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

Running title: Infant RSV and risk of wheeze and asthma

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Abstract

Aim: Infant respiratory syncytial virus infection (RSV) has been associated with asthma later in life. We explored the risk of recurrent wheeze or asthma in children with infant RSV-associated hospitalization compared to other respiratory infections.

Methods: We performed a retrospective cohort study using Danish national hospital discharge registers. Infants under 6 months, born between January 1995 and October 2018, and with a RSV hospital admission were compared to infants hospitalized for injuries, non-RSV acute upper respiratory tract infection (AURTI), pneumonia and other respiratory pathogens, non-pathogen coded lower respiratory tract infections (LRTI), pertussis, or non-specific respiratory infections. Infants were followed until recurrent wheeze or asthma diagnosis, death, migration, age 10 years, or study end. We estimated cumulative incidence rate ratios (CIRR) and hazard ratios (HR) adjusted for sex, age at inclusion, hospital length of stay (LOS), maternal smoking, 5 minute APGAR score (APGAR5), prematurity, and congenital risk factors (CRF).

Results: We included 68130 infants, of whom 20920 (30.7%) had RSV hospitalization. The cumulative incidence rate of recurrent wheeze or asthma was 16.6 per 1000 person-years after RSV hospitalization, higher than after injury (CIRR: 2.69; 95% CI: 2.48-2.92), AURTI (1.48; 1.34-1.58), or pertussis (2.32; 1.85-2.91), similar to pneumonia and other respiratory pathogens (1.15; 0.99-1.34) and LRTI (0.79; 0.60-1.04), but lower than non-specific respiratory infections (0.79; 0.73-0.87).

Adjusted HRs for recurrent wheeze or asthma after RSV hospitalization compared to injuries decreased 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, 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.

Keywords: RSV, respiratory syncytial virus, asthma, recurrent wheeze, register study, retrospective cohort study, hospitalizations.

Introduction

RSV causes a common respiratory infection among infants and young children [1, 2], and can present with a broad spectrum of respiratory symptoms. Those under 6 months of age are often most severely 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 infections or asthma [1, 5]. This 'priming' may be due to structural damage in the lungs or alterations in airway epithelial cells and immune development [6]. Specifically, asthma has been associated with earlier 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 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 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.

Materials and methods

Data

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 (MBR), as well as the Civilian Registration System (CRS). The DNPR provides nationwide longitudinal registration of administrative and clinical data on all hospital admissions since 1977. Since 1995 ICD-10 codes are used to classify diagnoses [8]. The CODR contains dates and cause of death for all deaths in Denmark, classified with ICD-10 codes since 1994 [9]. MBR provides information on all births and maternal information collected from antenatal visits and the CRS [10]. The CRS contains basic personal information for all inhabitants [11, 12]. Data was available up to October 10, 2018 and registries were linked with unique personal identifiers.

Study population

Infants born after January 1, 1995 with an inpatient hospitalization or emergency department visit within the first 6 months of life were eligible for inclusion. Included ICD-10 codes are defined below.

Hospitalization definition

We consolidated hospital contacts that occurred on the same or the following day. Such hospitalizations were considered to belong to the same *event*, and we used the first admission date as the start date for all diagnosis during that event.

RSV cohort

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

Comparison cohorts

Six comparison cohorts were defined based on hospital admissions with non-RSV conditions: 1) non-RSV acute upper respiratory tract infections (AURTI; ICD-10 codes: J00, J02-J06); 2) injuries (ICD-10 codes: S and T); 3) pertussis (A37.0, A37.9); 4) non-RSV pneumonia and other respiratory pathogens (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, J40); and 6) non-specific respiratory infections (ICD-10 codes: J12.9, J18, J20.9, J21.9, J22). Each comparison cohort included infants with a hospitalization within the first 6 months of life who did not have an RSV-associated hospitalization during that time. Infants with pre-existing wheeze or asthma or a diagnosis thereof up to 30 days after the inclusion admission were excluded. Patients were assigned to the various cohorts based on the first occurring hospitalization. If during the inclusion admission, multiple 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 influenzae* (J14, J20.1, B96.3, A49.2), other bacterial pneumonia (J15, J17.0) and other pneumonia (J16, J17.2, J17.3, J17.8, J18). The occurrence of pertussis was sufficiently large to be used as a separate cohort. Non-specific respiratory infections formed a separate cohort because RSV infection is often coded as such rather than with RSV-specific ICD-10 codes.

