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Supplementary appendix

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Respiratory Syncytial Virus Infection during Infancy and Asthma during Childhood in the

USA (INSPIRE): A Population-Based, Prospective Birth Cohort Study

Supplementary Appendix

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Supplementary Methods

Overview of the Study Hypothesis, Population, and Design

The Infant Susceptibility to Pulmonary Infections and Asthma Following Respiratory Syncytial Virus Exposure study (INSPIRE) is a population-based birth cohort specifically designed to test the main hypothesis that not being infected with respiratory syncytial virus (RSV) during infancy decreases the risk of childhood asthma (**Figure 1**). Eligible infants were enrolled between birth and age 4 months and recruited from 11 participating pediatric practices across middle Tennessee in the USA. The full eligibility criteria are shown in **Table S1**. In brief, infant inclusion required term gestation, birthweight ≥2,250 grams, no serious medical conditions, and birth between June and December of 2012 or 2013. Thus, by study design, children were ≤6 months of age at the beginning of their first RSV season (November to March in our region[1,2]). The catchment zone encompassed urban, suburban, and rural areas. Annual follow-up for the ascertainment of childhood asthma and recurrent wheeze was conducted. If a participant missed an annual visit, we then attempted to contact them using multiple methods (including phone calls, short text messages, email, or regular mail). Participants continued in the study even if they missed a prior annual visit. The detailed methods for INSPIRE have been previously reported.[3]

Study Approval and Informed Consent

The Institutional Review Board of Vanderbilt University granted ethical approval for this study (approval # 111299) and one parent of each child provided written informed consent for their participation.

Determination of RSV Infection during Infancy

For the ascertainment of RSV infection during infancy, we first conducted intensive passive and active surveillance during each child's first RSV season by 1) performing bi-weekly phone, email, or in person follow-up, 2) frequently educating and reminding parents to call at the onset of any acute respiratory symptom, and 3) approaching all children who were seen at one of the participating pediatric practices for an unscheduled visit. An acute respiratory infection was defined as parental report of 1) one of the following major symptoms or diagnoses: wheezing, difficulty in breathing, or presence of a positive RSV test, or 2) any two of the following minor symptoms or diagnoses: fever, runny nose/nasal congestion/snotty nose, cough, ear infection, or hoarse cry. If a child met these pre-specified criteria, we then conducted an in-person respiratory illness visit at which time we administered a parental questionnaire, performed a physical exam, collected a nasal wash, and —in those who required a health care encounter— completed a structured medical chart review. The nasal wash was used for the molecular detection of RSV by reverse transcription-quantitative PCR (RT-qPCR) with virus-specific primers and fluorogenic hydrolysis probes, the AgPath-ID One-Step RT-PCR Kit (ThermoFisher Scientific, Massachusetts, USA), and the StepOnePlus Real Time PCR System (ThermoFisher Scientific, Massachusetts, USA) per a previously described protocol.[4] In addition, we collected blood samples from all participating children at age 1 year and measured RSV serum antibody titers by an enzyme-linked immunosorbent assay using published protocols.[5,6] Briefly, this technique uses RSV A and B lysate antigens produced in a human epithelial type 2 (HEp-2) cell line and detects serum antibodies against a range of RSV proteins (including the F, G, N, and P proteins). Serum antibody titers >200 to either RSV A or RSV B lysates were considered positive. Laboratory testing for RSV was done in core laboratories, not by the principal investigator's laboratory (TVH), and the laboratory staff responsible for the molecular and serologic detection of RSV infection during infancy were blinded to all other participant's data (including outcome data).

To classify children as not infected *vs.* infected with RSV in the first year of life, we used a hierarchical categorization with mutually exclusive group membership based on 1) the results of the RSV RT-qPCR tests in nasal washes collected throughout the close surveillance during each child's first RSV season, and 2) the results of the RSV serology in blood collected from all participating children at age 1 year (**Figure 2**).

Determination of the Severity of RSV Infection during Infancy

In all children with an in-person respiratory illness visit, we assessed the severity of the RSV infection during infancy using the Respiratory Severity Score (RSS). The RSS is an ordinal scale based on respiratory rate, flaring or retractions, heart rate, and wheezing that was slightly modified from other composite scores derived for acute respiratory infections.[7,8] It ranges from 0 to 12, with higher values indicating more severe disease, and values can distinguish disease severity as measured by both upper and lower respiratory tract infection, as well as level of health care utilization.[8]

<u>Definition of Outcomes</u>
Our primary outcome was 5-year current asthma, which was defined as parental report of: 1) physician-diagnosed asthma or use of asthma medications (including short-acting beta agonists, inhaled steroids, leukotriene receptor antagonists, or long-acting beta agonists) at any time point prior to age 5 years, and 2) any of the following occurring in the 12 months prior to the 5-year visit: asthma symptoms (such as "any wheezing or whistling in the chest", "chest sounded wheezy during or after exercise", and "dry cough at night apart from a cough associated with a cold or chest infection"), asthma-related systemic steroid use, or acute health care utilization (including urgent care visits, emergency department encounters, or hospitalizations) for asthma.

