with multiple rhinovirus species			
^b There was no significant difference in the rhinovirus cycle threshold (Ct) values between rhinovirus-C with and without IgE sensitization (median Ct value, 27 vs. 29; P=0.14)			
^c Defined by having one or more positive values for serum allergen-specific IgE at the index hospitalization			
^d Defined as admission to intensive care unit and/or use of mechanical ventilation (continuous positive airway pressure and/or intubation during inpatient stay, regardless of location) at any time during the index hospitalization			

eTable 3. Associations of respiratory viruses with risks of developing recurrent wheeze, excluding infants with coinfection, according to IgE sensitization at the enrollment

Virus group and IgE sensitization status	Unadjusted model ^a	Adjusted model ^a
	HR (95%CI)	HR (95%CI)
Overall	(n=613)	(n=613)
RSV-only	reference	reference ^b
Rhinovirus-A	2.02 (1.22-3.34)	1.86 (1.11-3.11)
Rhinovirus-B	n/c	n/c
Rhinovirus-C	3.90 (2.53-6.02)	3.76 (2.40-5.90)
IgE sensitization	(n=122)	(n=122)
RSV-only	reference	reference ^c
Rhinovirus-A	2.50 (0.85-7.35)	2.45 (0.75-8.02)
Rhinovirus-B	n/c	n/c
Rhinovirus-C	4.76 (1.88-12.1)	4.63 (1.61-13.3)
No IgE sensitization	(n=491)	(n=491)
RSV-only	reference	reference ^c
Rhinovirus-A	1.84 (1.04-3.25)	1.77 (0.99-3.14)
Rhinovirus-B	n/c	n/c
Rhinovirus-C	3.56 (2.17-5.84)	3.37 (2.04-5.56)
Abbreviations: CI, confidence interval; HR, hazard ratio; RSV, respiratory syncytial virus.		
n/c: Not computed given that there were no outcomes in this virus group (n=2).		
^a Cox proportional hazards model accounting for patient clustering within the sites as random-effects.		
^b Adjusted for patient-level confounders, including age, sex, race/ethnicity, parental history of asthma, household sibling, use of mechanical ventilation during the index hospitalization, and IgE sensitization (aeroallergen and/or food) at the enrollment.		
^c Because of the limited sample size, the model adjusted only for age and sex, and accounted for patient clustering within the sites as random-effects.		

eTable 4. Associations of respiratory viruses (RSV-only infection versus RSV/rhinovirus coinfection) with risks of developing recurrent wheeze, according to IgE sensitization at the enrollment

Virus group and IgE sensitization status	Unadjusted model ^a		Adjusted model ^a	
	HR (95%CI)		HR (95%CI)	
Overall	(n=642)		(n=642)	
RSV-only	reference		reference ^b	
RSV/rhinovirus-A	1.00 (0.58-1.74)		1.07 (0.54-1.62)	
RSV/rhinovirus-B	0.51 (0.73-5.37)		0.55 (0.67-4.98)	
RSV/rhinovirus-C	1.47 (0.35-1.33)		1.63 (0.31-1.21)	
IgE sensitization	(n=121)		(n=121)	
RSV-only	reference		reference ^c	
RSV/rhinovirus-A	1.69 (0.08-4.44)		1.62 (0.08-4.64)	
RSV/rhinovirus-B	n/c		n/c	
RSV/rhinovirus-C	0.96 (0.25-4.44)		1.39 (0.68-2.82)	
No IgE sensitization	(n=521)		(n=521)	
RSV-only	reference		reference ^c	
RSV/rhinovirus-A	0.95 (0.60-1.87)		0.99 (0.57-1.80)	
RSV/rhinovirus-B	n/c		n/c	
RSV/rhinovirus-C	1.63 (0.29-1.32)		1.14 (0.53-1.21)	

Abbreviations: CI, confidence interval; HR, hazard ratio; RSV, respiratory syncytial virus.
n/c: Not computed given the limited sample size of this virus group.

