

Supplementary material for “Time-varying association between severe respiratory syncytial virus infections and subsequent severe asthma and wheeze, and influences of age at the infection”

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## Appendix 1 Information of databases and case definitions

### Databases

SMR01 records information on gender and the Scottish Index of Multiple Deprivation (SIMD), age at admission, date of admission (year, month and week), length of hospital stay, and the presence of congenital disease(s) (including congenital heart disease, Down syndrome, cystic fibrosis, and bronchopulmonary dysplasia). SMR02 records information on the child's birth date (ddmmyy), maternal smoking history during pregnancy, mode of delivery, the number of previous pregnancies, the number of births of this pregnancy, breastfeeding status on mother's discharge, gestational age, birth weight, APGAR score at 5 minutes, and admission to the neonatal unit after birth.

**Table S1. Detailed list of ICD-10 codes to ascertain exposure status and outcome**

Definitions	ICD-10 code
Respiratory tract infection (RTI) codes (A)	J00-J06; J09-J18; J20-22
RSV-specific codes (B)	J12.1; J20.5; J21.0; B97.4
RSV-RTI	A AND B
Unintentional accident codes	V01-99, X00-59, X85-99, Y00-09, Y35-99
Asthma codes	J45.0; J45.1; J45.8; J45.9; J46
Wheeze codes	R06.2

## Appendix 2 Additional results and sensitivity analysis

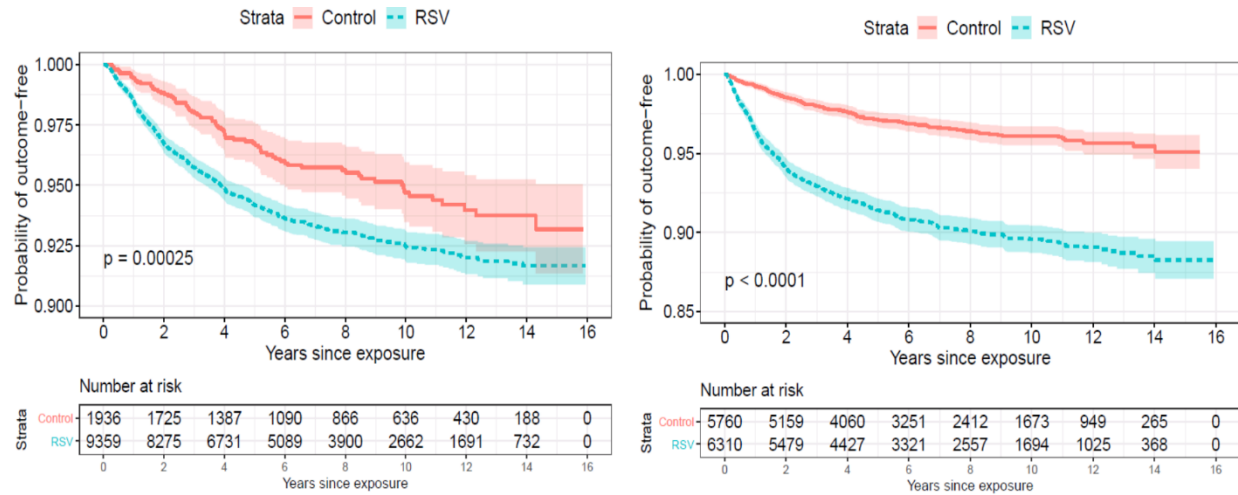


Figure S1. Kaplan–Meier curves for outcome-free survival by the age at first RSV-RTI admission (left: 0-5 months; right: 6-23 months). Y-axis shows the cumulative survival of outcome-free (%), and x-axis shows the years since exposure.

Table S2. Characteristics of children with RSV-RTI admissions (the exposed group) and unintentional accident admissions (the unexposed group) in the first 2 years of life.

Children having RSV-RTI admissions under 2 years

Children having unintentional accident admissions under 2 years

No.

Proportion (%)<sup>1</sup>

No.

Proportion (%)

P value<sup>2</sup>

Total no.

17249

100

8686

100

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No. with complete data<sup>3</sup>

15669

90.8

7696

88.6

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Years of follow-up [median (IQR)]

6.9 (3.1-10.9)

NA

6.9 (3.4-10.8)

NA

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Age at the index admission

<6 m

9359

59.7

1936

25.2

<0.001

6-11 m

3892

24.8

1431

18.6

12-23 m

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1 Proportion of complete data was calculated among all data. Proportion by age at exposure, gender, smoking status during pregnancy, social-economic quintile, delivery mode, gestational age, multiple births at this pregnancy, the presence of congenital diseases, and length of hospital stay at the index admission was calculated among all the children with complete data.

2 Chi-square test for categorical variables.

3 Missing data on gender (114), Scottish index of multiple deprivation defines 1 as most deprived and 5 as least deprived (57), smoking during pregnancy (1942), gestational age (20), and delivery mode (517).

