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

Running title: early-life RSV and subsequent asthma

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Abstract

Background

Early-life severe respiratory syncytial virus (RSV) infection has been associated with subsequent risk of asthma and recurrent wheeze. However, changes in the association over time and the interaction effect of the age at first RSV infection are less well understood. We aimed to assess the time-varying association between RSV and subsequent asthma and wheeze admission and explore how the association was affected by the age at RSV infection.

Methods

We retrospectively followed up a cohort of 23,365 children for a median of 6.9 years using Scottish health databases. Children who were born between 2001 and 2013 and had RSV-associated respiratory tract infection (RTI) admissions under 2 years were in the exposed group; those with unintentional accident admissions under 2 years comprised the control group. The Cox proportional-hazards model was used to report adjusted hazard ratios (HR) of RSV admissions on subsequent asthma and wheeze admissions. We did subgroup analyses by

follow-up years. We also explored how this association was affected by the age at first RSV admission.

Results

The association was strongest in the first 2 years of follow-up and decreased over time. The association persisted for 6 years in children whose first RSV-RTI admission occurred at 6-23 months of age, with an adjusted HR of 3.9 (95%CI 3.1-4.9) for the first 2 years, 2.3 (95%CI 1.6-3.2) for 2-<4 years, and 1.9 (95%CI 1.2-2.9) for 4-<6 years of follow up. In contrast, the association was only significant for the first 2 years after first RSV-RTI admissions occurring at 0-5 months.

Discussions

We found a more persistent association for subsequent asthma and wheeze in children whose first severe RSV infection occurred at 6-23 months compared to those whose first severe RSV infection occurred at 0-6 months. This provides new evidence for further assessment of the association and RSV intervention programmes.

Key words: severe RSV infections; asthma; wheeze; time since RSV infection; age at first RSV infection

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Introduction

Respiratory syncytial virus (RSV) causes substantial respiratory tract infection (RTI) hospital admissions in young children globally and in Europe [1-3]. In addition to causing mild to severe respiratory infections, early-life RSV infections have been linked with subsequent recurrent wheeze and asthma in later childhood and adolescence [4, 5]. The association is of great interest as it may indicate an additional benefit of RSV preventive interventions in young children to reduce the risk of subsequent development of asthma and wheeze [6]. This in turn may influence the cost effectiveness of future novel interventions and the level of priority of the interventions.

The association between early-life RSV infections and subsequent asthma and wheeze has been reported in many observational studies, but most of the studies are either small or have not adjusted for potential confounders [4], thus limiting the quality of the evidence. Two randomised trials have assessed the effect of anti-RSV monoclonal antibody in term and preterm infants on subsequent wheeze and asthma, and found no significant difference in the incidence of medically attended wheezing or asthma between the placebo and treatment groups at 1-3 years and 6 years [7, 8]. However, both trials were only powered to detect a large difference (about 4% and 10%) in the asthma and wheeze incidence between groups. In trials assessing such an indirect effect (i.e. reducing subsequent asthma through preventing RSV infections), a difference of this magnitude seems difficult to occur because the difference is a product of severe RSV-RTI incidence, the effect of RSV prevention on RSV-RTI, and the difference in asthma and wheeze incidence between children with severe RSV-RTI and those without [9].

The focus has long been RSV infections in early life – in the first, second, and third year of age. In this narrow age band, there may be a time window for viral respiratory infections to be more strongly linked to subsequent asthma and wheezing illnesses than other times [10, 11]. However, limited evidence exists as to how the age at first severe RSV infections influences the subsequent risk of asthma and wheeze [10, 11]. The influence of age at first severe RSV infection is of relevance to planning of future RSV vaccination programmes.

In this study, we assessed the association between early-life RSV and subsequent asthma and wheeze using the national population-based linked Scottish healthcare databases. The large size of this study offers an opportunity to explore how the age at first severe RSV infection influences the association with subsequent asthma and wheeze. The availability of information on environmental and host factors during the prenatal and neonatal period also allows for adequate adjustment for these factors. This study could help identify the age band at which severe RSV infections are more closely linked to subsequent development of asthma and wheeze, thus providing new evidence for future assessment of the association in trials, and to inform development of RSV intervention strategies.

Methods

Study design and data sources

We conducted a retrospective cohort analysis using Scottish Morbidity Record (SMR01) and Maternity Inpatient and Day Case Record (SMR02). SMR01 includes all inpatient and day cases at hospitals in Scotland; SMR02 includes day cases or inpatient maternity care in Scotland, collecting information on pregnancy and childbirth with high completeness [3, 12, 13]. In this

study, records between January 2001 and December 2016 from the two databases were linked using a unique patient identifier.

