



### A retrospective cohort study on infant respiratory tract infection hospitalizations and recurrent wheeze and asthma risk: impact of respiratory syncytial virus

van Wijhe, Maarten; Klint Johannesen, Caroline; Simonsen, Lone; Jørgensen, Inger Merete; K. Fischer, Thea

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- 1 A retrospective cohort study on infant respiratory tract infection hospitalizations and recurrent wheeze
- 2 and asthma risk: impact of respiratory syncytial virus
- 3 **Running title:** Infant RSV and risk of wheeze and asthma
- 4 Maarten van Wijhe<sup>a,b</sup>, Caroline Klint Johannesen<sup>a,e</sup>, Lone Simonsen<sup>b</sup>, Inger Merete Jørgensen<sup>c</sup>, the
- 5 RESCEU Investigators<sup>d</sup>, Thea K Fischer<sup>a,e,f</sup>
- 6 Authors affiliations: 1 institution per author (JID supplement guidelines)
- 7 <sup>a</sup>Statens Serum Institute, Denmark
- 8 <sup>b</sup>Department of Science and Environment, Roskilde University, Denmark
- 9 <sup>c</sup>Department of Pediatric and Adolescent Medicine, Nordsjællands Hospital, Denmark
- <sup>d</sup>Members of the study group are listed at the end of the text.
- <sup>11</sup> <sup>e</sup>Department of Clinical Research, Nordsjællands University Hospital, Hilleroed, Denmark<sup>f</sup>Department of
- 12 Public Health, University of Denmark, Copenhagen, Denmark
- 13 **Corresponding author:** Maarten van Wijhe, Statens Serum Institut, Copenhagen Denmark.Email:
- 14 wijhe@ruc.dk, telephone: +45 46 74 39 34

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#### 1 Abstract

2 Aim: Infant respiratory syncytial virus infection (RSV) has been associated with asthma later in life. We

3 explored the risk of recurrent wheeze or asthma in children with infant RSV-associated hospitalization

4 compared to other respiratory infections.

5 Methods: We performed a retrospective cohort study using Danish national hospital discharge registers.

- 6 Infants under 6 months, born between January 1995 and October 2018, and with a RSV hospital
- 7 admission were compared to infants hospitalized for injuries, non-RSV acute upper respiratory tract
- 8 infection (AURTI), pneumonia and other respiratory pathogens, non-pathogen coded lower respiratory
- 9 tract infections (LRTI), pertussis, or non-specific respiratory infections. Infants were followed until
- 10 recurrent wheeze or asthma diagnosis, death, migration, age 10 years, or study end. We estimated
- 11 cumulative incidence rate ratios (CIRR) and hazard ratios (HR) adjusted for sex, age at inclusion, hospital
- 12 length of stay (LOS), maternal smoking, 5 minute APGAR score (APGAR5), prematurity, and congenital
- 13 risk factors (CRF).
- 14 **Results:** We included 68130 infants, of whom 20920 (30.7%) had RSV hospitalization. The cumulative
- 15 incidence rate of recurrent wheeze or asthma was 16.6 per 1000 person-years after RSV hospitalization,
- 16 higher than after injury (CIRR: 2.69; 95% CI: 2.48-2.92), AURTI (1.48; 1.34-1.58), or pertussis (2.32;

17 1.85-2.91), similar to pneumonia and other respiratory pathogens (1.15; 0.99-1.34) and LRTI (0.79; 0.60-

- 18 1.04), but lower than non-specific respiratory infections (0.79; 0.73-0.87).
- 19 Adjusted HRs for recurrent wheeze or asthma after RSV hospitalization compared to injuries decreased
- 20 from 2.37 (95% CI: 2.08-2.70) for 0 to <1 year to 1.23 (0.88-1.73) for 6 to <10 years for term-born
- children, and from 1.48 (1.09-2.00) to 0.60 (0.25-1.43) for preterm-born children. Sex, maternal smoking,
- 22 LOS, CRF, and APGAR5 were independent risk factors.
- Conclusions: Infant RSV hospitalization is associated with recurrent wheeze and asthma hospitalization,
   predominantly in preschool age. If causal, RSV-prophylaxis, including vaccines, may significantly reduce
   disease burden of wheeze and asthma.
- 26 **Keywords**: RSV, respiratory syncytial virus, asthma, recurrent wheeze, register study, retrospective
- 27 cohort study, hospitalizations.

### 1 Introduction

2 RSV causes a common respiratory infection among infants and young children [1, 2], and can present 3 with a broad spectrum of respiratory symptoms. Those under 6 months of age are often most severely 4 affected and have the highest incidence of hospitalizations [3, 4]. Respiratory infections in the early stages of life can have health consequences in later life such as a predisposition to subsequent pulmonary 5 infections or asthma [1, 5]. This 'priming' may be due to structural damage in the lungs or alterations in 6 7 airway epithelial cells and immune development [6]. Specifically, asthma has been associated with earlier 8 RSV infection, whether this association is causal remains unclear [7]. Alternatively, it may be severe lower respiratory tract infections (LRTI) in general, that are associated with the occurrence of asthma 9 10 later in life. If early life RSV infection predisposes infants to asthma, prophylaxis, including vaccines, against RSV may be able to contribute to a reduction in long-term disease burden besides preventing 11 12 initial hospitalizations.