^a Cox proportional hazards model accounting for patient clustering within the sites as random-effects.

^b Adjusted for patient-level confounders, including age, sex, race/ethnicity, parental history of asthma, household sibling, use of mechanical ventilation during the index hospitalization, and IgE sensitization (aeroallergen and/or food) at the enrollment.

^c Because of the limited sample size, the model adjusted only for age and sex, and accounted for patient clustering within the sites as random-effects.

eTable 5. Associations of respiratory viruses with risks of developing recurrent wheeze, with or without asthma at age 4 years, according to IgE sensitization status at the enrollment; analysis excludes 44 children without recurrent wheeze but with asthma

Virus group and IgE sensitization status	Recurrent wheeze with subsequent development of asthma ^a				Recurrent wheeze without subsequent development of asthma ^b			
	Unadjusted model		Adjusted model		Unadjusted model		Adjusted model	
	HR (95%CI)		HR (95%CI)		HR (95%CI)		HR (95%CI)	
Overall	(n=505)		(n=505)		(n=519)		(n=519)	
RSV-only	reference		reference ^c		reference		reference ^c	
Rhinovirus-A	1.63 (0.93-2.85)		1.35 (0.76-2.40)		1.27 (0.73-2.20)		1.18 (0.68-2.06)	
Rhinovirus-B	2.53 (0.79-8.13)		2.21 (0.68-7.17)		0.60 (0.08-4.32)		0.57 (0.08-4.12)	
Rhinovirus-C	2.42 (1.44-4.08)		2.20 (1.29-3.75)		1.48 (0.85-2.56)		1.40 (0.80-2.43)	
IgE sensitization	(n=99)		(n=99)		(n=94)		(n=94)	
RSV-only	reference		reference ^d		reference		reference ^d	
Rhinovirus-A	2.60 (0.86-7.84)		1.12 (0.30-4.23)		1.03 (0.13-8.48)		1.09 (0.12-10.4)	
Rhinovirus-B	4.54 (0.60-34.6)		3.21 (0.32-31.8)		n/c		n/c	
Rhinovirus-C	3.28 (1.08-9.94)		4.00 (1.22-13.1)		2.62 (0.82-8.35)		2.61 (0.64-10.6)	
No IgE sensitization	(n=406)		(n=406)		(n=425)		(n=425)	
RSV-only	reference		reference ^d		reference		reference ^d	
Rhinovirus-A	1.44 (0.75-2.76)		1.32 (0.68-2.55)		1.30 (0.74-2.31)		1.21 (0.68-2.16)	
Rhinovirus-B	2.05 (0.50-8.49)		1.75 (0.42-7.28)		0.68 (0.09-4.88)		0.67 (0.09-4.81)	
Rhinovirus-C	2.27 (1.25-4.09)		2.00 (1.10-3.65)		1.26 (0.67-2.38)		1.21 (0.64-2.29)	
Abbreviations: CI, confidence interval; HR, hazard ratio; RSV, respiratory syncytial virus.								
n/c: Not computed given that there were no outcomes in this virus group.								
^a The outcome is recurrent wheeze by age 3 years with epidemiological definition of asthma at age 4 years (n=105); analysis excludes children who developed recurrent wheeze without subsequent development of asthma.								
^b The outcome is recurrent wheeze by age 3 years without epidemiological definition of asthma at age 4 years (n=119); analysis excludes children who developed recurrent wheeze with subsequent development of asthma.								
^c Adjusted for patient-level confounders, including age, sex, race/ethnicity, parental history of asthma, household sibling, use of mechanical ventilation during the index hospitalization, and IgE sensitization [aeroallergen and/or food] at the enrollment, and accounted for patient clustering within the sites as random-effects.								
^d Adjusted for patient-level confounders, including age, sex, race/ethnicity, parental history of asthma, household sibling, and use of mechanical ventilation during the index hospitalization, and accounted for patient clustering within the sites as random-effects.								