# Respiratory infections in preterm infants and subsequent asthma: a cohort study

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# Respiratory infections in preterm infants and subsequent asthma: a cohort study

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## ABSTRACT

**Objectives** To investigate if gestational age modifies the association of airway infections that result in hospital admission during the first year after birth, with subsequent asthma risk after age 5 years.

**Setting** Hospital inpatients and a general population comparison group in Sweden followed for subsequent diagnoses in primary and secondary care.

**Participants** National registers identified 42,334 children admitted to hospital for respiratory infection in their first year after birth during 1981-1995, individually matched with 211,594 children not admitted to hospital for infection during their first year.

**Primary outcome** Asthma diagnoses and prescribed asthma treatments after age 5 years identified through registers.

**Results** Cox regression was used to identify a hazard ratio (and 95% confidence interval) of 1.51 (1.47 to 1.51) for the association of respiratory infection before one year of age with asthma after age 5 years, after adjustment for sex, gestational age, chronic lung disease, maternal asthma and maternal smoking. When stratified by gestational age (and with additional adjustment for birth weight), there is statistically significant effect modification by gestational age, with the highest magnitude asthma risk among those born with a gestational age of less than 28 weeks, producing an adjusted hazard ratio of 2.22 (1.59 to 3.09). This higher magnitude asthma risk persisted until after age 10 years, but differences in risk by gestational age were less pronounced for asthma after age 16 years.

**Conclusions** Extremely preterm infants are most likely to have chronic respiratory sequelae following respiratory infections in early life.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

**Strengths**

- The vast majority of infants admitted to hospital with airway infections in their first year after birth in Sweden during the study period will have been identified.
- The use of prospectively recorded national register data allow for longitudinal analysis of asthma risk, with follow-up into early adulthood.

**Limitations**

- The infections are incompletely characterised, particularly during earlier years.
- Asthma was identified based on inpatient diagnoses and prescribed medication, but it was not possible to confirm the accuracy of diagnoses.

## INTRODUCTION

Respiratory infection in the first year after birth[1-3], and preterm birth[4-7] are both markers of subsequent asthma risk. How the interrelationship of these factors relates to persistent respiratory disease is incompletely understood.

The lungs of preterm infants are underdeveloped with immature airways and the association of prematurity with later respiratory disease indicates asthma's developmental origin[8-10]. Respiratory infections requiring hospital admission during the first year after birth may signal susceptibility to asthma or may be causally implicated in asthma aetiology; and these explanations are not necessarily mutually exclusive. Respiratory infection *epidemics* that produce infections among infants are associated with a raised risk of persistent respiratory disease[11], consistent with a causal explanation for at least a proportion of the association.

Earlier research has demonstrated that degree of prematurity is relevant to risk of persistent asthma and bronchiolitis in the first year[6]. This paper investigates whether the *combination*

(interaction) of early respiratory infection with prematurity, when the immature lungs may be particularly susceptible to long-term damage, represents a disproportionately raised risk for persistent respiratory disease. Swedish general population registers were used to identify a cohort of children who were admitted to hospital due to respiratory infection in their first year after birth and they were matched with a cohort of children not admitted to hospital for infection in their first year.

## METHODS

All children in Sweden admitted to hospital for severe infections that affect the airways in the 12 months following birth between 1981 and 1995 were identified (N=4233). They were individually matched with children who were not admitted to hospital for these infections in their first year (N=211594), with matching for gestational age, region of birth, and the month and year of their birth. Each exposed child was matched with five unexposed children, selected at random from among those with relevant characteristics. If fewer than five unexposed infants were available for matching with an exposed subject, all suitable children were selected. Follow-up to identify chronic airway disease (asthma) was up to 2010.

### Registers

This study utilised national Swedish register data that can be linked at the individual level using the unique personal identity number issued to all residents. Information on pregnancy and delivery, and other characteristics of mother and baby were obtained through the Medical Birth Register, which has recorded almost every delivery in Sweden since 1973. The

Patient Register has had complete national coverage of inpatient diagnoses since 1987 and included outpatient diagnoses since 2000. The Prescription Register has provided information on all prescribed medication since 2005.