2418  
15.4  
4329  
56.2

Gender

Male  
8818  
56.3  
4447  
57.8  
0.029  
Female  
6851  
43.7  
3249  
42.2

Scottish index of multiple deprivation (SIMD)

1  
4652  
29.7  
2448  
31.8  
<0.001  
2  
3488  
22.3  
1744  
22.7

3  
2737  
17.5  
1395  
18.1

4  
2480  
15.8  
1150  
14.9

5  
2312  
14.8  
959  
12.5

6

Smoking status during pregnancy

No  
10848  
69.2  
5349  
69.5  
0.672  
Yes  
4821  
30.8  
2347  
30.5

Delivery mode

Vaginal  
10856  
69.3  
5559  
72.2  
<0.001  
Caesarean (emergency and elective)  
4813  
30.7  
2137  
27.8

Gestational age

37 weeks or more  
13081  
83.5  
6822  
88.6  
<0.001  
Less than 37 weeks  
2588  
16.5  
874  
11.4

Number of births at this pregnancy

One birth  
 14827  
 94.6  
 7477  
 97.2  
 <0.001  
 More than one birth  
 842  
 5.4  
 219  
 2.8

With congenital diseases<sup>4</sup>

No  
 15407  
 98.3  
 7469  
 97.1  
 <0.001  
 Yes  
 262  
 1.7  
 227  
 2.9

Length of stay at the index admission

0-3 days  
 10457  
 66.7  
 5965  
 77.5  
 <0.001  
 4 days or more  
 5212  
 33.3  
 1731  
 22.5

## Summary of Table S2:

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4 Including any of congenital heart disease, Down syndrome, bronchopulmonary dysplasia and cystic fibrosis



Compared to the control group (accident admission group), first RSV-RTI admissions usually occurred at younger age, and children admitted with RSV-RTI were more frequently female, born prematurely, born through caesarean and through multiple births, and more frequently had four or more days of hospital stay at the index admission. In contrast, children with RSV-RTI were less frequently from the most deprived areas, and less frequently had congenital diseases than those admitted due to an accident (appendix). No significant difference was observed in maternal smoking status during pregnancy between exposed and control group.

Table S3. Rates and hazard ratios of first asthma and wheeze admission in children with RSV-RTI or accident admission under 2 years old using all data (25,935 children)

Time (years since exposure)	Rates per 1,000 child-years (95%CI) for the unexposed group	Rates per 1,000 child-years (95%CI) for the exposed group	Crude HR (95%CI)	p-value
<2 years	7.2 (6.0-8.6)	22.8 (21.2-24.5)	3.1 (2.6-3.8)	<0.001
2-<4 years	5.4 (4.3-6.8)	10.3 (9.1-11.5)	1.9 (1.5-2.4)	<0.001
4-<6 years	4.2 (3.1-5.5)	6.5 (5.5-7.7)	1.6 (1.1-2.2)	0.007
6 years or more	2.2 (1.7-3.0)	3.0 (2.5-3.5)	1.3 (1.0-1.8)	0.07

Table S4. Rates and hazard ratios of first asthma and wheeze admission in children with RSV-RTI or accident admission in children with less than 3 RTI admissions in the first 2 years of age (21,471 children)

Time (years since exposure)	Rates per 1,000 child-years (95%CI) for the unexposed group	Rates per 1,000 child-years (95%CI) for the exposed group	Adjusted HR (95%CI) <sup>5</sup>	p-value
<2 years	5.5 (4.4-6.7)	14.4 (13.1-15.8)	3.5 (2.7-4.6)	<0.001
2-<4 years	5.3 (4.1-6.7)	9.2 (8.0-10.4)	1.5 (1.1-2.1)	0.006
4-<6 years	3.8 (2.7-5.1)	5.9 (4.9-7.1)	1.5 (1.0-2.2)	0.071
6 years or more	2.1 (1.5-2.8)	2.6 (2.1-3.2)	1.3 (0.8-1.9)	0.271

Table S5. Rates and hazard ratios of first asthma admission in children with RSV-RTI or accident admission (23,718 children).

Time (years since exposure)	Rates per 1,000 child-years (95%CI) for the unexposed group	Rates per 1,000 child-years (95%CI) for the exposed group	Adjusted HR (95%CI) <sup>6</sup>	p-value
<b>Exposure at 0-23 months</b>				
<2 years	4.4 (3.4-5.6)	12.8 (11.6-14.2)	4.0 (3.0-5.3)	<0.001
2-<4 years	4.5 (3.4-5.9)	9.2 (8.1-10.5)	2.2 (1.4-3.2)	<0.001
4-<6 years	4.3 (3.1-5.8)	6.5 (5.5-7.8)	1.5 (1.0-2.2)	0.194
6 years or more	2.4 (1.7-3.2)	2.8 (2.3-3.4)	1.2 (0.8-1.9)	1.000
<b>Exposure at 0-5 months</b>				
<2 years	2.4 (1.1-4.5)	8.2 (7.0-9.6)	3.8 (1.9-7.4)	<0.001
2-<4 years	5.8 (3.4-9.9)	8.1 (6.8-9.7)	1.4 (0.9-2.4)	0.153
4-<6 years	6.0 (3.4-9.9)	6.6 (5.2-8.2)	1.2 (0.7-2.1)	0.521
6 years or more	2.8 (1.6-4.6)	2.7 (2.0-3.4)	1.0 (0.6-1.8)	0.906
<b>Exposure at 6-23 months</b>				
<2 years	5.0 (3.8-6.5)	19.6 (17.2-22.2)	3.8 (2.8-5.1)	<0.001
2-<4 years	4.1 (2.9-5.6)	10.9 (8.9-13.1)	2.7 (1.8-3.9)	<0.001
4-<6 years	3.7 (2.4-5.3)	6.5 (4.9-8.5)	1.7 (1.1-2.8)	0.021
6 years or more	2.2 (1.5-3.1)	3.0 (2.2-4.1)	1.3 (0.8-2.1)	0.230