Our secondary outcomes were 1) recurrent wheeze, which was ascertained annually between ages 1-4 years and defined as parental report of ≥2 episodes of wheeze since the prior birthday, and 2) 5-year current asthma inflammatory subtype (atopic *vs.* non-atopic), which was ascertained using the aforementioned definition of 5-year current asthma and two different definitions of atopy: a) evidence of aeroallergen sensitization at age 3 years (see below), or b) parental report of ever physician diagnosis of allergic rhinitis or atopic dermatitis at age 5 years.

The primary and secondary outcomes were all assessed using the validated International Study of Asthma and Allergy in Children (ISAAC) questionnaire.[9] In addition, the evidence of aeroallergen sensitization at age 3 years was determined by either 2a) a positive skin prick testing (a wheal ≥3 mm larger than negative control) to common aeroallergens (weeds, grasses, trees, dogs, cats, dust mites, and molds) during the 3-year follow-up visit, or 2b) a positive (≥0.35 kU/L) ImmunoCAP Phadiatop specific IgE panel (ThermoFisher Scientific, Massachusetts, USA) in blood obtained during the 3-year follow-up visit (only performed if skin prick testing was not possible).

<u>Power Calculations</u>
Power calculations were performed at the study design phase with a required initial sample size of 1,900 children and attrition proportion of ~25% at ages 4-6 years for a final sample size of 1500 children. We estimated that 60% of children would be infected with RSV in their first year of life, which would result in 600 children with no RSV infection during infancy and 900 children with RSV infection during infancy (2:3 unexposed to exposed ratio).[10] The expected prevalence of childhood asthma in infants with no RSV infection was 11%.[11] Given these incidence ratios of exposure and outcome estimates, we calculated a minimum detectable risk ratio (RR) of childhood asthma of 1.50 or 0.62 in infants with RSV infection relative to infants with no RSV infection with 80% power and a type 1 error of 0.05.

<u>Statistical Analyses</u>

Estimation of the Proportion of Children with RSV Infection during Infancy
The proportion of children with RSV infection during infancy was calculated using the following formula:

> # of children with molecular or serologic evidence of RSV infection during infancy
> --
> # of children with available data to assess their RSV infection status during infancy

The Wilson method was used to estimate the 95% confidence intervals (CI) of this proportion.[12]

Statistical Comparisons
Descriptive statistics are presented as median (interquartile range) for continuous variables and frequencies (%) for categorical variables.

For initial group comparisons, we used Mann-Whitney U or (as no expected cell counts were <5) chi-squared tests as appropriate. To examine the association of not being infected with RSV during infancy with 5-year current asthma and recurrent wheeze between ages 1-4 years, we used modified Poisson regression and generalized estimating equations (GEE) with a Poisson random component and log link for repeated measures (using an independent working correlation) to estimate unadjusted and adjusted RRs and corresponding 95% CIs. The working variance-covariance matrices were corrected using the Huber-White robust sandwich method.[13] To examine the association of the severity of the RSV infection during infancy (as measured by the RSS) with 5-year current asthma in children who had an in-person respiratory illness visit with a positive nasal wash for RSV by RT-qPCR, we used logistic regression to estimate unadjusted and adjusted odds ratios and corresponding 95% CIs. For children

who had more than one in-person respiratory illness visit, only the RSS from the first documented RSV infection by RT-qPCR was included in statistical analyses. To examine the association of not being infected with RSV during infancy with 5-year current asthma inflammatory subtype, we used multinomial logistic regression to estimate unadjusted and adjusted odds ratios and corresponding 95% CIs.

We *a priori* selected covariates to be included in the adjusted models based on published literature and by creating a causal directed acyclic graph (**Figure S1**).[14] These included the child's sex, race and ethnicity (categorized as "Black non-Hispanic", "White non-Hispanic", "Hispanic", and "Other" for all statistical analyses), any breastfeeding, daycare attendance during infancy, exposure to secondhand smoking *in utero* or during early infancy, and maternal asthma.[15] Supplementary models were created by replacing these with other covariates (for example, daycare attendance during infancy with the presence of another child aged <6 years at home during infancy). The GEE models also included an interaction term between RSV infection during infancy and child's age as a time-varying covariate.

In exploratory analyses of our primary outcome, we used separate models to test for multiplicative interactions and examine effect modifications of RSV infection during infancy on 5-year current asthma by child's sex, race and ethnicity, daycare attendance during infancy, maternal asthma, and the presence of another child aged <6 years at home during infancy by including cross-product terms in the adjusted models.

Statistical significance was defined as $p<0.05$. Statistical analyses were performed using R version 4.0.1.[16]

Estimation of the Preventable Fraction
To assess the potential impact of avoidinng RSV infection during infancy on our primary outcome, we calculated the preventable fraction using the following formula based on the calculation of population attributable fraction by Miettinen:[17,18]

$$\frac{Pc * (\text{adjusted RR} - 1)}{\text{adjusted RR}}$$

where Pc is the proportion of RSV infection during infancy among children with 5-year current asthma and the adjusted RR is the adjusted RR of the association of being infected with RSV during infancy with 5-year current asthma. In addition, we estimated the 95% CI for the preventable fraction using the formula by Jewell,[19] as implemented in the R epiR package (available at: https://cran.r-project.org/web/packages/epiR/index.html).

