Infant respiratory infections and later respiratory hospitalisation in childhood

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ABSTRACT Acute respiratory infections (ARI) cause significant morbidity in infancy. We sought to quantify the relationship between ARI and development of respiratory morbidity in early childhood.

Population-based longitudinal hospitalisation data were linked to perinatal, birth and death records for 145 580 Western Australian children from 1997 to 2002. We conducted Cox regression with sensitivity analyses to quantify the risk of recurrent ARI in infancy for respiratory hospitalisation after the age of 3 years.

ARI in infancy was significantly related to respiratory hospitalisation before (hazard ratio (HR) 3.5, 95% CI 3.1–3.8) and after (HR 3.0, 95% CI 2.6–3.4) adjusting for known risk factors including maternal smoking during pregnancy, season of birth, delivery mode and gestational age. We noted a dose response with the number and length of infant ARI hospitalisations and increasing risk with no effect modification by gestational age. Results were similar when later respiratory hospitalisations were restricted to asthma hospitalisations only.

Recurrent hospitalisations for ARI in infancy significantly increase the risk of respiratory morbidity and asthma requiring hospitalisation after the age of 3 years in a dose-response fashion. The increase in relative risk is not modified by gestational age. Efforts to reduce the occurrence of infant ARI are likely to have significant public health benefits.

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Introduction

Acute respiratory infections (ARI) such as bronchiolitis, whooping cough, pneumonia and influenza are a major cause of morbidity in young children, with hospitalisation rates in industrialised countries ranging from 31–63/1000 in non-Indigenous children [1, 2] to 116–427/1000 in Indigenous children [2, 3]. Those at highest risk of respiratory infections include boys, autumn-born infants, those born prematurely, low socioeconomic status, those whose mothers smoked during pregnancy and those with birth defects such as congenital heart disease and chronic lung disease [4, 5].

Numerous studies have identified associations between early ARI and subsequent asthma [6–11], but, with the exception of an analysis of a population cohort of Danish twins [10] these have been smaller prospective studies of 140–259 patients recruited and prospectively followed, with 55–100% having a family history of atopy and/or asthma. There has also been debate whether the relationship between ARI and asthma is causal or purely association, and it has been suggested that the severity of early ARI may have a part to play in the development of asthma [12]. In addition, some of the risk factors for asthma and later respiratory morbidity are the same as the risk factors for ARI, such as Caesarean delivery [13–15] and preterm birth [16, 17]. Large total-population based studies on otherwise healthy populations adjusting for known risk factors may improve our understanding of these relationships through the conduct of subgroup and sensitivity analyses. Linked administrative data provides this opportunity [18].

The aim of this study was to use total-population based data on an otherwise healthy population of children to assess the relationship between early ARI requiring hospitalisation and subsequent hospitalisation for respiratory causes including asthma, and investigate any effect modification with other known risk factors for respiratory morbidity.

Methods

Setting and data sources

The Western Australian Data Linkage System (WADLS) is a unique system that brings together data from numerous administrative and health datasets, many of which have 100% coverage of data on the total population [18]. Using the WADLS, we designed a retrospective cohort study of 245 249 singleton live births in Western Australia between 1996 and 2005. Full details of data cleaning are found elsewhere [4, 19]. In brief, our study consisted of longitudinal data from the Midwives Notification System, Birth Register, Death Register, Hospital Morbidity Database System and the Western Australian Register for Developmental Anomalies.

These datasets contain information on maternal and infant perinatal factors such as age, sex, birthweight, gestational age, pregnancy and labour complications, Aboriginal status of the mother and infant and some maternal conditions including asthma and smoking during pregnancy. Percentage of optimal birthweight, a measure taking into account gestational duration, fetal sex, maternal age, maternal height and parity [20] was used as a measure of fetal growth and appropriateness of fetal growth and grouped into three categories (low <85%, normal 85–114% or high ⩾115%). Socioeconomic status was derived from the Socio-Economic Index for Areas (SEIFA) [21], using postcode of residence at the time of birth. SEIFA is comprised of several indices, the main index being that of relative disadvantage, which is derived from low income, low educational attainment, high unemployment and jobs in unskilled occupations. SEIFA scores are measured at the collection district level, the smallest unit available for population-based analyses, and grouped into quantiles. Birth defects recorded on the Western Australia Register for Developmental Anomalies were defined as the presence of one or more structural or functional anomalies that are present at conception or occur before the end of pregnancy and diagnosed by 6 years of age [22]. The use of these population-based linked data was approved by the Western Australian Department of Health Human Research Ethics Committee and the Western Australian Aboriginal Health Ethics Committee.