**Measures**

The Patient Register was used to identify respiratory infections in the first year after birth that resulted in hospital admission; and these diagnoses are listed in Table 1. This register also identified diagnoses of lung disease through ICD codes consistent with asthma in children and young adults. To avoid surveillance bias (incidental reporting of asthma in children admitted or investigated for other diseases) asthma was only defined as the outcome here when it was the sole diagnosis made at the hospital visit. The Prescription Register – which records all treatments dispensed though pharmacies (including all prescriptions from primary care) was used to identify pharmaceutical treatments for asthma in children and young adults and the selected treatments are presented in table 1. The Medical Birth Register provided information on gestational age, birth weight, maternal age at delivery, maternal smoking during pregnancy, maternal asthma, sex of the child, parity and a diagnosis of neonatal chronic lung disease (CLD: ICD-8 776.6 and ICD-9 770H): these measures were categorised as presented in table 2.

**Statistical analysis**

Cox regression was used to estimate hazard ratios associated with asthma after 5 years of age (hospital diagnosis or treatment), with follow-up to first asthma event, exit from the study population or end of the study period, whichever came first. The following independent measures were also included in models individually, then mutually adjusted for

each other: respiratory infection in the first year after birth, gestational age, sex, maternal age at delivery, parity, maternal smoking, a maternal diagnosis of asthma, CLD and year of delivery (all modelled as series of binary dummy variables in the categories shown in tables 2 and 3). The non-stratified models (table 3) were not adjusted for birth weight, as it was collinear with gestational age while the stratified models (tables 4 and 5) and interaction tests were adjusted for a continuous measure of birth weight. Log-minus-log plots were used to assess whether the proportional hazards assumption was violated: the curves comparing the exposed and unexposed cohorts did not converge and proportionality was maintained.

The main analysis concerns the *combination* of early infection with gestational age and this was investigated in models for the association of first-year infection with asthma after age 5 years, stratified by gestational age, with adjustment for all of the potential confounding factors described above, with the addition of birth weight modelled as a continuous measure. To assess effect modification by gestational age for the association of early infection with asthma, interaction testing using the entire (non-stratified) study population was undertaken. The interaction terms for gestational age (categorical) by infection were adjusted for the main effect (gestational age and infection), as well as for all of the previously described potential confounding factors.

To assess whether the combination of prematurity with first year infection is a risk for asthma that persists beyond early childhood, the above analysis stratified for gestational age was repeated, but with truncated follow-up to identify asthma after age 10 years and after age 16 years.

SPSS software was used and statistical significance was defined as confidence intervals that do not include 1.00 and p values below 0.05.

**RESULTS**

As the two cohorts were matched, the distributions for gestational age and year of birth are almost identical (table 2). This matching is also reflected in the very similar distributions for birth weight. Children admitted to hospital with infections were more often male and their mothers were more likely to be younger, smokers, with a diagnosis of asthma and to have had a greater number of previous pregnancies. CLD was also more common in the infection cohort, particularly among the extremely preterm infants (12.3% compared with 7.9% among the extremely preterm).

Respiratory infection during the first year is statistically significantly associated with a raised risk of asthma after age 5 years, both before and after adjustment for potential confounding factors (table 3). Female sex, neonatal lung disease, maternal asthma, fewer previous pregnancies are associated with a statistically significant raised asthma risk in the adjusted model. Gestational age was a matching characteristic, so associations with this measure are not presented.