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 ICD-10-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.

Children were followed until the first recorded ICD-10 hospital record with recurrent wheeze, asthma, or 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, whichever came first. Recurrent wheeze was defined as at least two hospital visits where wheeze-specific codes were registered within a year of each other, the second occurrence was used as the end of follow-up. If an asthma-related ICD-10 code was registered in between these two records, the date of the first asthma episode was used as the end point. As only several children were identified with an immunosuppressive condition as a censoring event, this group is not further discussed.

Covariates

We considered the following covariates: maternal smoking, APGAR score at 5 minutes (APGAR5, ≤ 7 or >7), cystic fibrosis (CF), broncho-pulmonary dysplasia (BPD), Down syndrome, congenital heart disease (CHD), prematurity (gestational age <37 weeks), sex, and hospital length of stay (LOS) during the inclusion admission. Maternal smoking was coded as smoker or non-smoker. When it was recorded that a mother stopped smoking during pregnancy, they were grouped with the smokers. An APGAR score under 7 indicates that some additional care is required following birth and it may be a proxy for susceptibility for respiratory conditions and other neonatal outcomes [13]. Due to low numbers, infants with CF, BPD, 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+ 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.

Statistical analysis

We calculated incidence rates per 1000 person-years of follow-up as well as the cumulative incidence rate ratios (CIRR) for each of the cohorts. Associations between risk factors and time to recurrent wheeze or asthma were explored with univariate and multivariate Cox proportional hazard models. Separate baseline hazards were fitted for each inclusion age (by month of age). Similar to previous research, RSV, non-specific respiratory infections, and maternal smoking were added as time-varying coefficients in the multivariate model [14]—included here as step functions for the time intervals 0 to <1 year, 1 to <2 years, 2 to <3 years, 3 to <6 years, and 6 to ≤10 years. As prematurity was a strong risk factor and interacted with several other covariates, we fitted two models, one for term-born children and one for preterm-born children. Only infants with complete information were used in the analysis—univariate analyses revealed 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

before October 10, 2008. Second, we excluded all children with more than one respiratory related hospitalization (ICD-10 J-codes) during the first six months of life. Finally, we restricted the outcomes to asthma after the age of five years only. Statistical analyses were done using R (version 4.1.0).

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.

Results

A total of 68130 infants were included in the study, of whom 20920 (30.7%) were in the RSV cohort—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 pathogens, 13.1% for LRTI, 4.9% for pertussis, 13.8% for unspecific respiratory infections, and 4.5% for the injury cohort. Distributions of covariates are presented in Table 1. Overall, the median follow-up time to recurrent wheeze or asthma diagnosis was 0.9 years (interquartile range: 0.5-1.7) corresponding to a 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.

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

(1.27, 95% CI: 0.96-1.68) tended to an increased risk, and pneumonia and other respiratory pathogens (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).

Hazards

Figure 1 shows the adjusted hazard ratios (HR) (univariate HR and survival curves are presented in 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 <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-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% 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: 1.76-3.47). The pertussis cohort did not show an increased hazard compared to injuries. Comparing the hazard rates for the RSV cohort to the other cohorts (Supplementary Figure 3), we note that, particularly in the first year of life, the hazard rates for the RSV cohort were higher compared to AURTI, pertussis, and pneumonia and other respiratory pathogens, while compared to LRTI and non-specific respiratory infections, the hazard rate for the RSV cohort was consistently lower after the first year of follow-up.

Male sex (term: 1.62, 95% CI: 1.52-1.73; preterm: 1.32, 95% CI: 1.15-1.54) and congenital risk factors (term: 1.77, 95% CI: 1.54-2.03; preterm: 1.74, 95% CI: 1.45-2.08) were independent risk factor for both preterm and term children, while APGAR5 score (term: 1.197, 95% CI: 0.94-1.51; preterm: 1.42, 95% 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 (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% 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.