Figure Creation
Figures were created using the R *ggplot2* package,[20] GraphPad Prism version 8.4.3 (available at: https://www.graphpad.com/), Biorender (available at: https://biorender.com/), drawio (available at: https://app.diagrams.net/), and DAGitty (available at: http://www.dagitty.net/). Minor aesthetic edits to figures (such as paneling, text insertion, or label formatting) were made with Inkscape version 1.0.2 (available at: https://inkscape.org/).

Table S1. Eligibility criteria for children enrolled in the study.

Inclusion Criteria	Exclusion Criteria
• Singleton birth to a mother age ≥18 years	• Bronchopulmonary dysplasia
• Estimated gestational age ≥37 weeks	• Cystic fibrosis
• Birth weight ≥2,250 grams	• Primary or acquired immunodeficiency (including maternal infection with human immunodeficiency virus)
• Birth between June 1 and December 31 of 2012 or 2013	
• Parent or guardian able to understand and provide informed consent	• Significant pulmonary, cardiovascular, or neurological disease
• No intent to relocate from middle Tennessee within 5 years of enrollment	• Need for mechanical ventilation prior to enrollment
	• Any medical condition that may jeopardize the integrity of the data to be collected

Table S2. Baseline characteristics of eligible children enrolled in the study with and without 5-year follow-up data.[*†]

Baseline characteristics	5-year follow-up data available		
	No (n=575)	Yes (n=1,371)	p-value[‡]
Age at enrollment (days)	57 (17-81)	55 (16-77)	0.23
Female sex	273 (47%)	653 (48%)	0.95
Race and ethnicity			
Black non-Hispanic	107 (19%)	236 (17%)	
White non-Hispanic	364 (63%)	903 (66%)	0.68
Hispanic	55 (10%)	115 (8%)	
Other	49 (9%)	117 (9%)	
Respiratory syncytial virus season			
2012-2013	239 (42%)	619 (45%)	0.15
2013-2014	336 (58%)	752 (55%)	
Birth month			
June	69 (12%)	201 (15%)	
July	94 (16%)	219 (16%)	
August	89 (15%)	240 (18%)	0.16
September	69 (12%)	192 (14%)	
October	83 (14%)	186 (14%)	
November	87 (15%)	164 (12%)	
December	84 (15%)	169 (12%)	
Gestational age (weeks)	39 (39-40)	39 (39-40)	0.34
Birth weight (grams)	3,377 (3,036-3,660)	3,433 (3,150-3,746)	0.0002
Birth by cesarean section	185 (32%)	426 (31%)	0.63
Any breastfeeding	399 (77%)	1,129 (83%)	0.0017
Daycare attendance during infancy	119 (28%)	471 (35%)	0.0093
Presence of another child aged <6 years at home during infancy	293 (51%)	690 (50%)	0.80
Exposure to secondhand smoking *in utero* or during early infancy	196 (34%)	229 (17%)	<0.0001
Maternal asthma	113 (20%)	266 (19%)	0.99
Type of insurance			
Federal or state	387 (67%)	672 (49%)	<0.0001
Private	184 (32%)	688 (50%)	
Other	5 (1%)	10 (1%)	

[*]Data presented as median (interquartile range) for continuous variables or number (%) for categorical variables.

[†]Data calculated for children with complete data.

[‡]The *p*-values for the comparison between the groups using a Mann-Whitney U or Pearson chi-squared test are shown.

Table S3. Sensitivity analyses of the association of not being infected with RSV during infancy with 5-year current asthma restricted to children who had RSV RT-qPCR testing.[*†]

Outcome	Unadjusted analysis			Adjusted analysis[‡]		
	Nº of children with outcome / total nº of children included in statistical analyses (%)	RR (95% CI)	*p*-value	Nº of children with outcome / total nº of children included in statistical analyses (%)	RR (95% CI)	*p*-value
Five-year current asthma	170/810 (20.99%)	0.80 (0.61-1.05)	0.11	170/805 (21.12%)	0.76 (0.58-1.00)	0.051

Definition of abbreviations: CI = Confidence interval, RR = Risk ratio, RSV = Respiratory syncytial virus, RT-qPCR = Reverse transcription-quantitative PCR.

[*]The estimates were obtained from models using modified Poisson regression. For all models, the reference group included children with a nasal wash positive for RSV by RT-qPCR.

[†]The statistical analyses were conducted in children with complete data.

[‡]The adjusted models included child's sex, race and ethnicity, any breastfeeding, daycare attendance during infancy, exposure to secondhand smoking *in utero* or during early infancy, and maternal asthma as covariates.

Table S4. Sensitivity analyses of the association of not being infected with RSV during infancy with childhood asthma-related outcomes.[*†]

Outcome	Unadjusted analyses			Adjusted analyses[‡]		
	Nº of children with outcome / total nº of children included in statistical analyses (%)	RR (95% CI)	p-value	Nº of children with outcome / total nº of children included in statistical analyses (%)	RR (95% CI)	p-value
Ever physician diagnosis asthma	157/1,308 (12.00%)	0.87 (0.65-1.17)	0.36	157/1,304(12.04%)	0.91 (0.68-1.23)	0.54
Ever use of asthma medications	635/1,412 (44.97%)	0.78 (0.69-0.88)	<0.0001	634/1,406 (45.09%)	0.79 (0.70-0.89)	<0.0001
Five-year asthma symptoms, asthma-related systemic steroid use, or health care utilization for asthma	312/1,219 (25.90%)	0.86 (0.71-1.05)	0.14	310/1,215 (25.51%)	0.86 (0.71-1.05)	0.13

Definition of abbreviations: CI = Confidence interval, RR = Risk ratio, RSV = Respiratory syncytial virus.