Here we studied the relation between severe RSV infection in early life and the risk of subsequent asthma,
comparing RSV hospitalizations to hospitalizations for other viral or bacterial respiratory infections.

### 15 Materials and methods

16 Data

17 We performed a retrospective cohort study using Danish national registers. Data were obtained from the Danish National Patient Register (DNPR), Cause of Death Register (CODR), Medical Birth Register 18 19 (MBR), as well as the Civilian Registration System (CRS). The DNPR provides nationwide longitudinal 20 registration of administrative and clinical data on all hospital admissions since 1977. Since 1995 ICD-10 21 codes are used to classify diagnoses [8]. The CODR contains dates and cause of death for all deaths in 22 Denmark, classified with ICD-10 codes since 1994 [9]. MBR provides information on all births and 23 maternal information collected from antenatal visits and the CRS [10]. The CRS contains basic personal 24 information for all inhabitants [11, 12]. Data was available up to October 10, 2018 and registries were 25 linked with unique personal identifiers.

#### 1 Study population

2 Infants born after January 1, 1995 with an inpatient hospitalization or emergency department visit within

3 the first 6 months of life were eligible for inclusion. Included ICD-10 codes are defined below.

4 *Hospitalization definition* 

5 We consolidated hospital contacts that occurred on the same or the following day. Such hospitalizations

6 were considered to belong to the same *event*, and we used the first admission date as the start date for all

7 diagnosis during that event.

#### 8 RSV cohort

9 The main cohort of interest were infants with mention of RSV in primary or secondary discharge codes
10 (ICD-10 codes: J12.1, J20.5, J21.0, B97.4) in the first 6 months of life. Children with any diagnosis of
11 wheeze, asthma, or immunosuppression (see outcome definitions below) prior to or within 30 days after
12 the start of the RSV-associated hospital event, were excluded.

#### 13 Comparison cohorts

14	Six comparison cohorts were defined based on hospital admissions with non-RSV conditions: 1) non-
15	RSV acute upper respiratory tract infections (AURTI; ICD-10 codes: J00, J02-J06); 2) injuries (ICD-10
16	codes: S and T); 3) pertussis (A37.0, A37.9); 4) non-RSV pneumonia and other respiratory pathogens
17	(see below); 5) non-RSV-coded LRTI (ICD-10 codes: J20.0, J20.2, J20.3, J20.7-J20.9, J21.2-J21.9, J22,
18	J40); and 6) non-specific respiratory infections (ICD-10 codes: J12.9, J18, J20.9, J21.9, J22). Each
19	comparison cohort included infants with a hospitalization within the first 6 months of life who did not
20	have an RSV-associated hospitalization during that time. Infants with pre-existing wheeze or asthma or a
21	diagnosis thereof up to 30 days after the inclusion admission were excluded. Patients were assigned to the
22	various cohorts based on the first occurring hospitalization. If during the inclusion admission, multiple
23	cohorts could be assigned, they were excluded from the study.

The cohort with non-RSV pneumonia and other respiratory pathogens was composed of other viral and
 bacterial pathogens and included adenovirus (J12.0, B97.0, B34.0), coronavirus (B972, B34.2),
 enterovirus (B97.1, B34.1), metapneumovirus (J12.3, J21.1), rhinovirus (J20.6, B97.8), parainfluenza
 virus (J12.2, J20.4), influenza (J09-J11), other viral pneumonia (J12.8, J12.9, J17.1), *Haemophilus*

5 *influenzae* (J14, J20.1, B96.3, A49.2), other bacterial pneumonia (J15, J17.0) and other pneumonia (J16,

- 6 J17.2, J17.3, J17.8, J18). The occurrence of pertussis was sufficiently large to be used as a separate
- 7 cohort. Non-specific respiratory infections formed a separate cohort because RSV infection is often coded
- 8 as such rather than with RSV-specific ICD-10 codes.

### 9 *Outcome definitions*

While asthma is our main outcome of interest, wheezing is a common clinical indication of respiratory
distress. For children, up to about 6 years of age, asthma is often coded as wheezing rather than the ICD10-specific codes for asthma (wheeze ICD-10 codes: R062, J209, asthma ICD-10 codes: J45, J46). The
main reason is that younger children often cannot participate sufficiently in the pulmonary testing
requested for an asthma diagnosis. Regardless, asthma-specific codes are frequently used in children
under 6 years of age in Denmark.

16 Children were followed until the first recorded ICD-10 hospital record with recurrent wheeze, asthma, or 17 an immunosuppressive condition (ICD-10 codes: C, B20-B24, O98.7, Z21, D37-D48), death due to any cause, reaching 10 years of age, migration out of the country, or the end of the study on October 10, 2018, 18 whichever came first. Recurrent wheeze was defined as at least two hospital visits where wheeze-specific 19 20 codes were registered within a year of each other, the second occurrence was used as the end of follow-21 up. If an asthma-related ICD-10 code was registered in between these two records, the date of the first 22 asthma episode was used as the end point. As only several children were identified with an 23 immunosuppressive condition as a censoring event, this group is not further discussed.