Discussion

RSV can cause a severe respiratory infection especially among the very young. As many as 4% of all children in the United Kingdom are hospitalized during their first year of life due to RSV infection, and 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 five years of age in Denmark [3]. It has become increasingly clear that respiratory infections in early life may increase the risk of respiratory diseases later in life, including asthma [6]. Using Danish health registers, we found that RSV hospitalization is associated with considerable increased risk for recurrent 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

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, but when restricting the outcomes to only asthma after age 6 years, RSV remained a significant risk factor. Reasons for the apparent disparity with Shi et al, could lie in differences in outcome definitions, local coding practices and included co-variates. Declines in risk after the initial potential causal exposure have been observed before [16-20], and are not surprising, especially when those most at risk of recurrent wheeze or asthma are diagnosed early. Alternatively, diagnoses later in life may be frequently made of outside hospital settings (and, thus, be overlooked in this study), or risks may be most pronounced in 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, 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 risk for recurrent wheeze or asthma. This finding has also been noted for pneumonia related readmission after infant LRTI [21]. Another explanation may be that many RSV infections are missed and coded as non-specific infections. Results from a small study from Denmark point in the same direction, where adjustment for the frequency of respiratory episodes removed the association between particular causative pathogens and asthma in later life [22]. Our associations held when correcting for important covariates. Of special note are preterm-born children, who had generally lower HR. This emphasizes the fact that prematurity itself is a strong risk factor. Besides prematurity, male sex, a high APGAR score, congenital risk factors, maternal smoking, and initial hospital LOS were independent risk factors in our study. The latter is interesting as our estimates suggests that more severe respiratory infection during infancy increases the risk for recurrent wheeze or asthma.

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

We utilized discharge and population registers allowing correction for important confounders, but residual confounding cannot be excluded. The quality of Danish health registers is high. Nevertheless, the validity of our results depends on the diligence of nurses and doctors in noting information [26]. In particular, for maternal smoking approximately 10% of children had missing information. This may have 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 or hospitalization—non-hospital cases are not included. Similarly, the incidence of (less severe) recurrent wheeze or asthma-related respiratory complaints may be higher than shown here. Furthermore, maternal 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 the risk of asthma after RSV infection.

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

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

Conclusion

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

Footnote page

Study Group Members

The RESCEU investigators are as follows:

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

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

Conflicts of interest

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

Previous presentation

This work has previously been presented at the European Society for Clinical Virology 2019 conference, 11-14 September 2019, Copenhagen, Denmark, and the ISIRV Webinar Series, online, on 1 February 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

contains aggregated results and no personal data. The publication is, therefore, not covered by the European General Data Protection Regulation. The results in this manuscript only reflect the authors' views, and the European Commission is not responsible for any use that may be made of the information it contains.

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Figure 1. Multivariate adjusted Hazard Ratios for recurrent wheeze and asthma for preterm- and term-born children. Estimates based on extended Cox proportional hazard model with time varying coefficients for RSV, non-specific respiratory infections, and maternal smoking; reference group for cohort effects is the injury cohort. A) fixed effects, B) time varying effects. Term model: n = 55041, excluded = 4946 (8.2%); preterm model: n = 6002, excluded = 852 (12.4%). CRF: congenital risk factors; APGAR5: APGAR score at 5 minutes; LOS: length of hospital stay; RSV: respiratory syncytial virus; AURTI: acute upper respiratory tract infections; LRTI: lower respiratory tract infections.

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Response to reviewer comments

Reviewer #1:

This manuscript by Dr. van Wijhe and colleagues analyzes a large registry based retrospective cohort to examine the impact of an RSV-associated hospitalization in the first 6 months of life on subsequent wheeze and asthma risk. The manuscript is well-written, addresses an important topic and the analysis appears to be well-done. As such, I only have a few comments.

1. I presume that some infants were hospitalized more than once, for separate illness episodes, during the first 6 months of life. It is not clear in the manuscript how these infants were handled in the analysis. It seems that these infants should likely be excluded, at least if the primary or secondary ICD codes for 2 or more hospitalizations were respiratory.

Answer: Thank you for the comment. In the current analyses children with more than one hospitalization event are indeed included and we use the first hospital event as the start of follow-up. We agree that we should investigate the influence of multiple hospitalizations further, they these children may have a certain predisposition for respiratory problems.