[*]The estimates were obtained from models using modified Poisson regression. For all models, the reference group included children infected with RSV during infancy.

[†]The statistical analyses were conducted in children with complete data.

[‡]The adjusted models included child's sex, race and ethnicity, any breastfeeding, daycare attendance during infancy, exposure to secondhand smoking *in utero* or during early infancy, and maternal asthma as covariates.

Table S5. The association of the severity of the RSV infection during infancy (as measured by the respiratory severity score) with 5-year current asthma in children who had an in-person respiratory illness visit with a positive nasal wash for RSV by Reverse Transcription-Quantitative PCR.

Outcome	Unadjusted analysis			Adjusted analysis[‡]		
	Nº of children with outcome / total nº of children included in statistical analyses (%)	OR (95% CI)	p-value	Nº of children with outcome / total nº of children included in statistical analyses (%)	OR (95% CI)	p-value
Five-year current asthma	59/237 (24.89%)	1.27 (1.10-1.48)	0.0012	59/234 (25.21%)	1.24 (1.05-1.45)	0.0092

Definition of abbreviations: CI = Confidence interval, OR = Odds ratio, RSV = Respiratory syncytial virus.

[*]The estimates were obtained from models using logistic regression.

[†]The statistical analyses were conducted in children with complete data.

[‡]The adjusted models included child's sex, race and ethnicity, any breastfeeding, daycare attendance during infancy, exposure to secondhand smoking *in utero* or during early infancy, and maternal asthma as covariates.

Table S6. Effect modification of the association of not being infected with RSV during infancy with 5-year current asthma by selected covariates.[*†‡]

Effect modifier	Category	Unadjusted analyses			Adjusted analyses		
		Nº of children with outcome / total nº of children included in statistical analyses (%)	p-value for interaction term	RR (95% CI)	Nº of children with outcome / total nº of children included in statistical analyses (%)	p-value for interaction term	RR (95% CI)
Child's sex	Female	230/1,257 (18.30%)	0.29	0.64 (0.43-0.95)	224/1,237 (18.11%)	0.22	0.61 (0.42-0.91)
	Male			0.83 (0.62-1.12)			0.84 (0.62-1.14)
Child's race and ethnicity	Black non-Hispanic			0.57 (0.32-1.00)			0.60 (0.34-1.05)
	White non-Hispanic	230/1,257 (18.30%)	0.69	0.84 (0.62-1.12)	224/1,237 (18.11%)	0.84	0.80 (0.60-1.07)
	Hispanic			0.88 (0.35-2.24)			0.79 (0.31-2.06)
	Other			0.59 (0.24-1.46)			0.60 (0.25-1.44)
Daycare attendance during infancy	No	230/1,253(18.36%)	0.23	0.67 (0.50-0.90)	224/1,237 (18.11%)	0.18	0.66 (0.50-0.88)
	Yes			0.91 (0.60-1.38)			0.93 (0.62-1.40)
Maternal asthma	No	230/1,256 (18.31%)	0.47	0.83 (0.57-1.18)	224/1,237 (18.11%)	0.41	0.84 (0.58-1.22)
	Yes			0.69 (0.51-0.94)			0.69 (0.51-0.94)

Definition of abbreviations: CI = Confidence interval, RR = Risk ratio, RSV = Respiratory syncytial virus.

[*]The estimates were obtained from models using modified Poisson regression. For all models, the reference group included children infected with RSV during infancy.

[†]The statistical analyses were conducted in children with complete data.

[‡]The unadjusted models included RSV infection during infancy, the effect modifier, and a cross-product term of these. The adjusted models included RSV infection during infancy, the effect modifier, a cross-product term of these, and the following covariates if not already included: child's sex, race and ethnicity, any breastfeeding, daycare attendance during infancy, exposure to secondhand smoking *in utero* or during early infancy, and maternal asthma.

Table S7. Supplementary adjusted models of the association of not being infected with RSV during infancy with the primary and secondary outcomes using other covariates.[*†‡]

Outcome	Nº of children with outcome / total nº of children included in statistical analyses (%)	Estimate (95% CI)	p-value
Primary outcome			
Five-year current asthma	230/1,253 (18.41%)	0.74 (0.58-0.94)	0.013
Secondary outcomes			
Recurrent wheeze			
One-year	250/1,703 (14.69%)	0.54 (0.42-0.69)	<0.0001
Two-year	242/1,624 (14.83%)	0.76 (0.60-0.96)	0.019
Three-year	191/1,412 (13.49%)	0.80 (0.61-1.05)	0.11
Four-year	166/1,452 (11.40%)	0.86 (0.65-1.15)	0.31
5-year current asthma inflammatory subtype – Definition 1[§]			
None	1,023/1,213 (84.34%)	Reference	
Non-atopic	91/1,213 (7.50%)	0.55 (0.35-0.87)	0.011
Atopic	99/1,213 (8.16%)	0.90 (0.58-1.37)	0.62
5-year current asthma inflammatory subtype – Definition 2[§]			
None	1,013/1,234 (82.09%)	Reference	
Non-atopic	81/1,234 (6.56%)	0.51 (0.32-0.83)	0.0063
Atopic	140/1,234 (11.35%)	0.80 (0.56-1.16)	0.24

Definition of abbreviations: CI = Confidence interval, RSV = Respiratory syncytial virus.