For the exposed group, we included children who were born between January 2001 and December 2013, and had RSV-RTI admissions based on International Classification of Diseases, Tenth Edition (ICD-10) in the first 2 years of life. Briefly, RSV-RTI was defined as an admission with both RTI as well as RSV diagnostic codes in any of main and another five diagnosis fields (Appendix p1)[3]. For the control group, we included children who were born during the same period, and had unintentional accident admissions in any diagnosis fields (V01-99, X00-59, X85-99, Y00-09, Y35-99) when aged below 2 years. The first admission was the index admission when a child was admitted with RSV-RTI or unintentional accident on two or more occasions. Follow-up was defined as the time from the 5th week after the index admission to the occurrence of the outcome or end of the study (52nd week 2016 by the International Organization for Standardization week date standard), whichever came first. We defined the 'washout' period of 4 weeks to exclude the bias due to the primary RSV infection episode's associated wheezing [14]. The outcome was first asthma or wheeze admission (i.e. J45, J46 and R06.2) in any diagnosis fields. We included wheeze in the main analysis as it is one of the key clinical features associated with asthma in young children [15]. Children were excluded in these analyses if they had asthma or wheeze admissions before the follow-up.

Statistical analysis

The association was analysed using the Cox proportional hazards regression model. Since the proportional hazards assumption did not hold for the RSV exposure variable, we used an extended Cox model with time-dependent coefficient [16-18]. We split the follow-up period

into 0-<2 years, 2-<4 years, 4-<6 years and >=6 years, and conducted subgroup analyses for each of these groups and reported hazard ratios (HRs) of the RSV-RTI group compared to the control group to facilitate interpretation.

We considered the following potential confounding variables based on previous literature [4, 19]: age at index admission (0-5 months; 6-23 months), gender, quintiles of Scottish index of multiple deprivation, maternal smoking status during pregnancy (yes; no), mode of delivery (caesarean; vaginal), gestational age (<37 weeks; >=37 weeks), the number of births at this pregnancy (1; >1), the presence of congenital diseases (yes; no), and the length of hospital stay for the index admission (0-3 days; >=4 days). We included the length of hospital stay because severity of RSV infection might be associated with subsequent risk of asthma [14]. We also considered birth weight, APGAR score at 5 minutes, admission to neonatal unit after birth, the number of previous pregnancies, and breastfeeding status at the mother's discharge. The covariates were selected following a stepwise procedure by the Akaike Information Criterion [20]. In exploratory analyses, we tested for any interactions between RSV infection and other covariates. Since a significant interaction was found between age at exposure (the index admission) and the exposure status ($P<0.05$), we conducted separate analyses for children who had the index admission at 0-5 months and 6-23 months of age. Children with missing data on any covariates were excluded in the main analysis. We reported first asthma and wheeze admission rates per 1,000 child-years, and estimated 95% confidence intervals (CI) by assuming a Poisson distribution for the number of admissions. We reported unadjusted and adjusted HR estimates and 95%CI from Cox models. In the stratified analyses by follow-up time, we also

reported multiplicity-adjusted p-values using the Bonferroni method and reported the multiplicity-adjusted CI [21].

In sensitivity analyses, we reported unadjusted HRs of RSV-RTI after including children with incomplete data on the covariates. We excluded wheeze and assessed the association for asthma admission alone. To assess how the estimates were affected by the children most susceptible to respiratory morbidity, we excluded children who had >=3 episodes of RTI admission at 0-23 months of age [22]. We compared RSV-RTI to RTI with RSV not being coded as the causal pathogen by ICD-10 (Appendix pp5-6). Statistical analyses were done using R (version 3.6.1).

Results

Overall study population and characteristics

Between January 2001 and December 2013, there were 17,642 children having an RSV-RTI admission, and 8,779 children having an unintentional accident admission under 2 years of age (Figure 1). We excluded 486 children who were admitted with a diagnosis of asthma or wheeze before the follow-up started, and 2,570 children who had incomplete data on the covariates. The remaining children with complete data (23,365) were included in the main analyses. The median (IQR) follow-up time was 6.9 (IQR 3.3-10.9) years, and altogether there were 166,232.3 child-years of follow-up. There were 1,418 first asthma and wheeze admissions, representing an average rate of 8.5/1,000 child-years. The distribution of characteristics between the exposed and control group is in Appendix pp3-4.