We have rerun the analysis including only children with zero or one respiratory hospital event (defined as any J-code in a hospital event) in the first six months of life. In this sub-analysis 6204 children were removed (9.9%). Specifically for RSV 85.3% of children remained within the cohort. In the survival analysis maternal smoking was added as a fixed effect rather than a time varying covariate due to non-convergence. Overall, the confidence intervals are wider and the hazard ratios closer to the null, but 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 was 1.2 years and over half of all asthma diagnoses occurred prior to 2 years of age. I am concerned that this is misdiagnosed asthma. Did these children continue to receive asthma diagnoses as they aged? What would the results of the analysis be if the authors looked only at asthma diagnosis after age 5 (and excluded wheeze)? Although the authors do discuss the difference in their study a meta-analysis, it is insufficient and should be discussed in more detail. In particular, how might local coding practices have contributed to the difference in their findings?

Answer: There is indeed a possibility of misdiagnosed asthma. We have taken-up the reviewers 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 asthma diagnoses children have received during the entire follow-up time (including the period after the first asthma diagnosis). In this analysis we have only looked at asthma and not recurrent wheeze.
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 at least 2 asthma diagnoses of which at least one was after 6 years of age. This might indicate some 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 considerable part of asthma care is done outside the hospital setting, it is not clear to which extend the children with only one diagnosis, or diagnoses before the age of 6 years, have been cared for outside the hospital setting.
We than reran the survival models, disregarding recurrent wheeze, and only counting asthma diagnoses after age 6 years. In this analysis this resulted in 519 asthma events. Due to a lack of events in certain 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 Supplementary Figure 7. RSV still is a significant risk factor for term children with a hazard ratio of 1.52 (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 that this extra analysis supports the findings in the meta-study Shi et al: when only including asthma after age 6, RSV remains a significant risk factor.
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."

3. 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.

Answer: Thank you for the comment, we can see that these statements may read as being in conflict, although their intent is the same: the results indicate that LRTI in general seem to increase the risk for asthma and wheeze, and RSV is a common cause for LRTI in infants. We have moved the first sentence the reviewer mentioned to the second and slightly changed the wording, this now reads as follows: "Interestingly, we found similar risk patterns for RSV, non-specific respiratory, and LRTI hospitalizations, 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 risk for recurrent wheeze or asthma. This finding has also been noted for pneumonia related readmission after infant LRTI [21]. Another explanation may be that many RSV infections are missed and coded as non-specific infections."

Reviewer #2:

General comments:

This is a well-written paper, investigating the risk of recurrent wheeze or asthma in children comparing infants admitted in their first six months of life with RSV-associated respiratory illness to those with other respiratory infections. Utilizing the Danish national hospital discharge registers of 68,130 infants, the authors observe infants with RSV hospitalization are associated with increased risk of recurrent wheeze/asthma, especially in the preschool age. The study adds evidence to association between severe RSV infections and subsequent respiratory health highlighting potential long-term benefits of RSV prevention programs including maternal vaccines and/or long acting RSV monoclonal antibodies.

Specific comments:

1. Line 156: Spell out the comparison group.

Answer: This section now reads: 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).

2. 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/.

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 interesting though that they find similar patterns. We have added the following sentence to the discussion, as the point the reviewer mentions:

"This finding has also been noted for pneumonia related readmission after infant LRTI [21]."

Table 1. Descriptive characteristics of the study populations. Hospitalization events of RSV, injuries, AURTI, pneumonia and other respiratory pathogens, LRTI, non-specific respiratory infections and 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 (%)	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							
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

NOTE. RSV: respiratory syncytial virus; AURTI: acute upper respiratory tract infections; LRTI: lower respiratory tract infections; CF: cystic fibrosis; BPD: broncho pulmonary dysplasia; DS: Down Syndrome; CHD: congenital heart disease; LOS: length of stay.

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

	Person-years follow-up	Total number of recurrent wheeze or asthma	Incidence per 1000 person-years	CIRR, injuries as reference (95% confidence interval)	CIRR, RSV versus other cohorts (95% confidence interval)
RSV	138847	2298	16.6	2.69 (2.48-2.92)	-
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	188	14.3	2.33 (1.99-2.74)	1.15 (0.99-1.34)
Non-RSV LRTI	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)
Injuries	125923	774	6.1	*Reference*	2.59 (2.48-2.92)

NOTE. RSV: respiratory syncytial cirus; AURTI: acute upper respiratory tract infections; LRTI: lower respiratory tract infections; CIRR: cumulative incidence rate ratio.