Hospitalisation measures

International Classification of Diseases, 10th revision (ICD-10) diagnosis codes were used to identify hospitalisations of interest. Early ARI was defined as hospitalisation in the first year of life with one of the following diagnoses listed in either the principal or 20 additional diagnosis codes: acute bronchiolitis (J21), pneumonia (J12–J18, B59, B05.2, B37.1 or B01.2), influenza (J10 or J11), whooping cough (A37), acute bronchitis (J20), unspecified acute lower respiratory infection (J22), asthma (J45) and symptom of wheeze (R06.2). Asthma diagnosis codes were included to allow for likely misclassification of ARI in the first year of life. The primary outcome variable was hospitalisation for asthma after the age of 3 years. However, in order to account for diagnostic shifts between bronchiolitis and asthma, as reported in this population [23] and elsewhere [24, 25], a respiratory morbidity indicator was developed that included any mention of the following ICD-10 diagnoses in either the principal or additional diagnosis fields: asthma (J45), acute bronchiolitis (J21), unspecified acute lower respiratory infection (J22) and symptom of wheeze (R06.2). We

assessed any changes in the composition of the ARI and respiratory hospitalisation categories over time. To test the robustness of these categories, we conducted sensitivity analyses. We restricted our exposure variable, ARI, to only hospitalisations in infancy coded for either bronchiolitis, pneumonia, influenza, whooping cough, bronchitis and unspecified acute lower respiratory infection and restricted our outcome variable to only hospitalisations after the age of 3 years with a diagnosis code of asthma.

Statistical analysis

We used Cox regression to estimate hazard ratios (HRs) where the outcome was time to first respiratory hospitalisation after the age of 3 years and the primary predictor was hospitalisation for ARI in the first year of life. Initial models included the primary predictor as a dichotomous variable (any ARI admission in the first year of life *versus* no admission). Further models then examined the number of ARI admissions (0, 1, 2 or ⩾3) in the first year of life as a categorical variable. Our sensitivity analyses included four models with the different combinations of exposure and outcome. Maternal smoking during pregnancy was not recorded in 1996 so those births were removed from the analysis (n=24 671), as were those who died before the age of 3 years (n=1133) and those births after 2002 that did not reach the age of 3 years at the end of the study period (December 31, 2005). Therefore, 145 580 children were available for analysis. The time variable for the Cox regression was calculated as the minimum of time to first respiratory morbidity hospitalisation, time to death or time to end of the study period, after the age of 3 years. As the end of the study period was the end of 2005, the maximum age of children at the end of follow-up was 10 years, with the median follow-up time being 6.5 years.

Models were adjusted for sex, gestational age (categorised as <32 weeks, 32–36 weeks and >36 weeks), maternal asthma during pregnancy, maternal smoking during pregnancy, number of previous pregnancies, maternal age, mode of delivery, season of birth, Aboriginal status, presence of a major birth defect, percentage of optimal birthweight, SEIFA quantiles and infant's year of birth as a continuous variable. Further models were stratified according to gestational age. If any records had missing data for these covariates, they were dropped from the fully adjusted models. Effect modification was assessed by interaction models with *a priori* selected predictors and the primary predictor of number of ARI admissions in infancy. Likelihood ratio (LR) tests were conducted to determine whether interaction models with the interaction terms, main effects and all other confounding factors were a better fit to the data than the models with only main effects and confounding factors. As a marker of severity, total length of stay in hospital in the first year of life for ARI was included in the model as a continuous variable on a log scale. Admissions for ARI were then segregated into those that had a length of stay ⩾3 days (severe ARI) and those that stayed in hospital <3 days (less severe ARI). We present unadjusted and adjusted hazard ratios and 95% confidence intervals for each of the Cox models using robust standard errors. The proportionality assumption in the final models was tested by assessing log–log plots to visually assess whether the curves were parallel and formally tested using Schoenfeld residuals. Using the *punafcc* function in STATA (StataCorp, College Station, TX, USA), we calculated the population attributable fraction and 95% confidence intervals for selected predictor variables in our final models. All data cleaning and analyses were conducted in IBM SPSS Statistics (version 22; Armonk, NY, USA) and STATA version 13.