Primary outcomes

During the whole follow-up period, the first asthma and wheeze admission rate in the exposed group was about 2.2 times higher than the control group (10.5 versus 4.7 per 1,000 child-years). Outcome-free survival curves over time are in Appendix p2. HR estimates remained similar after adjusting for confounders (Table 1). By follow-up periods, the adjusted HR was 3.6 (95%CI 2.9-4.5) during the first 2 years of follow-up, 1.8 (95%CI 1.3-2.4) for 2-<4 years, 1.4 (95%CI 0.9-2.0) for 4-<6 years, and 1.4 (95%CI 0.9-2.0) for 6 or more years of follow-up. The significant association remained in the first 4 years of follow-up after the Bonferroni adjustment (Table 1).

Subgroup analyses by age at first RSV-RTI admission

Subgroup analyses by age at first RSV-RTI admissions showed similar results that the HR estimate was highest during the first 2 years of follow-up. Children whose first RSV-RTI admission occurred at 0-5 months of age only showed a significantly greater association compared to the control group during the first 2 years of follow-up (adjusted HR 3.1, 95%CI 2.0-4.7); the estimates became insignificant during later follow-up periods. In contrast, children whose first RSV-RTI admission occurred at 6-23 months of age showed a significantly greater association during the first 6 years of follow-up compared to the control group, with an adjusted HR estimate of 3.9 (95%CI 3.1-4.9) for the first 2 years of follow-up, 2.3 (95%CI 1.6-3.2) for 2-<4 years, and 1.9 (95%CI 1.2-2.9) for 4-<6 years. After 6 years of follow-up, the adjusted HR estimate was 1.5 (95%CI 1.0-2.5) with a p-value of 0.06 for the 6-23 months age group.

Sensitivity analyses

In sensitivity analyses, the HR estimates were comparable after including children with incomplete data on the covariates, excluding children admitted with RTI on three or more

169 occasions, or excluding wheezing admissions (Appendix p5). The adjusted HR estimate of RSV-
170 RTI was 1.2 (95%CI 1.1-1.3) compared to non RSV-RTI group (appendix p6).

171 ## Discussion

172 Results from this national population-based study showed that children who had RSV-RTI
173 admissions in the first two years of life had an increased risk of subsequent asthma and wheeze
174 admission compared to those who had accident admissions at the same age after adjustment
175 for several prenatal and neonatal factors. The association decreased over time, and was found
176 to be statistically significant in the first 4 years after the RSV-RTI admission. The association was
177 affected by the age at first RSV-RTI admission; the association persisted until 6 years after the
178 first RSV-RTI admission that occurred at 6-23 months, while persisted only until 2 years after
179 the first RSV-RTI admission that occurred at 0-5 months.

180 The attenuation of the association over follow-up time in our study is consistent with previous
181 findings that the strength of the association decreased with age in systematic reviews,
182 prospective studies [4, 23-28], and another large retrospective study [29] given the similar
183 baseline age of included children. The decreasing association over time may be a reflection of
184 the gradual change in the effect of the first RSV-RTI admission on subsequent asthma and
185 wheeze admission. Another possible explanation is that children are gradually exposed to other
186 unobserved risk factors for asthma and wheeze over time, confounding the association for RSV
187 [24]. The diagnosis of asthma in young children (e.g. <5 years) is based on recognising a
188 characteristic pattern of signs and symptoms (including wheeze) in the absence of an
189 alternative explanation [15, 30]. Given the challenges in asthma diagnosis in young children, it
190 may be also possible that some children who were under 3 years in the first 2 years of the

191 follow-up had wheezing exacerbated by viral RTIs. HRs remained similar after excluding wheeze
192 admissions (Appendix p5).
193 Contrary to our statistically non-significant results after 6 years of follow-up, an earlier study
194 including Scottish children born between 1996 and 2011 found that the asthma admission rate
195 remained significantly higher in children who had RSV admissions at 0-23 months than those
196 without until 18 years old [19]. In contrast to our analysis, the study included all episodes of
197 asthma admissions instead of only the first asthma admission, and did not adjust for
198 confounders.
199 Our results show that the subsequent risk of asthma and wheeze admission persisted for a
200 longer time among children whose first RSV-RTI admission occurred at 6-23 months than those
201 had a severe infection at 0-5 months. The COAST study found a similar pattern for both RSV and
202 rhinovirus infections, and showed that compared to infections during infancy, having RSV or
203 rhinovirus wheezing illnesses at the second and third year of age was associated with a more
204 profound increase in asthma risk at 6 years [11]. Similarly, an Australian cohort study found that
205 the asthma admission rate was 2-7 times higher among children hospitalised with RSV disease
206 at 6-23 months compared to those hospitalised with RSV disease at 0-5 months [10].
207 Interestingly, a study assessing changes in the lung function between different wheezing
208 phenotypes found that low levels of lung function were observed in the first few months after
209 birth in transient early wheezers, while the loss of lung function in persistent wheezers
210 occurred during preschool years [31, 32]. These findings agree with our age-at-exposure-based
211 subgroup results, and indicate that age at first RSV-RTI admission may influence the effect of
212 the RSV infection on subsequent risk of asthma and wheeze.