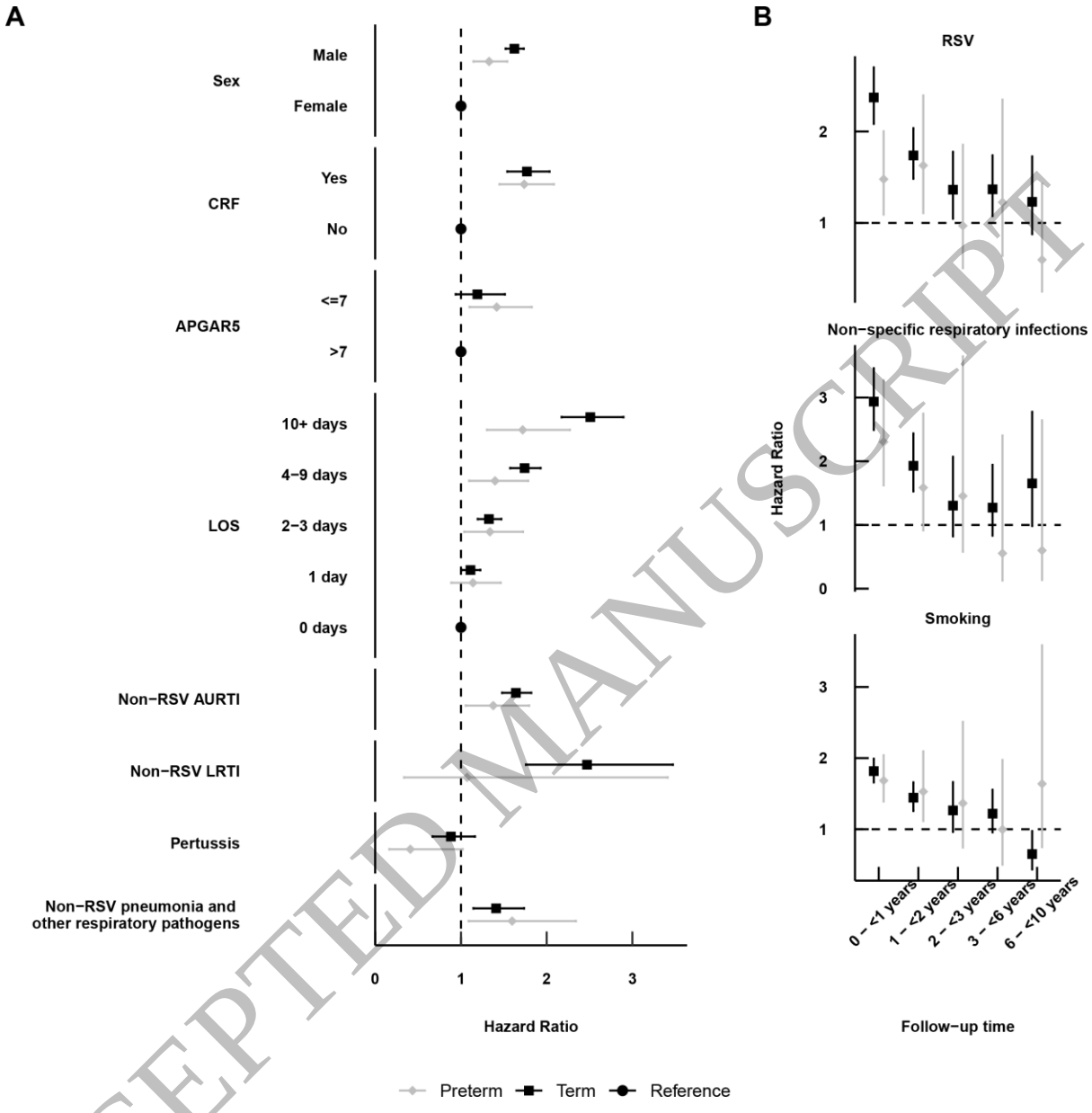

Figure 1
159x160 mm (0.7 x DPI)