Results

From the cohort of 145 580 children available for analysis, 7911 (5.4%) had at least one ARI hospitalisation in the first year of life with a median length of stay of 3 days. For those that had at least one ARI hospitalisation, the median number of ARI admissions in the first year of life was 1 (mean 1.33, range 1–17). The most common principal diagnosis in the ARI category was bronchiolitis (62%) followed by pneumonia (10%). Slightly fewer than 3000 children (2.1%) had a hospitalisation for respiratory causes after the age of 3 years. The most common principal diagnosis after the age of 3 years was asthma (71%), followed by unspecified acute lower respiratory infection (11%). The composition of the ARI and respiratory hospitalisation categories did not change over the duration of the study (data not shown).

Hospitalisation for ARI in the first 12 months of life was significantly associated with respiratory hospitalisation after the age of 3 years, before and after adjusting for known perinatal risk factors (HR 3.5, 95% CI 3.1–3.8; adjusted HR 3.0, 95% CI 2.6–3.4). 27% of observations had missing covariate data and were consequently dropped from the fully adjusted models. The magnitude of the hazard ratio for ARI was significantly larger than the hazard ratios for all the other risk factors (table 1). There was a dose–response effect with the number of ARI hospitalisations in the first year of life (fig. 1 and table 2) in the direction of a stronger risk of respiratory hospitalisation after 3 years with increasing number of ARI admissions in infancy.

Restricting the exposure to infant hospitalisations coded for acute lower respiratory infections only (removing asthma and wheeze) did not change the hazard ratios (table 3). Restricting the outcome to hospitalisations after the age of 3 years coded for asthma only slightly lowered the magnitude of the

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TABLE 1 Hospitalisations for acute respiratory infection (ARI) before the age of 12 months, maternal and infant characteristics and subsequent risk of respiratory morbidity after the age of 3 years