213 The similar HR estimates after excluding children who had >=3 episodes of RTI admission in the
214 first 2 years of life suggest that our estimates are not driven by the group of children most
215 susceptible to respiratory morbidity. This is different from another study, which found that the
216 association between RSV-RTIs in the first 3 years of life and asthma by age 7 years became
217 insignificant after adjusting for the number of respiratory infections [33]. The difference has
218 several possible explanations. In the study by Bønnelykke et al, about 90% of the children had
219 respiratory episodes, so their control group consisted mainly of children with respiratory
220 episodes due to different pathogens. Our analyses comparing RSV-RTI admission to non RSV-RTI
221 also showed little difference in the risk of subsequent asthma and wheeze admission (Appendix
222 p6), consistent with results from a previous study [14]. Second, we studied severe RSV-RTIs
223 (versus any respiratory episodes). Our multivariate analysis showed that increased severity of
224 RSV-RTI (i.e. longer hospital stay) was associated with higher risk of subsequent wheeze and
225 asthma admission. Similar association between disease severity and recurrent wheezing has
226 also been found in previous literature [34, 35].
227 There are some limitations in our study. First, we used ICD-10 codes to identify RSV-RTI, wheeze
228 and asthma admissions. Coding practices and viral testing practices may affect the
229 ascertainment in both exposure and outcome. The potential biases in the outcome have been
230 discussed above. For exposure, based on laboratory records from 2009 onwards, the total
231 counts and age distribution of RSV-coded admissions were comparable to that of RSV-
232 confirmed admissions as described in our previous study [3]. But we were unable to assess bias
233 in testing as we did not have access to laboratory-confirmed RSV-negative records, and there
234 was a large proportion of RTI admissions with no causal pathogens coded [3]. In particular, this

could have affected our analyses comparing to non RSV-RTI admission group. We were also unable to assess possible bias due to rhinovirus co-infection; rhinovirus infection is also associated with subsequent risk of wheezing illness [11]. About 10% of children had incomplete data on covariates, but this did not seem to affect the estimates as the unadjusted HR estimates remained similar when these children were included. The timing of inclusion into this study did not seem to affect the HR estimates as the rate ratio between the comparison groups during the first half of the study period was similar to that during the second half (2.1 during 2001-2007 versus 2.3 during 2008-2013). We did not have access to complete death or immigration records. Only <1% of the children died at RSV-RTI and accident admission, and HR estimates remained similar after excluding them (appendix p6). Deaths from other causes and immigration are likely to be non-differential between the exposed and the control group, thus our HR estimates might have been biased towards the null. We only had access to hospital records and were unable to investigate RSV lower respiratory infection episodes, asthma or wheeze episodes causing outpatient visits. The incidence of asthma and wheeze associated with RSV-RTI is likely to be larger than our estimates. Lastly, this was an observational study and, therefore, causal inference cannot be made. A causal association may be better determined in RSV intervention trials which are adequately powered to answer this research question.

We excluded children having asthma or wheeze admissions before the follow-up in our analysis to ensure the temporal sequence, and adjusted for prenatal and neonatal factors to reduce confounding and bias. The estimates could have been affected by other unobserved confounders (e.g. familial predisposition) [36]. It has been of debate whether RSV infection

causes subsequent asthma and wheeze by modifying airway and immune development, contributing to inception of asthma and wheezing illnesses [31, 36, 37], or RSV infection acts as a predisposition marker for some host factors (e.g. familial predisposition), which leads to later development of asthma and wheeze [14]. Information on family history of asthma was unavailable in our study, and a recently published systematic review found that the odds ratio for asthma and wheeze with severe RSV infections was lower (2.5, 95%CI 1.2-4.9 based on 52 data points) when combining studies that adjusted for familial predisposition compared to pooling studies that did not make the adjustment (4.2, 95%CI 2.4-7.4 based on 77 data points) [5]. However, given the weak association between family history of asthma / atopy and RSV-LRTI (pooled odds ratio of 1.5, 95% CI 1.2–1.9) estimated in a systematic review [38], familial predisposition seems unlikely to fully explain the link between early-life severe RSV-RTI and subsequent asthma and wheeze.