We considered the following covariates: maternal smoking, APGAR score at 5 minutes (APGAR5,  $\leq$  7 or 2 3 >7), cystic fibrosis (CF), broncho-pulmonary dysplasia (BPD), Down syndrome, congenital heart disease 4 (CHD), prematurity (gestational age <37 weeks), sex, and hospital length of stay (LOS) during the 5 inclusion admission. Maternal smoking was coded as smoker or non-smoker. When it was recorded that a 6 mother stopped smoking during pregnancy, they were grouped with the smokers. An APGAR score under 7 7 indicates that some additional care is required following birth and it may be a proxy for susceptibility 8 for respiratory conditions and other neonatal outcomes [13]. Due to low numbers, infants with CF, BPD, 9 Down syndrome, or CHD, were combined into one group. We included LOS as a proxy for severity of the respiratory condition during admission and it was coded as 0 days, 1 day, 2-3 days, 4-9, days and 10+ 10 11 days. We also tested for seasonal effect by including month of admission but these factors were not statistically relevant and did not affect other estimates; these results are, therefore, not further discussed. 12

#### 13 Statistical analysis

We calculated incidence rates per 1000 person-years of follow-up as well as the cumulative incidence rate 14 ratios (CIRR) for each of the cohorts. Associations between risk factors and time to recurrent wheeze or 15 16 asthma were explored with univariate and multivariate Cox proportional hazard models. Separate baseline 17 hazards were fitted for each inclusion age (by month of age). Similar to previous research, RSV, nonspecific respiratory infections, and maternal smoking were added as time-varying coefficients in the 18 multivariate model [14]—included here as step functions for the time intervals 0 to <1 year, 1 to <2 years, 19 20 2 to <3 years, 3 to <6 years, and 6 to  $\leq$ 10 years. As prematurity was a strong risk factor and interacted 21 with several other covariates, we fitted two models, one for term-born children and one for preterm-born 22 children. Only infants with complete information were used in the analysis—univariate analyses revealed 23 little impact of this choice. Several sensitivity analyses were performed to test the robustness of the results. First we tested the impact of restricting the analysis to cohorts with full follow-up, i.e., those born 24

2 hospitalization (ICD-10 J-codes) during the first six months of life. Finally, we restricted the outcomes to

3 asthma after the age of five years only. Statistical analyses were done using R (version 4.1.0).

#### 4 Informed consent

According to Danish law, ethics approval is exempt for this kind of register-based research. Due to the
nature of this research, there was no involvement of patients or members of the public in the design or
reporting of this study. Direct dissemination to study participants is not possible. The publication only
contains aggregated results and no personal data. The publication is, therefore, not covered by the
European General Data Protection Regulation.

#### 10 Results

A total of 68130 infants were included in the study, of whom 20920 (30.7%) were in the RSV cohort-11 12 most, 94.3%, of these were due to RSV-related LRTI. Overall, recurrent wheeze or asthma was registered in 11.0% of infants in the RSV cohort, 7.2% for AURTI, 9.2% for pneumonia and other respiratory 13 pathogens, 13.1% for LRTI, 4.9% for pertussis, 13.8% for unspecific respiratory infections, and 4.5% for 14 the injury cohort. Distributions of covariates are presented in Table 1. Overall, the median follow-up time 15 16 to recurrent wheeze or asthma diagnosis was 0.9 years (interquartile range: 0.5-1.7) corresponding to a 17 median age of 1.2 years (interquartile range: 0.7-1.9)—3036 (64.4%) of asthma and 586 (71.1%) of recurrent wheeze diagnoses were made before the second year of life. 18

## 19 Incidence rates

Except for pertussis, respiratory infections seemed associated with a higher risk of recurrent wheeze or
asthma compared to injuries (Table 2); RSV had a CIRR of 2.69 (95% CI: 2.48-2.92). Compared to RSV,
non-specific respiratory infections seemed to have an elevated risk (1.26, 95% CI: 1.15-1.38). LRTI

2 (0.87, 95% CI: 0.75-1.01) tended to a lower risk, although neither was statistically significant.

Preterm children tended to have a lower CIRR than term children (Supplementary Figure 1, and
Supplementary Table 2), and preterm children were more at risk of recurrent wheeze or asthma, with
20.31 cases per 1000 follow-up years versus 11.19 (CIRR: 1.82, 95% CI: 1.66-1-82).