[*]For the outcomes of 5-year current asthma and recurrent wheeze at each of the measured time points, the estimates presented are risk ratios obtained from modified Poisson regression models. For the outcome of 5-year current asthma inflammatory subtype, the estimates presented are odds ratios from multinomial logistic regression models. For all models, the reference group included children infected with RSV during infancy.

[†]The statistical analyses were conducted in children with complete data.

[‡]The models included child's sex, race and ethnicity, any breastfeeding, presence of another child aged <6 years at home during infancy, exposure to secondhand smoking *in utero* or during early infancy, and maternal asthma as covariates.

[§]For definition 1 of 5-year current asthma inflammatory subtype, atopy was ascertained using evidence of aeroallergen sensitization by skin prick testing or blood specific IgE testing at age 3 years. For definition 2 of 5-year current asthma inflammatory subtype, atopy was ascertained by parental report of ever physician-diagnosed allergic rhinitis or atopic dermatitis at age 5 years.

Table S8. Effect modification of the association of not being infected with RSV during infancy with 5-year current asthma by presence of another child aged <6 years at home during infancy.[*†‡]

Effect modifier	Category	Unadjusted analyses			Adjusted analyses		
		Nº of children with outcome / total nº of children included in statistical analyses (%)	p-value for interaction term	RR (95% CI)	Nº of children with outcome / total nº of children included in statistical analyses (%)	p-value for interaction term	RR (95% CI)
Presence of another child aged <6 years at home during infancy	No	230/1,257 (18.30%)	0.47	0.82 (0.58-1.15)	230/1,253 (18.36%)	0.43	0.82 (0.58-1.14)
	Yes			0.69 (0.48-0.97)			0.67 (0.48-0.95)

Definition of abbreviations: CI = Confidence interval, RR = Risk ratio, RSV = Respiratory syncytial virus.

[*]The estimates were obtained from models using modified Poisson regression. For all models, the reference group included children infected with RSV during infancy.

[†]The statistical analyses were conducted in children with complete data.

[‡]The unadjusted models included RSV infection during infancy, presence of another child aged <6 years at home during infancy, and a cross-product term of these. The adjusted models included RSV infection during infancy, presence of another child aged <6 years at home during infancy, a cross-product term of these, and the following covariates: child's sex, race and ethnicity, any breastfeeding, exposure to secondhand smoking *in utero* or during early infancy, and maternal asthma.

Figure S1: Directed acyclic graph of the potential causal role of RSV infection during infancy in the development of childhood asthma.

Figure created with DAGitty (available at: http://www.dagitty.net/). *Definition of abbreviations:* RSV = Respiratory syncytial virus.
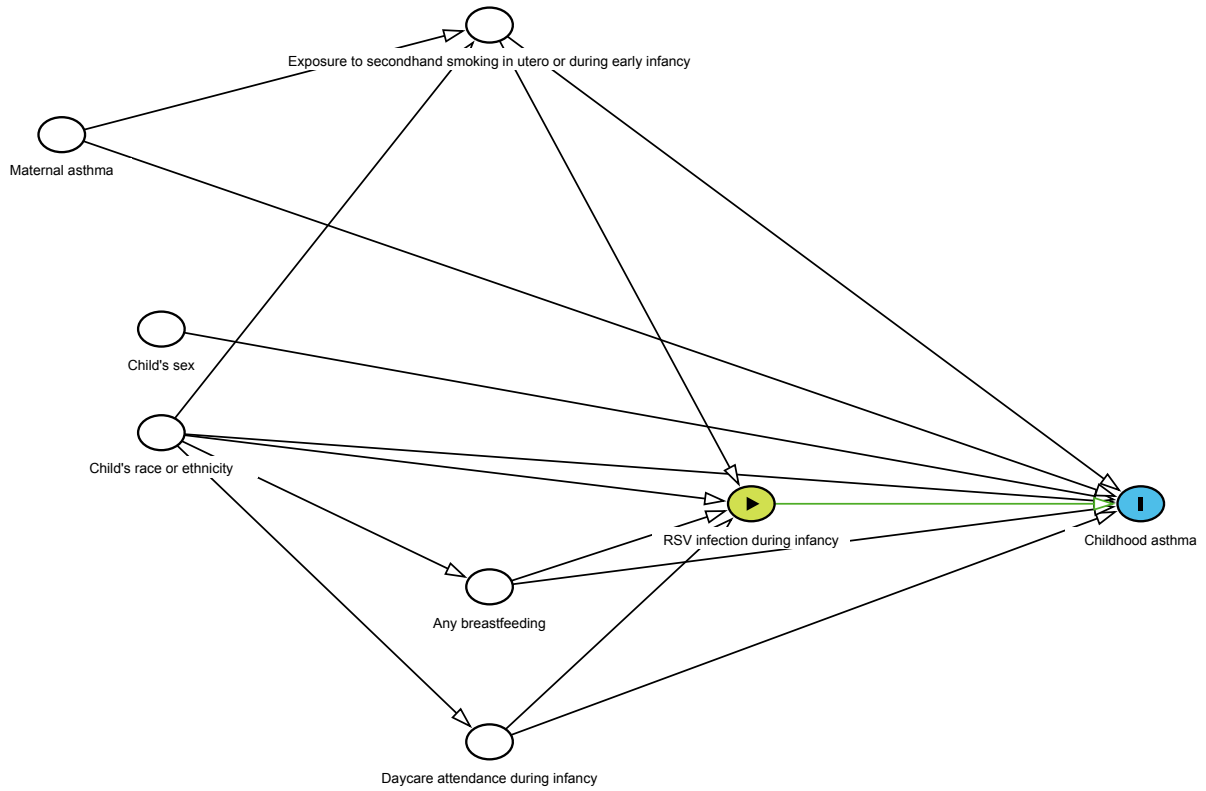
Figure S2: Epidemiological curve of RSV infections in the study as assessed by the percent of positive nasal washes for RSV by RT-qPCR per month.