	Respiratory morbidity ⩾3 years		Unadjusted	Adjusted
	Yes	No		
ARI <12 months				
Yes	484 (6.1)	7427 (93.9)	3.46 (3.14–3.81)	2.97 (2.62–3.37)
No	2500 (1.8)	135 169 (98.2)	Ref.	Ref.
Sex				
Male	1806 (2.4)	72 611 (97.6)	1.47 (1.37–1.58)	1.33 (1.22–1.45)
Female	1178 (1.6)	69 985 (98.3)	Ref.	Ref.
Gestational age weeks				
<32	69 (6.5)	988 (93.5)	3.28 (2.58–4.17)	2.19 (1.62–2.98)
32–36	208 (2.5)	8074 (97.5)	1.28 (1.11–1.48)	1.03 (0.86–1.23)
>36	2691 (2.0)	132 587 (98.0)	Ref.	Ref.
Maternal asthma				
Yes	357 (2.8)	12 563 (97.2)	1.56 (1.40–1.74)	1.43 (1.27–1.62)
No	2623 (2.0)	129 606 (98.0)	Ref.	Ref.
Maternal smoking				
Yes	643 (2.3)	27 063 (97.7)	1.26 (1.15–1.38)	1.05 (0.94–1.17)
No	1810 (1.8)	98 464 (98.2)	Ref.	Ref.
Maternal age years				
<20	227 (2.7)	8243 (97.3)	1.35 (1.15–1.59)	1.07 (0.85–1.35)
20–24	585 (2.3)	24 152 (97.7)	1.15 (1.02–1.31)	1.05 (0.89–1.24)
25–29	933 (2.1)	44 155 (97.9)	1.02 (0.91–1.14)	0.96 (0.83–1.10)
30–34	793 (1.8)	43 184 (98.2)	0.91 (0.81–1.03)	0.92 (0.80–1.06)
⩾35	445 (2.0)	22 400 (98.1)	Ref.	Ref.
Previous pregnancies n				
0	845 (2.0)	41 045 (98.0)	Ref.	Ref.
1	853 (1.9)	43 858 (98.1)	0.94 (0.86–1.04)	0.95 (0.84–1.07)
2	572 (2.1)	27 373 (98.0)	1.01 (0.91–1.13)	1.06 (0.93–1.22)
3	710 (2.3)	29 893 (97.7)	1.14 (1.04–1.27)	1.06 (0.92–1.22)
Mode of delivery				
Vaginal	1829 (2.0)	88 052 (98.0)	Ref.	Ref.
Instrumental	383 (2.0)	18 998 (98.2)	0.96 (0.86–1.07)	1.02 (0.88–1.17)
Elective Caesarean	408 (2.0)	19 708 (98.0)	1.06 (0.95–1.18)	1.08 (0.95–1.23)
Emergency Caesarean	360 (2.3)	15 411 (97.7)	1.19 (1.07–1.34)	1.14 (0.99–1.31)
Percentage of optimal birthweight				
Low <85%	385 (2.6)	14 510 (97.4)	1.29 (1.16–1.44)	1.07 (0.94–1.23)
Normal 85–114%	2127 (2.0)	104 633 (98.0)	Ref.	Ref.
High >114%	277 (2.1)	12 980 (97.9)	1.06 (0.93–1.19)	1.01 (0.88–1.17)
SEIFA quantile [#]				
91–100%	150 (1.6)	9419 (98.4)	Ref.	Ref.
76–90%	329 (1.8)	17 568 (98.2)	1.17 (0.96–1.42)	1.15 (0.92–1.44)
26–75%	1280 (2.0)	63 601 (98.0)	1.23 (1.04–1.45)	1.23 (1.01–1.51)
11–25%	484 (2.1)	22 560 (97.9)	1.33 (1.11–1.60)	1.19 (0.95–1.48)
0–10%	370 (2.7)	13 586 (97.4)	1.69 (1.39–2.04)	1.36 (1.08–1.72)
Season of birth				
Summer	698 (2.0)	34 748 (98.0)	1.05 (0.95–1.17)	1.02 (0.90–1.17)
Autumn	882 (2.4)	36 374 (97.6)	1.23 (1.11–1.37)	1.17 (1.03–1.33)
Winter	794 (2.2)	35 505 (97.8)	1.21 (1.09–1.35)	1.13 (1.00–1.29)
Spring	610 (1.7)	35 969 (98.3)	Ref.	Ref.
Aboriginal status				
Aboriginal	341 (3.3)	10 059 (96.7)	1.73 (1.54–1.93)	1.18 (1.00–1.39)
Non-Aboriginal	2643 (2.0)	132 467 (98.0)	Ref.	Ref.
Birth defect				
Yes	290 (3.6)	7859 (96.4)	1.79 (1.58–2.02)	1.48 (1.27–1.73)
No	2694 (2.0)	134 737 (98.0)	Ref.	Ref.
Year of infant's birth [¶]			1.07 (1.04–1.10)	1.08 (1.03–1.12)

Data are presented as n (%) or hazard ratio (95% CI), unless otherwise stated. SEIFA: Socio-Economic Index for Area; Ref.: reference. [#]: 91–100% represents those that are least disadvantaged while 0–10% represents those that are the most disadvantaged; [¶]: modelled as a continuous variable.