Table 4 shows the association of hospital admission for infection in the first year with asthma after age 5 years, *stratified by gestational age*. Infection is associated with asthma across all of the gestational age groups after adjustment for potential confounding factors. The highest magnitude association is among the most preterm infants. A notably raised risk

was also observed among those with uncertain gestational age. Interaction testing among the entire study population confirms statistically significant effect modification by the most premature gestational age group, at less than 28 weeks compared with the infants who were born at term. The interaction results were not statistically significant for the other gestational age groups, including where it was unspecified. After adjustment for the main effects the hazard ratio (and 95% confidence interval) is 1.41 (1.02 to 1.95; p for interaction=0.034) and with additional adjustment for the potential confounding factors it is 1.40 (1.01 to 1.93; p for interaction=0.042).

Early Infection is associated with asthma after age 10 and after age 16 years for all gestational age groups, but although still statistically significant, the notably increased magnitude for the most premature is somewhat reduced after age 16 years (table 5).

The analysis was repeated excluding those with missing maternal smoking information and the results were not notably altered (data not shown).

**DISCUSSION**

In this register-based cohort study, hospital admission for respiratory infection in the 12 months following birth was associated with an increased risk of asthma after age 5 years, particularly among those born extremely prematurely.

Another study using Swedish register data found that early infection and prematurity were independently associated with later increased corticosteroid use[6]. While the results between the earlier study and ours are similar for associations with infection, the cohorts in

our study were matched for gestational age, which was considered as a potential modifying factor for the effect of early infections. Here, asthma after age 5 years was identified through prescribed corticosteroids and other asthma medication, as well as inpatient or outpatient hospital diagnoses. We used several strategies to ensure that the associations are with asthma rather than other comorbidity associated with prematurity and early infection. Only diagnoses of asthma made after age 5 years were included, as these are more likely to represent persistent asthma. We limited diagnoses to instances where asthma was the sole diagnosis recorded by the outpatient or inpatient discharge summary to minimise surveillance bias, where admission for another condition results in an incidental diagnosis of asthma: this can produce a conservative estimate of association. While it can be difficult to differentiate between the effects of infection and susceptibility to infection, we attempted to tackle this through adjustment for a variety of potential confounding factors, including birth weight within gestational age categories to provide fine-grain control for foetal development. The extremely preterm infants more often had CLD, possibly signalling to both susceptibly to early infection and also asthma: we therefore adjusted for neonatal CLD.

This study has some potential limitations. Identification of asthma through registers does not provide information about disease phenotype, including whether allergic sensitisation is implicated and confirmation of individual diagnoses is not possible. The infections defining the exposed cohort are not always well characterised (particularly from the earlier periods), but all will affect the lungs and were sufficiently serious to result in hospital admission. Prior to 1990, respiratory syncytial virus (RSV) was often diagnosed as an unspecified viral infection, so we included some non-specific infections. Earlier studies found that RSV was responsible for the majority of bronchiolitis diagnoses during the first year after birth[12 13],

while rhinovirus was associated with 18% of bronchiolitis diagnoses, although hospital admission was less common[14]. It is possible that use of more specific diagnoses, not available through the Patient Register, would result in higher magnitude associations. We were unable to examine delivery mode as a potential confounding factor as this was not available in our data set: caesarean section has been linked with an increased asthma risk in term infants[15]. Number of older siblings is an important indicator of asthma risk. While this was not measured directly, we adjusted for parity as a reliable indicator of number of older siblings. Also, it has been hypothesised that previous pregnancies – directly measured by parity - may influence immune-mediated disease risk through changes in the mother's immune profile[16]. The measure of maternal smoking was incomplete as it was not always included in the Medical Birth Register. The proportions without smoking data were almost identical in both the exposed and unexposed cohorts. When the analysis was restricted to mothers with complete smoking data, the results were not materially altered. Our study will have underestimated the total number of asthma diagnoses, as we did not have data from primary care, and because we excluded asthma with comorbid diagnoses to avoid confounding by comorbidity. The use of prescribed medication will have improved our ability to identify chronic asthma as this will identify those diagnosed and treated in primary care. The two strategies to identify asthma were combined to maximise reliable asthma identification and statistical power. Unavoidably, gestational age was unavailable for some infants: the higher magnitude asthma risk associated with infections in this group may be due to a proportion who were also very premature, and possibly other risks. As interaction testing by gestational age was undertaken, adjustment rather than internal stratification for this factor was performed. Despite this, use of a matching characteristic may still have resulted in underestimation of interaction effects between infection and gestational age.