Definition of abbreviations: RSV = Respiratory syncytial virus, RT-qPCR = Reverse transcription-quantitative PCR.
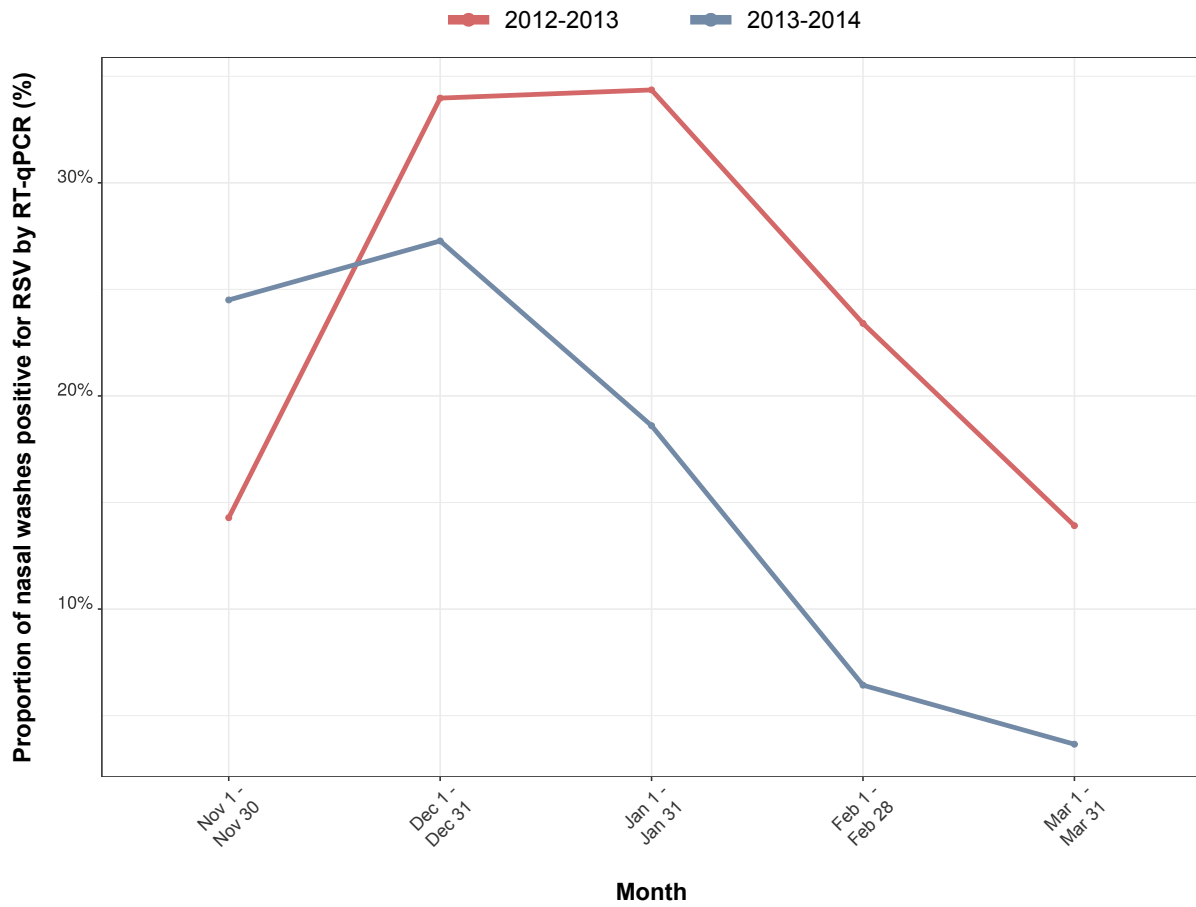
Figure S3: Flow diagram of the enrollment, RSV surveillance, and ascertainment of RSV infection during infancy of children included in the study.