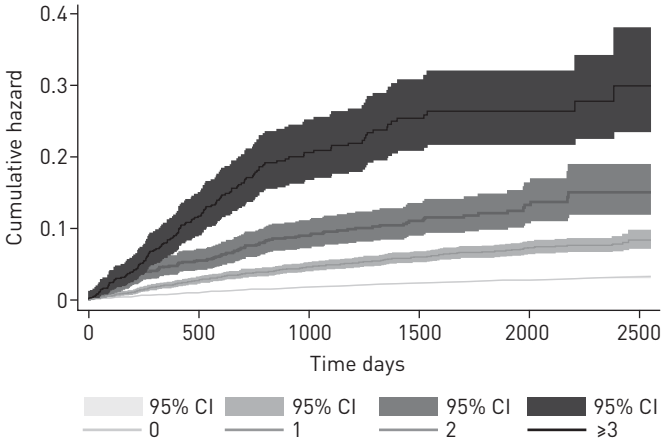

FIGURE 1 Cumulative hazard function of respiratory hospitalisation after the age of 3 years for increasing number of hospitalisations for acute respiratory infection before the age of 12 months.

hazard ratios, but did not result in significant changes (table 3). A similar phenomenon was noticed when the restricted exposure was assessed as a categorical variable to assess the dose–response relationship (data not shown). As the hazard ratios did not alter significantly, we used the larger ARI exposure category and hospitalisation for respiratory causes outcome category for all further models.

To assess whether the relationship between early ARI and subsequent respiratory hospitalisation risk was modified by infant or maternal characteristics, interactions with selected predictors and the number of ARI hospitalisations in infancy were included one at time into the model. The model did not show any effect modification with gestational age category (LR Chi-squared 6 degrees of freedom 4.30, p=0.64), mode of delivery (LR Chi-squared 9 degrees of freedom 6.49, p=0.69), season of birth (LR Chi-squared 9 degrees of freedom 2.47, p=0.98) and maternal smoking during pregnancy (LR Chi-squared 3 degrees of freedom 2.56, p=0.46). Table 3 presents a stratified analysis across gestational age groups. The dose–response relationship between risk of respiratory hospitalisation after the age of 3 years and recurrent ARI in infancy remained in all gestational age categories (table 4).

We further examined the effect of severity of ARI by investigating the total length of hospital stay for ARI in infancy. Including this in the model on a continuous log scale reduced the magnitude of the hazard ratios for frequency of ARI hospitalisations, but significantly improved the model (LR Chi-squared 1 degree of freedom 9.52, p=0.002; online supplementary table S1, model 1) indicating that the longer a child stays in hospital, the stronger the risk of later respiratory morbidity. The model was not significantly improved when recurrent ARI hospitalisations were separated into severe and less severe (LR Chi-squared 3 degrees of freedom 4.46, p=0.22; online supplementary table S1, model 2). The population attributable fraction of ARI in infancy was calculated as 10.7% (95% CI 10.0–11.4%), significantly higher than other risk factors (*e.g.* maternal smoking 1.2 (-1.5–3.8)%; or <32 weeks gestation 1.3 (0.9–1.6)%). Log–log plots were assessed for all the final models and parallel curves for all levels of the primary predictor variable were observed (p>0.1), indicating that the proportionality assumption was upheld.

TABLE 2 Number of hospitalisations for acute respiratory infection before the age of 12 months and subsequent risk of respiratory hospitalisation after the age of 3 years

	Respiratory hospitalisation ⩾3 years		Unadjusted	Adjusted
	Yes	No		
0	2500 (1.8)	135 169 (98.2)	Ref.	Ref.
1	296 (4.7)	5990 (95.3)	2.65 (2.35–2.99)	2.47 (2.13–2.87)
2	95 (8.6)	1006 (91.4)	4.91 (4.00–6.04)	3.67 (2.78–4.84)
⩾3	93 (17.8)	431 (82.2)	10.48 (8.51–12.90)	8.57 (6.51–11.28)

Data are presented as n (%) or hazard ratio (95% CI), unless otherwise stated. Hazard ratios adjusted for sex, gestational age, maternal asthma during pregnancy, maternal smoking during pregnancy, mode of delivery, maternal age, number of previous pregnancies, percentage of optimal birthweight, Socio-Economic Index for Area quantile, season of birth, Aboriginal status, presence of any birth defect and year of infant's birth. Ref.: reference.