#### 6 Hazards

7 Figure 1 shows the adjusted hazard ratios (HR) (univariate HR and survival curves are presented in 8 Supplementary Table 1 and Supplementary Figure 2). For term-born children the HR compared to injuries decreased over time from 2.37 (95% CI: 2.08-2.70) for 0 to <1 year to 1.37 (95% CI: 1.08-1.74) for 3 to 9 10 <6 years. At 6 to <10 years, the HR was not statistically significant at 1.23 (95% CI: 0.88-1.73). For preterm-born children the HR declined from 1.48 (95% CI: 1.09-2.00) to 0.60 (95% CI: 0.25-1.43). Non-11 12 specific respiratory infections showed similar results. Compared to injuries, infants hospitalized with pneumonia or other pathogens were at increased risk (term: 1.41, 95% CI: 1.15-1.74; preterm: 1.60, 95% 13 14 CI: 1.09-2.34). For AURTI the hazard was similarly increased (term: 1.64, 95% CI: 1.48-1.82; preterm: 1.37, 95% CI: 1.06-1.79), while for LRTI only term children had an increased hazard with 2.47 (95% CI: 15 1.76-3.47). The pertussis cohort did not show an increased hazard compared to injuries. Comparing the 16 17 hazard rates for the RSV cohort to the other cohorts (Supplementary Figure 3), we note that, particularly 18 in the first year of life, the hazard rates for the RSV cohort were higher compared to AURTI, pertussis, 19 and pneumonia and other respiratory pathogens, while compared to LRTI and non-specific respiratory 20 infections, the hazard rate for the RSV cohort was consistently lower after the first year of follow-up. 21 Male sex (term: 1.62, 95% CI: 1.52-1.73; preterm: 1.32, 95% CI: 1.15-1.54) and congenital risk factors 22 (term: 1.77, 95% CI: 1.54-2.03; preterm: 1.74, 95% CI: 1.45-2.08) were independent risk factor for both 23 preterm and term children, while APGAR5 score (term: 1.197, 95% CI: 0.94-1.51; preterm: 1.42, 95%

24 CI: 1.10-1.83) increased the hazard only for preterm children. Maternal smoking was a strong risk factor

in the first year of life and decreased over time from 1.82 (95% CI: 1.66-1.99) for 0 to <1 year to 0.65</li>
(95% CI: 0.44-0.97) for 6 to <10 years for term children, and from 1.68 (95% CI: 1.39-2.04) to 1.64 (95%</li>
CI: 0.75-3.59) for preterm children (Figure 1). Lastly, the hazard seems to increase with the hospital LOS
for the inclusion admission, with hazard rates of 2.51 (95% CI: 2.17-2.86) for term children and 1.72
(95% CI: 1.30-2.27) for preterm children for hospital stays of over 10 days compared to less than 1 day.
Overall, HR for preterm children were, with few exceptions, lower than for term children.

Our results did not change meaningfully when restricting to birth cohorts with full follow-up, or when
excluding infants with more than one respiratory hospitalization in the first 6 months of life. Restricting to
only asthma after age 6 years as an outcome (thus not considering recurrent wheeze), RSV remains a
significant risk factor with HR of 1.52 (95% CI: 1.07-2.15). See also Supplementary Figures 4-7.

### 11 Discussion

RSV can cause a severe respiratory infection especially among the very young. As many as 4% of all 12 13 children in the United Kingdom are hospitalized during their first year of life due to RSV infection, and 14 79.3% of hospitalizations for bronchitis/bronchiolitis in infants younger than 6 months can be attributed to RSV [15]. Similarly, severe RSV infections have an annual incidence of 7.1 per 1.000 children below 15 five years of age in Denmark [3]. It has become increasingly clear that respiratory infections in early life 16 may increase the tisk of respiratory diseases later in life, including asthma [6]. Using Danish health 17 registers, we found that RSV hospitalization is associated with considerable increased risk for recurrent 18 19 wheeze or asthma, particularly among term-born children.

A meta-analysis showed that, contrary to our results, infant RSV infection increased the risk of recurrent
wheeze or asthma in children between 6 to 12 years of age with odds ratios of 2.14 (95% CI: 1.33–3.45)
and 2.95 (95% CI: 1.96-4.46), respectively [1]. The authors also found no significant differences between
risk of recurrent wheeze or asthma for RSV or other respiratory infections [1]. We similarly compared
RSV to other groups of respiratory infections and found that RSV hospitalization, as well as non-specific

1 respiratory infections and LRTI, are major risk factors. The highest risk was found during the first year of life, and declined thereafter. We found no significant increased risk after age 6 years in the main analysis, 2 3 but when restricting the outcomes to only asthma after age 6 years, RSV remained a significant risk 4 factor. Reasons for the apparent disparity with Shi et al, could lie in differences in outcome definitions, 5 local coding practices and included co-variates. Declines in risk after the initial potential causal exposure 6 have been observed before [16-20], and are not surprising, especially when those most at risk of recurrent 7 wheeze or asthma are diagnosed early. Alternatively, diagnoses later in life may be frequently made of 8 outside hospital settings (and, thus, be overlooked in this study), or risks may be most pronounced in 9 early life when the lungs, airways and immune system are most plastic. Interestingly, we found similar risk patterns for RSV, non-specific respiratory, and LRTI hospitalizations, 10 11 which proposes a possible common pathway or shared genetic underpinnings for severe infection and asthma, but at least suggests that LRTI in general, and perhaps less so the specific pathogen, increase the 12

risk for recurrent wheeze or asthma. This finding has also been noted for pneumonia related readmission 13 after infant LRTI [21]. Another explanation may be that many RSV infections are missed and coded as 14 non-specific infections. Results from a small study from Denmark point in the same direction, where 15 adjustment for the frequency of respiratory episodes removed the association between particular causative 16 pathogens and asthma in later life [22]. Our associations held when correcting for important covariates. 17 Of special note are preterm-born children, who had generally lower HR. This emphasizes the fact that 18 prematurity itself is a strong risk factor. Besides prematurity, male sex, a high APGAR score, congenital 19 20 risk factors, maternal smoking, and initial hospital LOS were independent risk factors in our study. The 21 latter is interesting as our estimates suggests that more severe respiratory infection during infancy 22 increases the risk for recurrent wheeze or asthma.