Definition of abbreviations: INSPIRE = Infant Susceptibility to Pulmonary Infections and Asthma Following RSV Exposure Study, RSV = Respiratory syncytial virus, RT-qPCR = Reverse transcription-quantitative PCR.
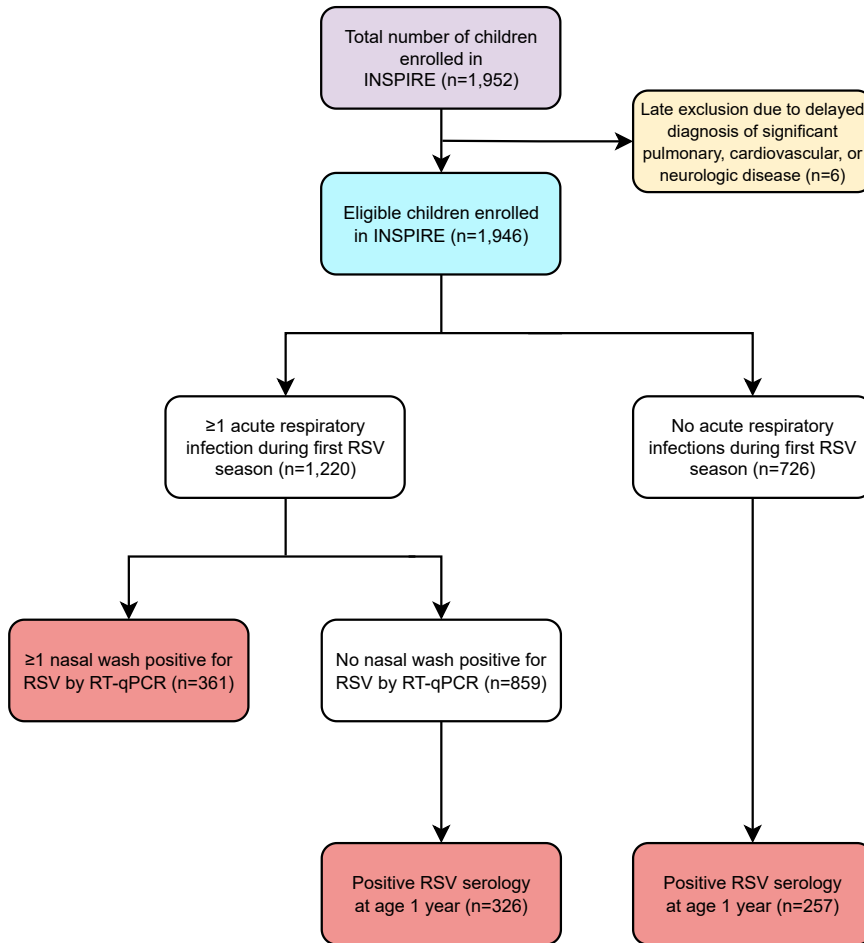
Figure S4: Graphical abstract of main study results.

Figure created with Biorender (available at: https://biorender.com/). *Definition of abbreviations:* aRR = Adjusted risk ratio, RSV = Respiratory syncytial virus.
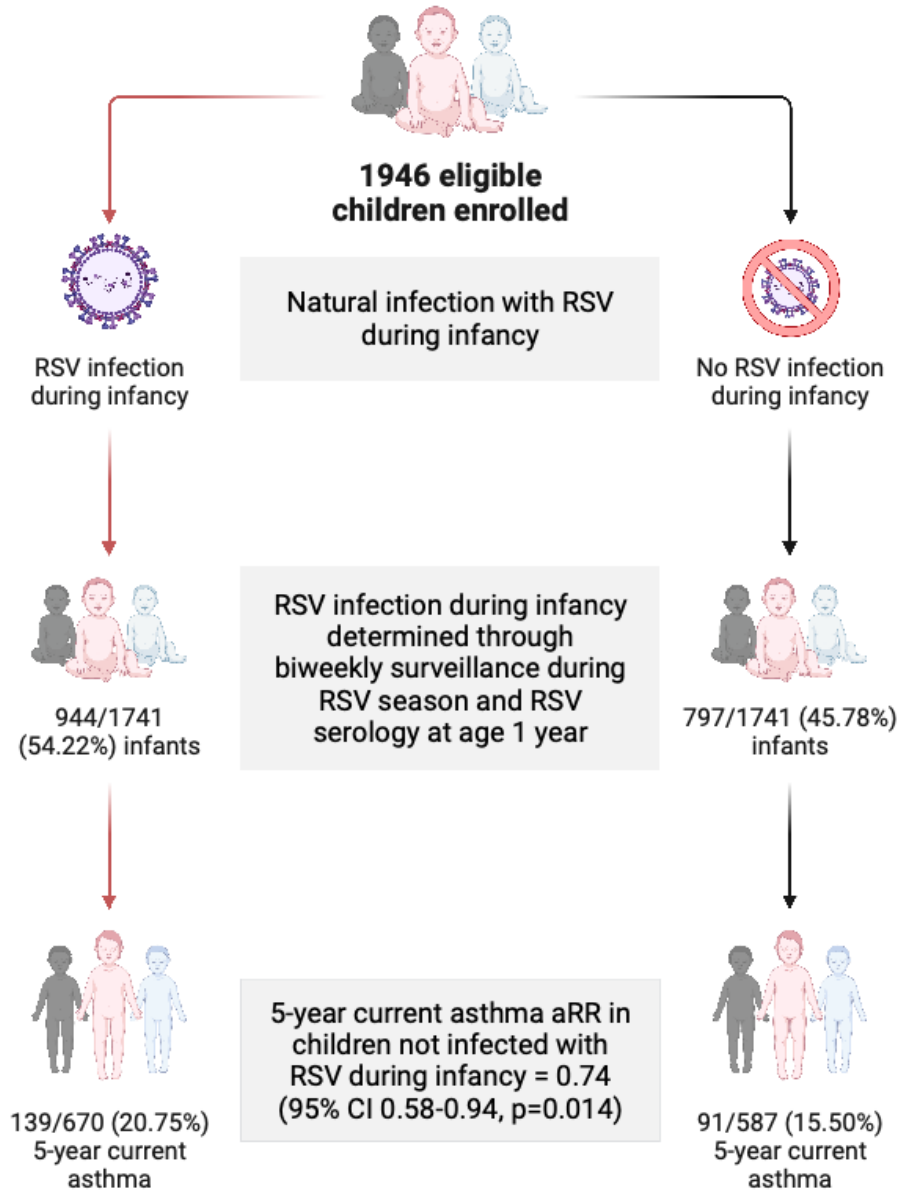
Figure S5: Predicted probabily of 5-year current asthma by the severity of the RSV infection during infancy (as measured by the RSS) in children who had an in-person respiratory illness visit with a positive nasal wash for RSV by Reverse Transcription-Quantitative PCR.