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TABLE 3 Sensitivity analysis of exposure and outcome measures

	Exposure (<12 months)		Outcome (⩾3 years)		Unadjusted	Adjusted
	Description	Subjects	Description	Subjects		
Model 1: full model as per tables 1 and 2	ARI	12385	Respiratory hospitalisation	3775	3.46 (3.14–3.81)	2.97 (2.62–3.37)
Model 2: restricted exposure	Respiratory infection only	11504	Respiratory hospitalisation	3775	3.48 (3.15–3.84)	2.97 (2.60–3.38)
Model 3: restricted outcome	ARI	12385	Asthma only	3121	3.13 (2.81–3.50)	2.92 (2.54–3.38)
Model 4: restricted exposure and outcome	Respiratory infection only	11504	Asthma only	3121	3.09 (2.75–3.46)	2.87 (2.48–3.34)

Data are presented as n or hazard ratio (95% CI), unless otherwise stated. Hazard ratios adjusted for sex, gestational age, maternal asthma during pregnancy, maternal smoking during pregnancy, mode of delivery, maternal age, number of previous pregnancies, percentage of optimal birthweight, Socio-Economic Index for Area quantile, season of birth, Aboriginal status, presence of any birth defect and year of birth of infant. ARI: acute respiratory infection.

Discussion

In a population-based cohort of children, we have shown that the strongest predictor of respiratory morbidity requiring hospitalisation after the age of 3 years is having one or more hospitalisations for ARI during infancy. This relationship remains after adjusting for several known risk factors for respiratory morbidity and is not modified by gestational age, maternal smoking during pregnancy, season of birth or mode of delivery. We also noted a clear dose response in that the more admissions for ARI in infancy, the stronger the association with hospitalisation for respiratory causes after 3 years.

We did not see any effect modification of *a priori* selected risk factors and the relationship of early ARI and later respiratory hospitalisations. Previous reports have suggested that infants with a predisposition to early viral infection, such as being born premature, are at a higher risk of recurrent severe respiratory infections requiring hospitalisation and later development of asthma [12, 26]. For confirmation of this association, we would expect to see some effect modification by gestational age, whereby those infants born prematurely would have a higher risk of later respiratory hospitalisation given early respiratory morbidity. In this analysis the overlapping hazard ratios across the various gestational age categories suggests the relationship of early

TABLE 4 Number of hospitalisations for acute respiratory infection before the age of 12 months and subsequent risk of respiratory hospitalisation after age 3 years in separate models according to gestational age

	Respiratory hospitalisation ⩾3 years		Adjusted
	Yes	No	
Model 1: gestational age <32 weeks			
0	34 (4.3)	749 (95.7)	Ref.
1	14 (8.1)	158 (91.9)	1.74 (0.76–3.98)
2	7 (12.5)	49 (87.5)	2.14 (0.58–7.91)
⩾3	14 (30.4)	32 (69.6)	6.89 (2.72–17.43)
Model 2: gestational age 32–36 weeks			
0	153 (2.1)	7277 (97.9)	Ref.
1	31 (4.9)	596 (95.1)	2.11 (1.27–3.49)
2	11 (7.7)	132 (92.3)	2.77 (1.17–6.52)
⩾3	13 (15.9)	69 (84.2)	7.34 (3.30–16.32)
Model 3: gestational age >36 weeks			
0	2301 (1.8)	126291 (98.2)	Ref.
1	249 (4.6)	5176 (95.4)	2.54 (2.17–2.98)
2	77 (8.7)	805 (91.3)	3.97 (2.95–5.34)
⩾3	64 (16.9)	315 (83.1)	8.94 (6.50–12.29)

Data are presented as n (%) or hazard ratio (95% CI), unless otherwise stated. Hazard ratios adjusted for sex, maternal asthma during pregnancy, maternal smoking during pregnancy, mode of delivery, maternal age, number of previous pregnancies, percentage of optimal birthweight, Socio-Economic Index for Area score, season of birth, Aboriginal status, presence of any birth defect and year of infant's birth. Ref.: reference.

and recurrent ARI with increased risk of later respiratory hospitalisation and asthma is similar in preterm infants and late term infants. MONTGOMERY *et al.* [27] conducted a similar analysis of a large Swedish population cohort. The authors did report effect modification with gestational age with the risk of subsequent asthma after 5 years, but only in those born at <28 weeks gestation and they did not explore recurrent ARI in infancy.