23 Our study has several limitations. First, it is often supposed that either mechanical damage or

24 immunological priming causes the increased risk of recurrent wheeze or asthma, or that RSV infection

identifies those with a predisposition to develop wheeze or asthma [6, 23-25]. Given the retrospective
 cohort design of our study, we could not differentiate between these hypotheses.

3 We utilized discharge and population registers allowing correction for important confounders, but 4 residual confounding cannot be excluded. The quality of Danish health registers is high. Nevertheless, the 5 validity of our results depends on the diligence of nurses and doctors in noting information [26]. In 6 particular, for maternal smoking approximately 10% of children had missing information. This may have 7 affected the analysis, although univariate and multivariate HR estimates do not differ meaningfully. Our data also limited the study to more severe cases of RSV requiring treatment in the emergency department 8 or hospitalization-non-hospital cases are not included. Similarly, the incidence of (less severe) recurrent 9 wheeze or asthma-related respiratory complaints may be higher than shown here. Furthermore, maternal 10 11 or paternal asthma status was not available for this study, nor did we have good information on allergic manifestations. The omission of such potential hereditary factors might have led to an overestimation of 12 the risk of asthma after RSV infection. 13

A main limitation of our study is the reliance on ICD-10 coding. Often, once the RSV season begins and 14 the first cases are laboratory-confirmed, diagnoses are based mainly on clinical assessment as RSV is 15 16 considered the most likely pathogen. Patients are then often coded with non-specific respiratory ICD-10 codes. We, therefore, included non-specific respiratory infections as a separate cohort-and our results 17 indicate that this group is similar to RSV. A Danish study including both ICD-10 and laboratory-18 confirmed RSV cases, showed that 12.1% of RSV-positive patients only had laboratory-confirmed RSV 19 20 without corresponding ICD-10 codes [3]. We likely missed a considerable number of RSV cases, 21 resulting in misclassification of RSV infection with other respiratory infections in comparator cohorts and 22 our risk estimates may be underestimated. Similarly, diagnoses of recurrent wheeze and asthma were also 23 defined by ICD-10 codes. Diagnosing asthma in young children is known among pediatricians to be a 24 challenge. The high number of asthma diagnoses before age three years is, therefore, surprising. It is

1 possible that at the time of inclusion, unrecognized wheeze or asthma were exacerbated by respiratory

2 infection.

### 3 Conclusion

4 While associations between RSV LRTI during infancy and development of childhood asthma are well

- 5 documented [1], causation has long been debated. We add to the evidence base that RSV requiring
- 6 hospitalization, and LRTI in general, increases the risk for recurrent wheeze or asthma predominantly in
- 7 the preschool age. As many respiratory hospitalizations in infants are attributable to RSV (Johannesen et
- 8 al, submitted), prevention of hospitalization with safe and effective prophylaxis, including vaccines, can
- 9 considerably reduce the burden of recurrent wheeze and asthma, especially among term-born children.

### 10 Footnote page

#### 11 Study Group Members

12 The RESCEU investigators are as follows:

Harish NAIR (University of Edinburgh), Harry CAMPBELL (University of Edinburgh), Philippe Beutels 13 (Universiteit Antwerpen), Louis Bont (University Medical Center Utrecht), Andrew Pollard (University 14 of Oxford), Peter Openshaw (Imperial College London), Federico Martinon-Torres (Servicio Galego de 15 Saude), Terho Heikkinen (University of Turku and Turku University Hospital), Adam Meijer (National 16 Institute for Public Health and the Environment), Thea Kølsen Fischer (Statens Serum Institut), Maarten 17 18 van den Berge (University of Groningen), Carlo Giaquinto (PENTA Foundation), Michael Abram 19 (AstraZeneca), Kena Swanson (Pfizer), Bishoy Rizkalla (GlaxoSmithKline), Charlotte Vernhes (Sanofi 20 Pasteur), Scott Gallichan (Sanofi Pasteur), Jeroen Aerssens (Janssen), Veena Kumar (Novavax), Eva Molero (Team-It Research). 21

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- 23
- 24

#### 1 Supplementary data

Supplementary materials are available at online The Journal of Infectious Diseaseswebsite. Consisting of
data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole

4 responsibility of the authors, so questions or comments should be addressed to the corresponding author.

#### 5 **Conflicts of interest**

- 6 The authors do not report any conflicts of interest. All authors have submitted the ICMJE Form for
- 7 Disclosure of Potential Conflicts of Interest.

