SUPPLEMENTARY MATERIAL

Symptoms and infections in children before and during the Coronavirus pandemic in the New Hampshire Birth Cohort Study

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Figure S1. Flow chart depicting the participants excluded/included in this study.

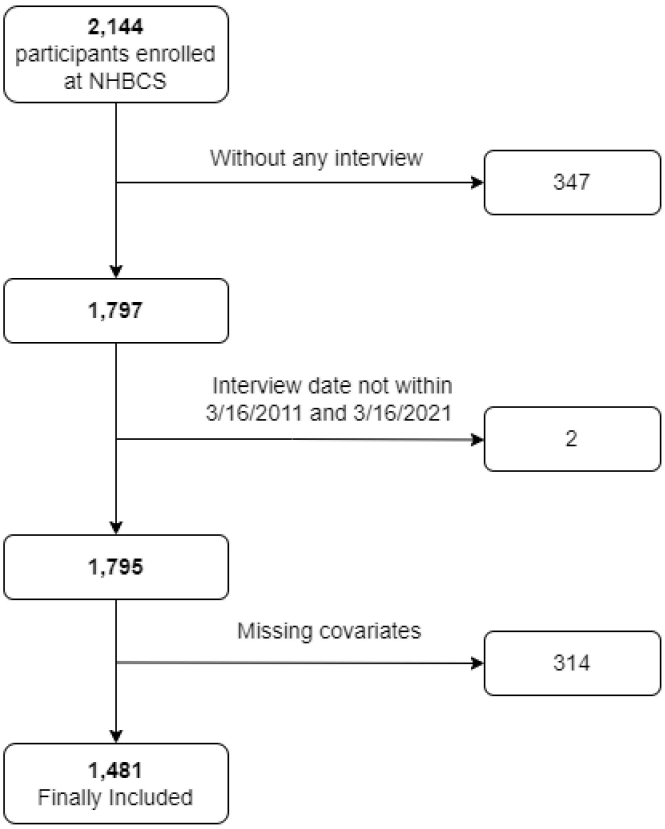

Table S1. Demographics for the participants included in the study (1,481); for those with missing values in the covariates (1,795) and for the full participants actively enrolled in NHBCS at 16th March, 2021 (2,144).

Variable	**Included in the study**	**With missing covariates**		**Full cohort 16th March 2021**	
Maternal characteristics	**Participants:** 1,481	**Participants:** 1,795	**Miss.**	**Participants:** 2,144	**Miss.**
	Mean (SD) or N (%)	Mean (SD) or N (%)		Mean (SD) or N (%)	
Age of enrollment (years)	31.6 (4.7)	31.4 (4.8)	0	31.24 (4.8)	0
Smoking status during pregnancy:			145		364
No	1,392 (94%)	1,541 (93%)		1,656 (93%)	
Yes	89 (6.0%)	109 (6.6%)		124 (7.0%)	
Maternal education:			225		430
Less than 11th grade	10 (0.7%)	11 (0.7%)		17 (1.0%)	
High school graduate or equivalent	160 (11%)	169 (11%)		198 (12%)	
Junior college graduate	251 (17%)	268 (17%)		296 (17%)	
College graduate	586 (40%)	613 (39%)		666 (39%)	
Any post-graduate schooling	474 (32%)	509 (32%)		537 (31%)	
Parity			32		148
0	649 (44%)	769 (44%)		860 (43%)	
1	548 (37%)	653 (37%)		739 (37%)	
≥ 2	284 (19%)	341 (19%)		397 (20%)	
Children characteristics					
Sex			0		107
Boys	730 (49%)	907 (51%)		1,028 (51%)	
Girls	751 (51%)	888 (50%)		1,009 (50%)	
Gestational age (weeks)	39.3 (1.6)	39.2 (1.8)	0	39.2 (1.8)	88
Birthweight (g)	3,447 (512)	3,425 (524)	98	3,418 (533)	232

Table S2.a. Unadjusted and adjusted risk ratios for caregivers reported respiratory infections and symptoms requiring a doctor visit in children aged up to 5 years old