Our results have confirmed that RSV-RTI admission in the first 2 years of life is associated with subsequent asthma and wheeze admission after adjustment for some prenatal and neonatal factors. The difference in the subsequent risk by age at first severe RSV-RTI suggests that RSV intervention targeting children older than 6 months may have a higher impact on subsequent severe asthma compared to targeting infants under 6 months. Future research is needed to confirm this association in different populations. It also merits exploration how the risk of subsequent asthma and wheeze associated with RSV changes after the implementation of RSV maternal vaccination.

Footnote page

Study Group Members

The RESCEU investigators are as follows: Xin Wang, Rachel M Reeves, You Li, Harry Campbell, Harish Nair (University of Edinburgh, Scotland); Maarten van Wijhe, Thea Kølsen Fischer, Lone Simonsen, Ramona Trebbien (Statens Serum Institut, Denmark); Sabine Tong (Sanofi); Mathieu Bangert, Clarisse Demont (Sanofi Pasteur); Toni Lehtonen (Finnish Institute for Health and Welfare, Turku University Hospital, Finland); Terho Heikkinen (University of Turku and Turku University Hospital, Finland); Anne Teirlinck, Michiel van Boven, Wim van der Hoek, Nicoline van der Maas, Adam Meijer (National Institute for Public Health and the Environment (RIVM), Netherlands); Liliana Vazquez Fernandez, Håkon Bøas, Terese Bekkevold, Elmira Flem (Norwegian Institute of Public Health, Norway); Luca Stona, Irene Speltra, Carlo Giaquinto (Penta, Italy); Arnaud Cheret (Janssen); Amanda Leach, Sonia Stoszek (GlaxoSmithKline); Philippe Beutels (University of Antwerp, Belgium); Louis Bont (University Medical Centre Utrecht, Netherlands); Andrew Pollard (University of Oxford, UK); Peter Openshaw (Imperial College, UK); Michael Abram (AstraZeneca); Kena Swanson (Pfizer); Brian Rosen (Novavax, Rockville, MD); Eva Molero (Synapse Research Management Partners).

Supplementary Data

Supplementary materials are available at The Journal of Infectious Diseases online. 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.

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Potential conflicts of interest

HC reports grants from European Union Innovative Medicines Initiative, grants and personal fees from World Health Organization; and grants from Bill and Melinda Gates Foundation during the conduct of the study. HN reports grants from World Health Organization, grants and personal fees from Sanofi Pasteur, personal fees from Janssen, personal fees from Bill and Melinda Gates Foundation, personal fees from Reviral, personal fees from AbbVie, grants from National institute of health research outside the submitted work. YL reports grants from World Health Organization, grants from Wellcome Trust outside the submitted work. All other authors report no potential conflicts.

Table 1. Rates and hazard ratios (HR) of first asthma and wheeze admission in children with RSV-RTI under 2 years and in the control group (23,365 children).

Time (years since exposure)	Rates per 1,000 child-years (95%CI) for the control group	Rates per 1,000 child-years (95%CI) for the RSV group	Unadjusted HR (95%CI)	Adjusted HR (95%CI)[1]	Adjusted HR (multiplicity-adjusted CI)[2]	Multiplicity-adjusted p-value
<2 years	7.0 (5.7-8.4)	22.2 (20.6-24.0)	3.2 (2.6-3.9)	3.6 (2.9-4.5)	3.6 (2.8-4.8)	<0.001
2-<4 years	5.6 (4.-7.1)	10.2 (9.0-11.5)	1.8 (1.4-2.4)	1.8 (1.3-2.4)	1.8 (1.2-2.6)	<0.001
4-<6 years	4.6 (3.4-6.2)	6.8 (5.6-8.0)	1.5 (1.0-2.1)	1.4 (0.9-2.0)	1.4 (0.8-2.2)	0.40
6 years or more	2.4 (1.7-3.2)	3.1 (2.5-3.7)	1.3 (0.9-1.8)	1.4 (0.9-2.0)	1.4 (0.8-2.2)	0.48

Table 2. Rates and hazard ratios (HR) of first asthma and wheeze admission in children with RSV-RTI admission at 0-5 months (11,295 children) and 6-23 months of age (12,070 children).