#### 8 **Previous presentation**

9 This work has previously been presented at the European Society for Clinical Virology 2019 conference,

10 11-14 September 2019, Copenhagen, Denmark, and the ISIRV Webinar Series, online, on 1 February

**11** 2021.

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According to Danish law, ethics approval is exempt for this kind of register-based research. Due to the nature of this research, there was no involvement of patients or members of the public in the design or reporting of this study. Direct dissemination to study participants is not possible. The publication only 1 contains aggregated results and no personal data. The publication is, therefore, not covered by the

2 European General Data Protection Regulation. The results in this manuscript only reflect the authors'

3 views, and the European Commission is not responsible for any use that may be made of the information

4 it contains.

## 5 **Corresponding author contact information**

6 Maarten van Wijhe, Statens Serum Institut, Copenhagen, Denmark. Email: Wijhe@ruc.dk. Telephone:

7 +45 46 74 39 34

- 2 born children. Estimates based on extended Cox proportional hazard model with time varying coefficients
- 3 for RSV, non-specific respiratory infections, and maternal smoking; reference group for cohort effects is
- 4 the injury cohort. A) fixed effects, B) time varying effects. Term model: n = 55041, excluded = 4946
- 5 (8.2%); preterm model: n = 6002, excluded = 852 (12.4%). CRF: congenital risk factors; APGAR5:
- 6 APGAR score at 5 minutes; LOS: length of hospital stay; RSV: respiratory syncytial virus; AURTI: acute
- 7 upper respiratory tract infections; LRTI: lower respiratory tract infections.

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#### 1 Response to reviewer comments

2 Reviewer #1:

3 This manuscript by Dr. van Wijhe and colleagues analyzes a large registry based retrospective cohort to

4 examine the impact of an RSV-associated hospitalization in the first 6 months of life on subsequent

5 wheeze and asthma risk. The manuscript is well-written, addresses an important topic and the analysis

6 appears to be well-done. As such, I only have a few comments.

7 1. I presume that some infants were hospitalized more than once, for separate illness episodes,

8 during the first 6 months of life. It is not clear in the manuscript how these infants were handled in the

9 analysis. It seems that these infants should likely be excluded, at least if the primary or secondary ICD

10 codes for 2 or more hospitalizations were respiratory.

11 Answer: Thank you for the comment. In the current analyses children with more than one

12 hospitalization event are indeed included and we use the first hospital event as the start of follow-up.

13 We agree that we should investigate the influence of multiple hospitalizations further, they these

14 children may have a certain predisposition for respiratory problems.

15 We have rerun the analysis including only children with zero or one respiratory hospital event (defined

16 as any J-code in a hospital event) in the first six months of life. In this sub-analysis 6204 children were

17 removed (9.9%). Specifically for RSV 85.3% of children remained within the cohort. In the survival

18 analysis maternal smoking was added as a fixed effect rather than a time varying covariate due to non-

19 convergence. Overall, the confidence intervals are wider and the hazard ratios closer to the null, but

20 they do show similar results and do not impact the conclusions.

The results of this analysis have been added to the supplementary material in Supplementary Figure 6
which shows the result of the survival analysis. We have added information on these extra analyses to
the methods, results, and discussion.

2. It is very difficult to accurately diagnose asthma prior to age 5, yet the median age in this study 25 was 1.2 years and over half of all asthma diagnoses occurred prior to 2 years of age. I am concerned 26 that this is misdiagnosed asthma. Did these children continue to receive asthma diagnoses as they aged? 27 What would the results of the analysis be if the authors looked only at asthma diagnosis after age 5 (and 28 excluded wheeze)? Although the authors do discuss the difference in their study a meta-analysis, it is 29 insufficient and should be discussed in more detail. In particular, how might local coding practices have 30 contributed to the difference in their findings?

31 Answer: There is indeed a possibility of misdiagnosed asthma. We have taken-up the reviewers

32 suggestion and performed another analysis focusing only on asthma diagnoses after age 6. We chose 6

years as this matches with the meta-study we reference. Furthermore, we have looked into how many 1 2 asthma diagnoses children have received during the entire follow-up time (including the period after the 3 first asthma diagnosis). In this analysis we have only looked at asthma and not recurrent wheeze. 4 In total, 5004 children received an asthma diagnosis, of which 3233 (64.61%) only received one diagnosis, a total of 530 received at least one asthma diagnosis after age 6 years, and 211 have received 5 at least 2 asthma diagnoses of which at least one was after 6 years of age. This might indicate some 6 7 misclassification, however, this is not clear from this data alone. Our study concerns hospital admissions, and we unfortunately did not have access to prescription medication or general practitioner data. As a 8 9 considerable part of asthma care is done outside the hospital setting, it is not clear to which extend the 10 children with only one diagnosis, or diagnoses before the age of 6 years, have been cared for outside the

11 hospital setting.

We than reran the survival models, disregarding recurrent wheeze, and only counting asthma diagnoses 12 13 after age 6 years. In this analysis this resulted in 519 asthma events. Due to a lack of events in certain 14 subgroups, term and preterm children were included in the same model. Moreover, proportionality was met in this case, thus time-varying covariates have been left out. The results are presented in 15 Supplementary Figure 7. RSV still is a significant risk factor for term children with a hazard ratio of 1.52 16 17 (95% CI: 1.07-2.15). Non-specific respiratory infections also have a significant HR, while non-RSV LRTI do not show a statistically significant effect. These results indicate that our findings are rather robust, and 18 19 that this extra analysis supports the findings in the meta-study Shi et al: when only including asthma 20 after age 6, RSV remains a significant risk factor.