Outcome	Unadjusted RR up to 5 years old [95% C.I.]	p-value	Adj. RR up to 5 years old [95% C.I.]	p-value
Any Upper RTI	**0.58** [0.46, 0.73]	**<0.001**	**0.45** [0.28, 0.77]	**0.003**
Any Lower RTI	**0.71** [0.46, 1.09]	0.117	**0.70** [0.43, 1.12]	0.134
Any Respiratory Symptom	**0.50** [0.41, 0.62]	**<0.001**	**0.49** [0.39, 0.60]	**<0.001**
Any Other Acute Symptom	**0.71** [0.56, 0.90]	**0.005**	**0.68** [0.53, 0.88]	**0.003**
Conjunctivitis	**0.44** [0.25, 0.74]	**0.002**	**0.47** [0.28, 0.77]	**0.003**
Otitis Media	**0.57** [0.44, 0.74]	**<0.001**	**0.57** [0.43, 0.77]	**<0.001**
Laryngitis	**0.82** [0.11, 5.83]	0.841		
RSV	**1.13** [0.62, 2.04]	0.691	**1.11** [0.58, 2.13]	0.758
Pertussis				
Bronchitis	**0.34** [0.09, 1.32]	0.119		
Bronchiolitis	**1.06** [0.54, 2.10]	0.859	**1.05** [0.45, 2.40]	0.918
Pneumonia	**0.26** [0.07, 0.95]	**0.042**		
Runny Nose	**0.44** [0.34, 0.56]	**<0.001**	**0.44** [0.34, 0.56]	**<0.001**
Cough	**0.73** [0.57, 0.94]	**0.016**	**0.69** [0.52, 0.91]	**0.008**
Difficulty in Breathing	**0.68** [0.41, 1.14]	0.144	**0.76** [0.46, 1.26]	0.283
Wheeze	**0.40** [0.23, 0.71]	**0.002**	**0.34** [0.20, 0.58]	**<0.001**
Sore Throat	**0.15** [0.03, 0.79]	0.025		
Diarrhea	**0.74** [0.41, 1.35]	0.330	**0.77** [0.40, 1.43]	0.391
Fever	**0.72** [0.56, 0.90]	**0.005**	**0.67** [0.51, 0.88]	**0.004**

Footnote: Estimates and 95% Cis are not given when GEE models do not converge due to the low number of events in the outcome.

Table S2.b. Unadjusted and adjusted risk ratios for caregivers reported respiratory infections and symptoms requiring a doctor visit in children aged from 5 to 11 years old

Outcome	Unadjusted RR 5 to 11 years old [95% C.I.]	p-value	Adj. RR 5 to 11 years old [95% C.I.]	p-value
Any Upper RTI	**0.43** [0.33, 0.55]	**<0.001**	**0.42** [0.30, 0.58]	**<0.001**
Any Lower RTI	**0.43** [0.26, 0.69]	**0.001**	**0.42** [0.22, 0.78]	**0.006**
Any Respiratory Symptom	**0.71** [0.60, 0.84]	**<0.001**	**0.73** [0.56, 0.96]	**0.024**
Any Other Acute Symptom	**0.76** [0.60, 0.96]	**0.020**	**0.69** [0.48, 1.01]	0.006
Conjunctivitis	**0.46** [0.28, 0.76]	**0.003**	**0.45** [0.21, 0.99]	**0.049**
Otitis Media	**0.42** [0.32, 0.55]	**<0.001**	**0.40** [0.27, 0.58]	**<0.001**
Laryngitis	**0.44** [0.08, 2.47]	0.352		
RSV	**0.86** [0.16, 4.74]	0.864		
Pertussis	**0.27** [0.05, 1.56]	0.144		
Bronchitis	**0.57** [0.23, 1.40]	0.221		
Bronchiolitis	**0.39** [0.04, 4.07]	0.429		
Pneumonia	**0.36** [0.18, 0.71]	**0.003**		
Runny Nose	**0.52** [0.39, 0.68]	**<0.001**	**0.90** [0.58, 1.39]	0.623
Cough	**0.73** [0.55, 0.95]	**0.022**	**0.90** [0.56, 1.42]	0.643
Difficulty in Breathing	**0.37** [0.18, 0.73]	**0.004**		
Wheeze	**0.56** [0.34, 0.93]	**0.026**		
Sore Throat	**0.95** [0.69, 1.30]	0.744		
Diarrhea	**0.55** [0.23, 1.30]	0.174		
Fever	**0.78** [0.61, 0.99]	**0.046**	**0.67** [0.45, 0.99]	**0.048**

Footnote: Estimates and 95% Cis are not given when GEE models do not converge due to the low number of events in the outcome.

Methods M1. Additional information on the New Hampshire Birth Cohort Study and the data used

Since January 2009 the NHBCS has been recruiting pregnant women through prenatal clinics in New Hampshire. Inclusion criteria were age 18 to 45 years, English literacy, use a private, unregulated water system at home (e.g., private well), not planning to move residence, and a singleton pregnancy. The flow of participants is shown in Figure S1.

Questions related to the children's health were completed by the caregiver at regular intervals from birth until the age of eleven years. The questionnaires took the form of telephone interviews or self-reported online questionnaires and at each interview the mother was asked about a range of health problems (yes/no) including: upper respiratory tract infections: conjunctivitis, otitis media and laryngitis; lower respiratory tract infections: respiratory syncytial virus (RSV), pertussis, bronchitis, bronchiolitis, and pneumonia; respiratory symptoms: runny nose, cough, difficulty in breathing wheeze and sore throat and other acute symptoms such as diarrhea and fever. Those who reported any of the aforementioned infections and symptoms were asked if the corresponding infection or symptom had resulted in a doctor's visit and, in that case, if the child had been prescribed any medicine.

An indicative power calculation was conducted according to the available cohort size, approximately 1,800, considering an average of 5 and 1 responses in the pre- and pandemic periods respectively, with those numbers varying for different analyses due to missing data. Assuming two-sided significance 5%, power is 80.3% for comparing risks: risk ratios, 0.65 pre- and peri-pandemic.