Time (years since exposure)	Rates per 1,000 child-years (95%CI) for the control group	Rates per 1,000 child-years (95%CI) for the RSV group	Unadjusted HR (95%CI)	Adjusted HR (95%CI)[3]	P-value from multivariate analysis
Exposure at 0-5 months of age					
<2 years	5.9 (3.7-8.9)	16.7 (14.8-18.7)	2.9 (1.9-4.4)	3.1 (2.0-4.7)	<0.001
2-<4 years	8.1 (5.2-11.9)	9.8 (8.2-11.5)	1.2 (0.8-1.9)	1.2 (0.8-1.9)	0.37
4-<6 years	6.9 (4.0-11.0)	6.5 (5.1-8.1)	1.0 (0.6-1.6)	1.0 (0.6-1.8)	0.92
6 years or more	3.0 (1.7-4.9)	2.8 (2.1-3.6)	0.9 (0.5-1.6)	1.0 (0.6-1.8)	0.98
Exposure at 6-23 months of age					
<2 years	7.3 (5.8-9.1)	30.7 (27.6-34.0)	4.2 (3.3-5.3)	3.9 (3.1-4.9)	<0.001
2-<4 years	4.8 (3.5-6.5)	10.8 (8.8-13.1)	2.3 (1.6-3.2)	2.3 (1.6-3.2)	<0.001
4-<6 years	3.8 (2.5-5.5)	7.2 (5.4-9.4)	1.9 (1.2-3.0)	1.9 (1.2-2.9)	0.01
6 years or more	2.1 (1.4-3.0)	3.5 (2.6-4.6)	1.6 (1.0-2.6)	1.5 (1.0-2.5)	0.065

1 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.

2 Adjusting for gender, 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.

3 Adjusting for gender, 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.

References

1. Li Y, Johnson EK, Shi T, Campbell H, Chaves SS, Commaille-Chapus C, et al. National burden estimates of hospitalisations for acute lower respiratory infections due to respiratory syncytial virus in young children in 2019 among 58 countries: a modelling study. Lancet Respir Med. 2021;9(2):175-85. Epub 2020/09/25. doi: 10.1016/s2213-2600(20)30322-2. PubMed PMID: 32971018.

2. Shi T, McAllister DA, O'Brien KL, Simoes EAF, Madhi SA, Gessner BD, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet. 2017;390(10098):946-58. Epub 2017/07/12. doi: 10.1016/s0140-6736(17)30938-8. PubMed PMID: 28689664; PubMed Central PMCID: PMCPMC5592248.

3. Reeves RM, van Wijhe M, Tong S, Lehtonen T, Stona L, Teirlinck AC, et al. Respiratory Syncytial Virus-Associated Hospital Admissions in Children Younger Than 5 Years in 7 European Countries Using Routinely Collected Datasets. J Infect Dis. 2020;222(Supplement_7):S599-s605. Epub 2020/08/21. doi: 10.1093/infdis/jiaa360. PubMed PMID: 32815542.

4. Shi T, Ooi Y, Zaw EM, Utjesanovic N, Campbell H, Cunningham S, et al. Association Between Respiratory Syncytial Virus-Associated Acute Lower Respiratory Infection in Early Life and Recurrent Wheeze and Asthma in Later Childhood. The Journal of Infectious Diseases. 2019. doi: 10.1093/infdis/jiz311.

5. Brunwasser SM, Snyder BM, Driscoll AJ, Fell DB, Savitz DA, Feikin DR, et al. Assessing the strength of evidence for a causal effect of respiratory syncytial virus lower respiratory tract

infections on subsequent wheezing illness: a systematic review and meta-analysis. The Lancet Respiratory Medicine. 2020;8(8):795-806. doi: 10.1016/S2213-2600(20)30109-0.

6. Bem RA. Is there a causal relationship between respiratory syncytial virus lower respiratory tract infection and chronic wheezing? The Lancet Respiratory Medicine. 2020;8(8):749-50. doi: 10.1016/S2213-2600(20)30118-1.