21 In the results we now write on page 8:

"Our results did not change meaningfully when restricting to birth cohorts with full follow-up, or when
excluding infants with more than one respiratory hospitalization in the first 6 months of life. Restricting
to only asthma after age 6 years as an outcome (thus not considering recurrent wheeze), RSV remains a
significant risk factor with HR of 1.52 (95% CI: 1.07-2.15). See also Supplementary Figures 4-7."
The authors state to partially counter reverse causation bias "However, our results do propose

that LRTI, and less so the specific pathogen, increase the risk for recurrent wheeze or asthma". While
this statement is true, the authors state above that "Interestingly, we found similar risk patterns for RSV,
non-specific respiratory, and LRT hospitalizations, which proposes a possible common pathway or
shared genetic underpinnings for severe infection and asthma. It also suggests that many RSV infections
are missed and coded as nonspecific infections." These two statements seem to be in conflict with one
another. Please reconcile them.

1 Answer: Thank you for the comment, we can see that these statements may read as being in conflict,

- 2 although their intent is the same: the results indicate that LRTI in general seem to increase the risk for
- 3 asthma and wheeze, and RSV is a common cause for LRTI in infants. We have moved the first sentence
- 4 the reviewer mentioned to the second and slightly changed the wording, this now reads as follows:
- 5 "Interestingly, we found similar risk patterns for RSV, non-specific respiratory, and LRTI hospitalizations,
- 6 which proposes a possible common pathway or shared genetic underpinnings for severe infection and
- 7 asthma, but at least suggests that LRTI in general, and perhaps less so the specific pathogen, increase
- 8 the risk for recurrent wheeze or asthma. This finding has also been noted for pneumonia related
- 9 readmission after infant LRTI [21]. Another explanation may be that many RSV infections are missed and
- 10 coded as non-specific infections."
- 11 Reviewer #2:
- 12 General comments:

13 This is a well-written paper, investigating the risk of recurrent wheeze or asthma in children comparing

14 infants admitted in their first six months of life with RSV-associated respiratory illness to those with

- 15 other respiratory infections. Utilizing the Danish national hospital discharge registers of 68,130 infants,
- 16 the authors observe infants with RSV hospitalization are associated with increased risk of recurrent
- 17 wheeze/asthma, especially in the preschool age. The study adds evidence to association between severe
- 18 RSV infections and subsequent respiratory health highlighting potential long-term benefits of RSV
- 19 prevention programs including maternal vaccines and/or long acting RSV monoclonal antibodies.
- 20 Specific comments:
- 21 1. Line 156: Spell out the comparison group.
- 22 Answer: This section now reads: Preterm children tended to have a lower CIRR than term children
- 23 (Supplementary Figure 1, and Supplementary Table 2) and, preterm children were more at risk of
- recurrent wheeze or asthma, with 20.31 cases per 1000 follow-up years versus 11.19 (CIRR: 1.82, 95%
  CI: 1.66-1-82).
- Line 214-216: You may consider referencing this paper which reported similar findings from a
   Kenyan cohort study, https://pubmed.ncbi.nlm.nih.gov/23347702/.
- 28 Answer: Thank you for the suggestion, and indeed this is an interesting read. The paper by Munywoki et
- al focused not so much on asthma or wheeze but on pneumonia related hospital readmissions. It is
- 30 interesting though that they find similar patterns. We have added the following sentence to the
- 31 discussion, as the point the reviewer mentions:
- 32 "This finding has also been noted for pneumonia related readmission after infant LRTI [21]."

- 1 Table 1. Descriptive characteristics of the study populations. Hospitalization events of RSV, injuries,
- 2 AURTI, pneumonia and other respiratory pathogens, LRTI, non-specific respiratory infections and
- 3 pertussis, Denmark 1995-2018. [Online only]