Previous studies have focused on a single pathogen such as respiratory syncytial virus (RSV) [9] or rhinovirus [28] or a specific clinical condition, such as bronchiolitis, and the relationship with subsequent asthma. However, in our previous analyses of linked administrative laboratory and hospitalisation data, we have shown that in the first 2 years of life, various respiratory pathogens are detected across a range of ARI diagnostic categories and not all possible causative pathogens, such as rhinovirus, are routinely tested for [29]. In addition, for the purpose of quantifying the risk of early respiratory infection on later respiratory hospitalisations and identifying potential effect modifiers in that relationship, the causative viral pathogen of the early infection is not of critical importance, as the clinical presentation of respiratory viruses in infancy is likely to be similar. Therefore, it is perhaps more useful to look at a combination of conditions in the first 12 months of life to indicate ARI, which is a strength of our analysis.

We did not have data on some additional known risk factors for later respiratory hospitalisations such as childcare attendance, duration of breastfeeding, family history of asthma and allergies and immunisation status, which is a limitation to our study. In addition, we currently do not have access to any data at the primary healthcare level on ARI and respiratory morbidity episodes not requiring hospitalisation, therefore our findings are based on the severe end of the clinical spectrum in terms of respiratory morbidity. Nonetheless, using longitudinal population-based data we have shown an independent significant dose response in the frequency of hospitalisation for ARI in infancy and risk of later respiratory morbidity and asthma requiring hospitalisation. There is growing debate around whether the relationship between early respiratory infection, particularly viral infection, and later development of respiratory morbidity or asthma is causal [12]. Causation has been demonstrated in mouse models with long-term impairment of lung function following early influenza infection [30]. Our retrospective observational study cannot demonstrate causation, rather the association between the exposure and outcome, where in this case, exposure may be just early signs of the disease (or its exacerbations). However, to assist in the reduction of later respiratory hospitalisations and asthma in childhood, attention should be focused on modifiable and preventable risk factors to target the recurrence of early ARI. Our earlier work reported on population-attributable fractions to hospitalisations for acute lower respiratory infection in children before the age of 2 years using this same dataset [4]. We identified some modifiable factors, such as elective Caeasarean, maternal smoking in pregnancy and teenage pregnancy, that could be targeted for public health campaigns. We also identified factors that in isolation are not easily modifiable, such as male sex, autumn-born babies and multiple previous pregnancies, but highlight susceptible subgroups to specifically target for disease intervention measures such as increased hand hygiene measures, timeliness of standard vaccinations and passive immunisation. In this current analysis, we have shown that the population-attributable fraction of ARI in infancy for later respiratory hospitalisation is ~11%, far greater than for other modifiable factors such as maternal smoking in pregnancy and preterm birth (~1%).

We have shown that RSV is the most commonly identified pathogen found in children hospitalised with respiratory infections in infancy [29]. Prophlyaxis with RSV monoclonal antibody, palivizumab, administered as monthly intramuscular infections, has been shown to be effective in reducing RSV-confirmed hospitalisations in high-risk populations and a reduction in wheezing days during the first year of life [31–33]. We have shown here that length of stay in hospital during infancy was a significant predictor to later respiratory morbidity, indicating that the more severe the initial ARI, the stronger the risk of later respiratory morbidity requiring hospitalisation. While this adds to the evidence that severity of early ARI may have an impact on later lung development [12], it also highlights the importance of reducing severity of ARI in the first year of life. Further studies are now needed to potentially understand the full effect of prophylaxis on preventing respiratory morbidity.

In conclusion, using population-based longitudinal data we have shown that the strongest predictor of respiratory morbidity and asthma requiring hospitalisation after 3 years of age is recurrent hospitalisation for ARI in infancy regardless of gestational age, season of birth, mode of delivery and maternal smoking during pregnancy. While these factors do not impact on the relationship between early infection and later morbidity, they are known risk factors for early infection. If prevention efforts are focused on early infection, the benefit is likely to extend to later morbidity.

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