Both unadjusted and adjusted risk ratios were computed for the participants stratified by age at reporting in younger than 5 and from 5 to 11 years old. Results are shown in Table S2.a, and Table S2.b, respectively.

Methods M2. Analytical methods: modelling strategy

We compared the probabilities of a positive response to the questions related to respiratory infections and symptoms, which required a doctor visit. With this goal, we defined a dummy variable indicating whether the interview took place in the pre-pandemic period (03/16/2020, effective restrictions date, or in the pandemic period (after that date). In this way, we included the same seasons/periods corresponding to nine years pre-pandemic and a one year pandemic period.

Each respiratory infection or symptom was treated as a repeated measure over all time points. The overall probabilities of occurrence, adjusted by time-period from last interview and their respective 95% confidence intervals summarize the respiratory infections and symptoms outcomes. In addition, we provide the pre-pandemic and pandemic period probabilities. We defined an event for a specific outcome (infection/symptom) as a 'yes' response to the corresponding question for that outcome in each interview and compute the proportions of events per outcome (#yes / [#yes + #no]). To account for the effect of different lengths of periods between two consecutive interviews, these proportions (or probabilities of event) were adjusted for the time interval since the last interview using generalized estimating equation (GEE) Poisson models with robust error variance and an exchangeable working

correlation matrix, where the time in months elapsed from the last interview was included as a covariate. The probabilities reported in Table 1 of the paper are the estimates obtained from the GEE models computed on the median interval length.

Related unadjusted and adjusted time-period risk ratios with their 95% bootstrapped confidence intervals are also reported from GEE models. As previously, unadjusted models included the time in months elapsed from the last interview date, and the season in which the interview took place. Adjusted models included, in addition, the age of the children at reporting and all the covariates given immediately below.

Several maternal and child characteristics were considered as covariates. Among the former we have: the mother's age, educational level and parity at enrollment, and the smoking status during pregnancy. Among the latter we included infant sex, gestational age at birth and birthweight. Breast feeding and attendance at daycare facilities were included, as reported at each interview.

Results were based on a case-complete approach including only participants with the main covariates present included. For the breastfeeding and daycare attendance variables, we defined a new category for missing data.

We computed the probabilities of responses reported quarterly since 2011 for any of the infections and symptoms and represented in trends plots (Figure 1 in the paper). In order to avoid the noise from seasonality, moving average lines accounting to three periods were added to smooth the original plots but the raw data were retained in the plots to maximize the visual information .

Methods M3. Analytical methods: multiple imputation

We used multivariate imputation by chained equations (MICE) [1] assuming that data were missing at random to check for any impact of missing covariate data in the computed adjusted risk ratios for children aged between 0 and 11 years. A total of 15 datasets were generated where the binary variables infant sex and smoking status were imputed from logistic regression models; values for the ordered variables parity and educational level were generated according to proportional odds models and the continuous gestational age and birthweight were imputed from predictive mean models. The results are shown in Table S3.

Table S3. Adjusted risk ratios for caregivers reported respiratory infections and symptoms requiring a doctor visit in children aged between 0 – 11 years.

Outcome	Adj. RR [95% C.I.]	p-value
Any Upper RTI	**0.52** [0.43, 0.64]	**<0.001**
Any Lower RTI	**0.60** [0.40, 0.90]	**0.014**
Any Respiratory Symptom	**0.63** [0.56, 0.96]	**0.024**
Any Other Acute Symptom	**0.66** [0.55, 0.80]	**<0.001**
Conjunctivitis	**0.49** [0.33, 0.72]	**<0.001**
Otitis Media	**0.53** [0.42, 0.67]	**<0.001**
Laryngitis		
RSV	1.00 [0.33, 1.90]	0.999
Pertussis		
Bronchitis	**0.58** [0.25, 1.32]	0.193
Bronchiolitis	**1.07** [0.48, 2.39]	0.873
Pneumonia	**0.25** [0.12, 0.52]	**<0.001**
Runny Nose	**0.53** [0.44, 0.64]	**<0.001**
Cough	**0.73** [0.59, 0.90]	**0.004**
Difficulty in Breathing	**0.64** [0.40, 1.05]	0.076
Wheeze	**0.47** [0.32, 0.68]	**<0.001**
Sore Throat	**0.49** [0.34, 0.72]	**<0.001**
Diarrhea	**0.68** [0.38, 1.21]	0.190
Fever	**0.73** [0.60, 0.90]	**0.002**

Footnote: Estimates and 95% CIs are not given when GEE models do not converge due to the low number of events in the outcome.

Methods M4. Software

All statistical analyses were performed using the statistical software R (www.r-project.org). The package geepack [2] was used for implementing the GEE models and the package MICE[3] to perform the multiple imputation.

References

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[2] Halekoh U, Højsgaard S, Yan J, 2006. The R package geepack for Generalized Estimating Equations. Journal of Statistical Software 15(2): 15(2):1-11.

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