7. O'Brien KL, Chandran A, Weatherholtz R, Jafri HS, Griffin MP, Bellamy T, et al. Efficacy of motavizumab for the prevention of respiratory syncytial virus disease in healthy Native American infants: a phase 3 randomised double-blind placebo-controlled trial. Lancet Infect Dis. 2015;15(12):1398-408. Epub 2015/10/30. doi: 10.1016/s1473-3099(15)00247-9. PubMed PMID: 26511956.

8. Scheltema NM, Nibbelke EE, Pouw J, Blanken MO, Rovers MM, Naaktgeboren CA, et al. Respiratory syncytial virus prevention and asthma in healthy preterm infants: a randomised controlled trial. Lancet Respir Med. 2018;6(4):257-64. Epub 2018/03/04. doi: 10.1016/s2213-2600(18)30055-9. PubMed PMID: 29500030.

9. Riddell CA, Bhat N, Bont LJ, Dupont WD, Feikin DR, Fell DB, et al. Informing randomized clinical trials of respiratory syncytial virus vaccination during pregnancy to prevent recurrent childhood wheezing: A sample size analysis. Vaccine. 2018;36(52):8100-9. Epub 2018/11/27. doi: 10.1016/j.vaccine.2018.10.041. PubMed PMID: 30473186; PubMed Central PMCID: PMCPMC6288067.

10. Homaira N, Briggs N, Oei J-L, Hilder L, Bajuk B, Jaffe A, et al. Association of Age at First Severe Respiratory Syncytial Virus Disease With Subsequent Risk of Severe Asthma: A

Population-Based Cohort Study. The Journal of Infectious Diseases. 2018;220(4):550-6. doi: 10.1093/infdis/jiy671.

11. Jackson DJ, Gangnon RE, Evans MD, Roberg KA, Anderson EL, Pappas TE, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. American journal of respiratory and critical care medicine. 2008;178(7):667-72. Epub 2008/06/19. doi: 10.1164/rccm.200802-309OC. PubMed PMID: 18565953.

12. Information Services Division Scotland, Public Health Scotland. National data catalogue: General Acute Inpatient and Day Case - Scottish Morbidity Record (SMR01) 2020 [updated 20 Nov 2020; cited 2021 20 Jan]. Available from: https://www.ndc.scot.nhs.uk/National-Datasets/data.asp?SubID=5.

13. Information Services Division Scotland, Public Health Scotland. Births in Scottish Hospitals: Technical Report. 2019.

14. Driscoll AJ, Arshad SH, Bont L, Brunwasser SM, Cherian T, Englund JA, et al. Does respiratory syncytial virus lower respiratory illness in early life cause recurrent wheeze of early childhood and asthma? Critical review of the evidence and guidance for future studies from a World Health Organization-sponsored meeting. Vaccine. 2020;38(11):2435-48. Epub 2020/01/20. doi: 10.1016/j.vaccine.2020.01.020. PubMed PMID: 31974017.

15. Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma: a national clinical guideline. 2014.

16. GRAMBSCH PM, THERNEAU TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika. 1994;81(3):515-26. doi: 10.1093/biomet/81.3.515.

17. Therneau TM. A Package for Survival Analysis in R. 2020.

18. Max Gordon, Reinhard Seifert. timeSplitter: A Function For Splitting A Time According To Time Periods. 2020.

19. Coutts J, Fullarton J, Morris C, Grubb E, Buchan S, Rodgers-Gray B, et al. Association between respiratory syncytial virus hospitalization in infancy and childhood asthma. Pediatric Pulmonology. 2020;55(5):1104-10. doi: 10.1002/ppul.24676.

20. Dirk F. Moore. Applied Survival Analysis Using R. Switzerland: Springer International Publishing; 2016. 226 p.

21. Bland JM, Altman DG. Multiple significance tests: the Bonferroni method. BMJ. 1995;310(6973):170. doi: 10.1136/bmj.310.6973.170.

22. Moore HC, Hall GL, de Klerk N. Infant respiratory infections and later respiratory hospitalisation in childhood. European Respiratory Journal. 2015;46(5):1334-41. doi: 10.1183/13993003.00587-2015.

23. Pérez-Yarza EG, Moreno A, Lázaro P, Mejías A, Ramilo O. The association between respiratory syncytial virus infection and the development of childhood asthma: a systematic review of the literature. Pediatr Infect Dis J. 2007;26(8):733-9. Epub 2007/09/13. doi: 10.1097/INF.0b013e3180618c42. PubMed PMID: 17848887.

24. Régnier SA, Huels J. Association between respiratory syncytial virus hospitalizations in infants and respiratory sequelae: systematic review and meta-analysis. Pediatr Infect Dis J. 2013;32(8):820-6. Epub 2013/03/23. doi: 10.1097/INF.0b013e31829061e8. PubMed PMID: 23518824.