	RSV (N=20920), n (%)	Injuries (N=17380), n (%)	Non-RSV AURTI (N=21624), n (%)	Non-RSV pneumonia and other respiratory pathogens (N=2041), n (%)	Non-RSV LRTI (N=358), n (%) n	Non-specific respiratory infections (N=4390), n (%	Pertussis (N=1417), n ) (%)
Age at inclusion							
0 - <1 months	3516 (16.8)	2406 (13.8)	3184 (14.7)	596 (29.2)	30 (8.4)	725 (16.5)	144 (10.2)
1 <2 months	5953 (28.5)	2318 (13.3)	4885 (22.6)	456 (22.3)	70 (19.6)	849 (19,3)	366 (25.8)
2 - <3 months	4275 (20.4)	2585 (14.9)	4360 (20.2)	336 (16.5)	70 (19.6)	789 (18)	337 (23.8)
3 - <4 months	3036 (14.5)	2972 (17.1)	3418 (15.8)	220 (10.8)	57 (15.9)	651 (14.8)	277 (19.5)
4 - <5 months	2348 (11.2)	3248 (18.7)	3046 (14.1)	229 (11.2)	56 (15.6)	633 (14.4)	182 (12.8)
5 - <6 months	1792 (8.6)	3851 (22.2)	2731 (12.6)	204 (10)	75 (20.9)	743 (16.9)	111 (7.8)
Hospital LOS during inclusion admission							
0 days	2691 (12.9)	14682 (84.5)	) 11414 (52.8	) 343 (16.8)	105 (29.3)	902 (20.5)	158 (11.2)
1 day	2900 (13.9)	1340 (7.7)	6301 (29.1)	297 (14.6)	88 (24.6)	717 (16.3)	193 (13.6)
2-3 days	5216 (24.9)	523 (3.0)	2695 (12.5)	437 (21.4)	67 (18.7)	937 (21.3)	283 (20.0)
4-9 days	8324 (39.8)	493 (2.8)	1059 (4.9)	673 (33.0)	86 (24.0)	1330 (30.3)	541 (38.2)
10+ days	1789 (8.6)	342 (2.0)	155 (0.7)	291 (14.3)	12 (3.4)	504 (11.5)	242 (17.1)
Female	9275 (44.3)	8217 (47.3)	9445 (43.7)	824 (40.4)	133 (37.2)	1766 (40.2)	731 (51.6)

Pre-existing conditions

Preterm (<37 weeks)	2645 (12.6)	1117 (6.4)	1963 (9.1)	350 (17.1)	30 (8.4)	619 (14.1)	130 (9.2)
CF	18 (0.1)	<10	<10	<10	<10	18 (0.4)	<10
BPD	89 (0.4)	32 (0.2)	59 (0.3)	55 (2.7)	<10	79 (1.8)	<10
DS	43 (0.2)	<10	68 (0.3)	<10	<10	36 (0.8)	<10
CHD	690 (3.3)	397 (2.3)	682 (3.2)	154 (7.5)	20 (5.6)	382 (8.7)	33 (2.3)
Maternal smoking							
Non-smoker	15269 (73)	12654 (72.8)	16223 (75)	1512 (74.1)	218 (60.9)	3035 (69.1)	1007 (71.1)
Smoker	3700 (17.7)	2918 (16.8)	3479 (16.1)	341 (16.7)	89 (24.9)	855 (19.5)	231 (16.3)
Unknown	1951 (9.3)	1808 (10.4)	1922 (8.9)	188 (9.2)	51 (14.2)	500 (11.4)	179 (12.6)
APGAR score after 5 minutes							
>7	20136 (96.3)	16723 (96.2)	20915 (96.7)	1938 (95)	342 (95.5)	4181 (95.2)	1377 (97.2)
≤7	353 (1.7)	341 (2)	332 (1.5)	67 (3.3)	<10	115 (2.6)	16 (1.1)
Outcome		$\mathbf{x}$					
Recurrent wheeze	346 (1.7)	122 (0.7)	236 (1.1)	19 (0.9)	<10	89 (2)	<10
Asthma	1952 (9.3)	652 (3.8)	1310 (6.1)	169 (8.3)	47 (13.1)	517 (11.8)	69 (4.9)
Death	49 (0.2)	91 (0.5)	76 (0.4)	32 (1.6)	<10	89 (2)	<10
1 NOTE. RSV: 1	espiratory syncytial	l virus; AURTI:	acute upper res	piratory tract infections; LF	RTI: lower respirator	y tract infections; CF: cystic fibro	osis; BPD: broncho

pulmonary dysplasia; DS: Down Syndrome; CHD: congenital heart disease; LOS: length of stay.

- 1 Table 2. Cumulative incidence rate ratios (CIRR) for recurrent wheeze or asthma for each cohort
- 2 compared to injuries and RSV hospitalizations.

	Person-years follow-up	Total number of recurrent wheeze or asthma	Incidence per 1000 person-year	CIRR, injuries as sreference (95% confidence interval)	CIRR, RSV versus other cohorts (95% confidence interval)
RSV	138847	2298	16.6	2.69 (2.48-2.92)	· P
Non-RSV AURTI	138052	1546	11.2	1.82 (1.67-1.98)	1.48 (1.39-1.58)
Non-RSV pneumonia and other respiratory pathogens	13110 I	188	14.3	2.33 (1.99-2.74)	1.15 (0.99-1.34)
Non-RSV LRT	I 2422	51	21.1	3.43 (2.58-4.55)	0.79 (0.60-1.04)
Non-specific respiratory infections	29103	606	20.8	3.39 (3.05-3.77)	0.79 (0.73-0.87)
Pertussis	10779	77	7.1	1.16 (0.92-1.47)	2.32 (1.85-2.91)
<b>Injuries</b> NOTE. RSV; respi	125923 iratory syncytial c	774 rirus; AURTI: acu	6.1 te upper respiratory tra	<i>Reference</i> act infections; LRTI: lower respi	2.59 (2.48-2.92) ratory tract infections; CIRR: cumulative incidence rat
	ratory syncytlarc	пиз, AUK11. dtu	te upper respiratory the	at meetions, EX11. lower respi	ratory that intections, CIXX. cumulative incluence i