The estimates were obtained from adjusted logistic regression models including child's sex, race and ethnicity, any breastfeeding, daycare attendance during infancy, exposure to secondhand smoking *in utero* or during early infancy, and maternal asthma as covariates. The RSS is an ordinal scale that ranges from 0 to 12 with higher values indicating more severe disease. *Definition of abbreviations:* RSS = Respiratory severity score, RSV = Respiratory syncytial virus.
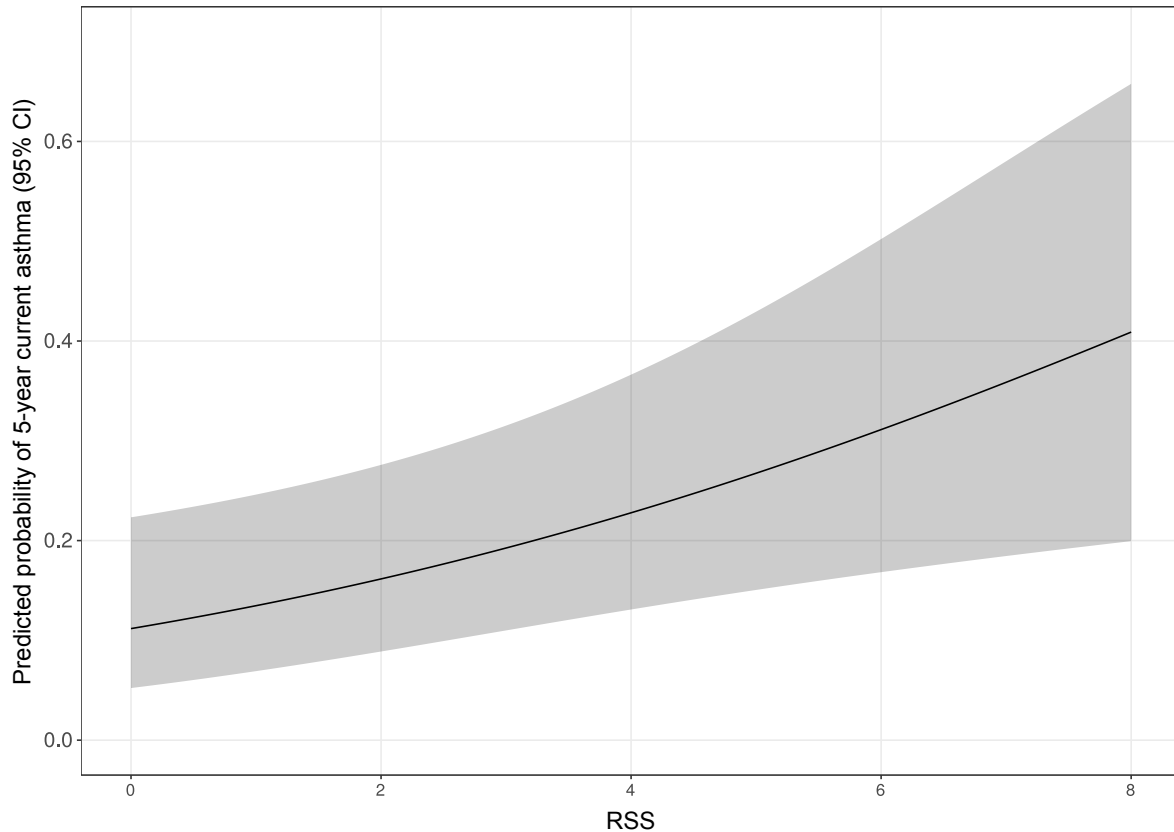
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