25. Stein RT, Sherrill D, Morgan WJ, Holberg CJ, Halonen M, Taussig LM, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. Lancet. 1999;354(9178):541-5. Epub 1999/09/02. doi: 10.1016/s0140-6736(98)10321-5. PubMed PMID: 10470697.

26. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. Am J Respir Crit Care Med. 2000;161(5):1501-7. Epub 2000/05/12. doi: 10.1164/ajrccm.161.5.9906076. PubMed PMID: 10806145.

27. Sigurs N, Gustafsson PM, Bjarnason R, Lundberg F, Schmidt S, Sigurbergsson F, et al. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. Am J Respir Crit Care Med. 2005;171(2):137-41. Epub 2004/11/02. doi: 10.1164/rccm.200406-730OC. PubMed PMID: 15516534.

28. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B, Björkstén B. Asthma and immunoglobulin E antibodies after respiratory syncytial virus bronchiolitis: a prospective cohort study with matched controls. Pediatrics. 1995;95(4):500-5. Epub 1995/04/01. PubMed PMID: 7700748.

29. Mejias A, Wu B, Tandon N, Chow W, Varma R, Franco E, et al. Risk of childhood wheeze and asthma after respiratory syncytial virus infection in full-term infants. Pediatr Allergy Immunol. 2020;31(1):47-56. Epub 2019/10/01. doi: 10.1111/pai.13131. PubMed PMID: 31566811.

30. Ducharme FM, Tse SM, Chauhan B. Diagnosis, management, and prognosis of preschool wheeze. The Lancet. 2014;383(9928):1593-604. doi: https://doi.org/10.1016/S0140-6736(14)60615-2.

31. Jackson DJ. Early-life viral infections and the development of asthma: a target for asthma prevention? Curr Opin Allergy Clin Immunol. 2014;14(2):131-6. doi: 10.1097/ACI.0000000000000047. PubMed PMID: 24569522.

32. Morgan WJ, Stern DA, Sherrill DL, Guerra S, Holberg CJ, Guilbert TW, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. American journal of respiratory and critical care medicine. 2005;172(10):1253-8. Epub 2005/08/18. doi: 10.1164/rccm.200504-525OC. PubMed PMID: 16109980.

33. Bønnelykke K, Vissing NH, Sevelsted A, Johnston SL, Bisgaard H. Association between respiratory infections in early life and later asthma is independent of virus type. J Allergy Clin Immunol. 2015;136(1):81-6.e4. Epub 2015/04/26. doi: 10.1016/j.jaci.2015.02.024. PubMed PMID: 25910716; PubMed Central PMCID: PMCPMC7112259.

34. Escobar GJ, Masaquel AS, Li SX, Walsh EM, Kipnis P. Persistent recurring wheezing in the fifth year of life after laboratory-confirmed, medically attended respiratory syncytial virus infection in infancy. BMC Pediatr. 2013;13:97-. doi: 10.1186/1471-2431-13-97. PubMed PMID: 23782528.

35. Al-Shawwa B., Al-Huniti N., Abu-Hasan M. Respiratory Syncytial Virus Bronchiolitis and Risk of Subsequent Wheezing: A Matter of Severity. Pediatric Asthma, Allergy & Immunology. 2006;19(1):26-30. doi: 10.1089/pai.2006.19.26.

443 36. Jartti T, Gern JE. Role of viral infections in the development and exacerbation of asthma
444 in children. Journal of Allergy and Clinical Immunology. 2017;140(4):895-906. doi:
445 https://doi.org/10.1016/j.jaci.2017.08.003.
446 37. Piedimonte G. Respiratory syncytial virus and asthma: speed-dating or long-term
447 relationship? Curr Opin Pediatr. 2013;25(3):344-9. Epub 2013/05/10. doi:
448 10.1097/MOP.0b013e328360bd2e. PubMed PMID: 23657245; PubMed Central PMCID:
449 PMCPMC3889210.
450 38. Shi T, Balsells E, Wastnedge E, Singleton R, Rasmussen ZA, Zar HJ, et al. Risk factors for
451 respiratory syncytial virus associated with acute lower respiratory infection in children under
452 five years: Systematic review and meta-analysis. J Glob Health. 2015;5(2):020416-. doi:
453 10.7189/jogh.05.020416. PubMed PMID: 26682048.
454