<sup>5</sup> Adjusting for gender, age group at exposure, Scottish index of multiple deprivation, smoking during pregnancy, gestational age, delivery mode, multiple births at this pregnancy, the presence of congenital diseases, and length of hospital stay at the index admission.

<sup>6</sup> Adjusting for gender, age group at exposure, Scottish index of multiple deprivation, smoking during pregnancy, gestational age, delivery mode, multiple births at this pregnancy, the presence of congenital diseases, and length of hospital stay at the index admission.

Table S6. Rates and hazard ratios of first asthma and wheeze admission in children with RSV-RTI or accident admission under 2 years old after excluding those who died at the index admission<sup>78</sup>

Time (years since exposure)	Rates per 1,000 child-years (95%CI) for the unexposed group	Rates per 1,000 child-years (95%CI) for the exposed group	Crude HR (95%CI)	Adjusted HR (95%CI)	p-value
<2 years	7.0 (5.7-8.5)	22.2 (20.5-23.9)	3.2 (2.6-3.9)	3.6 (2.9-4.5)	<0.001
2-<4 years	5.7 (4.4-7.2)	10.2 (9.0-11.6)	1.8 (1.4-2.3)	1.8 (1.3-2.4)	<0.001
4-<6 years	4.6 (3.4-6.2)	6.8 (5.7-8.0)	1.5 (1.0-2.0)	1.4 (0.9-2.0)	0.11
6 years or more	2.3 (1.7-3.1)	3.0 (2.5-3.6)	1.3 (0.9-1.8)	1.2 (0.9-2.0)	0.15

Table S7. Rates and hazard ratios of subsequent first-time asthma and wheeze admission compared to other controls.

	Rates per 1,000 child-years (95%CI)	Crude HR (95%CI)	Adjusted HR (95%CI)
Compared to nonRSV-RTI (RSV was not coded as the causal pathogen)			
nonRSV-RTI <sup>9</sup>	7.9 (7.5-8.2)	1.0	1.0
RSV-coded RTI	10.5 (9.9-11.1)	1.4 (1.3-1.5)	1.2 (1.1-1.3) <sup>10</sup>

7 Only very small proportion of children included in this cohort died at the admission: 0.2% (38 of 15669) in the RSV group, and 0.6% (45 of 7696) in the accident group.

8 Adjusting for gender, age group at exposure, Scottish index of multiple deprivation, smoking during pregnancy, gestational age, delivery mode, multiple births at this pregnancy, the presence of congenital diseases, and length of hospital stay at the index admission.

9 Including respiratory tract infections for which RSV was not coded as the causal pathogen.

10 Adjusting for gender, age group at exposure, Scottish index of multiple deprivation, smoking during pregnancy, gestational age, delivery mode, the presence of congenital diseases, and length of hospital stay at the index admission.

Table S8. Multivariate hazard ratios of other factors for subsequent first-time asthma and wheeze admission in children with RSV coded RTI admission and accident admission under 2 years old.

Factors	Adjusted HR (95%CI) <sup>11</sup>	P-value from multivariate analysis
<b>Gender</b>		
Male	Ref	
Female	0.7 (0.7-0.8)	<0.001
<b>Scottish index of multiple deprivation</b>		
1	Ref	
2	1.0 (0.8-1.1)	0.679
3	0.9 (0.8-1.1)	0.316
4	0.7 (0.6-0.8)	<0.001
5	0.7 (0.6-0.8)	<0.001
<b>Smoking during pregnancy</b>		
No	Ref	
Yes	1.1 (1.0-1.2)	0.06
<b>Delivery mode</b>		
Vaginal	Ref	
Caesarean (emergency and elective)	1.1 (1.0-1.3)	0.019
<b>Gestational age</b>		
37 weeks or more	Ref	
Less than 37 weeks	1.3 (1.1-1.4)	0.002
<b>Number of births of this pregnancy</b>		
One birth	Ref	
More than one birth	0.8 (0.6-1.0)	0.055
<b>With congenital disease(s)</b>		
No	Ref	
Yes	1.4 (1.0-1.8)	0.041
<b>Length of hospital stay at the index admission</b>		
Less than 4 days	Ref	
4 days or more	1.6 (1.4-1.8)	<0.001

<sup>11</sup> In addition to above factors, the multivariate model includes an interaction between age group at exposure and RSV admission under 2 years old. A time-dependent coefficient was added to RSV admission due to not following the proportional hazards assumption.