Both RSV and rhinovirus infections in infancy have been linked with subsequent childhood wheezing[1 3], but the association of early life infections with allergy and possible asthma risk has a complicated pattern. While some markers of infection, such as positive serology for Epstein-Barr virus (EBV) and cytomegalovirus (CMV) are associated with a reduced risk of allergic sensitisation[17], there is evidence that early infection with RSV may increase the risk of allergic asthma through its influence on regulatory T-cell function[18]. However, pre-existing atopy – or associated characteristics - may also influence subsequent infection risk, as rhinovirus bronchiolitis has been found to occur more frequently in infants who had prior allergic sensitization[19]. Whether or not allergy is implicated, respiratory infections in infancy, both RSV and non-RSV infections, are thought to contribute to airway impairment[3 20-23]. The possible non-mutually exclusive mechanisms include through structural damage[24], modification of the mucosal immunology of the lungs[25] or through epigenetic changes[26]. Treatment of infections by antibiotics has been suggested as a risk for asthma, but the evidence is weak; and reviews suggest that the association is due to confounding by indication.

Lung development continues throughout foetal life and babies who are born prematurely have developmental deficits of airway[27-30] and may result in chronic asthma[8], which can diminish with increasing age as lung function improves[31 32]. Atopic sensitization – and thus allergic asthma that may be more persistent in adulthood - is less common in those born preterm compared with term deliveries[33]. Thus, the combination of early infection and prematurity may conspire to increase both allergic and non-allergic risks for asthma, helping to explain the multiplicative effect of this combination of exposures for the risk of

subsequent asthma. The notably higher risk of asthma associated with this exposure combination continues throughout childhood, but appears to be less profound after age 16 years, possibly reflecting age-associated changes.

This study provides evidence that respiratory infections resulting in hospital admission during the first year after birth are a risk for subsequent asthma after age 5 years. The increase in childhood asthma risk is particularly high among extremely preterm infants.

**What is already known on this subject**

- Infants born preterm have an increased risk of airway disease and subsequent childhood asthma.

- Respiratory infection in infancy is also associated with an increased risk of childhood asthma, independent of gestational age.

**What this study adds**

- Extremely premature infants who experience respiratory infections before one year of age have an even higher increase in risk of subsequent asthma than term infants.

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**Contributors** SM and CPK conceived the study and prepared the first draft of the manuscript; and with SB they developed the methods. SB and PK were responsible for obtaining and preparing the data. OB and OH conducted the statistical analysis and produced the tables. All authors were involved in critical editing of the manuscript.

**Competing interests** None.

**Ethics approval** Karolinska Regional Ethics Committee, Stockholm

Data sharing: We do not have ethical permission to share the data, however they are register data and available to other academic researchers.

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**Table 1. Respiratory infections and prescribed asthma treatments**

| **Respiratory infections during the first year of life** | |
|---|---|
| Adenovirus infection | Pneumococcal pneumonia |
| Other specified Adenovirus infection | Pneumonia |
| Bordetella Pertussis | Pneumonia due to streptococcus |
| Bronchitis | Pneumonia due to Haemophilus influenzae |
| Bronchiolitis | Pneumonia due to respiratory syncytial virus |
| Bronchopneumonia organism unspecified | Other unspecified pneumonia |
| Coxsackie virus infection | Bacterial pneumonia unspecified |
| Cytomegalovirus | Other specified viral pneumonia |
| Echo virus infection | Pneumonia in other infectious diseases classified elsewhere |
| Influenza | Rhinovirus infection |
| Influenza with other respiratory manifestations | Other specified viral infections |
| Influenza unspecified | Suspected viral infections |
| Influenza with pleuropneumonia | Unspecified viral infections |
| **Prescribed treatments** | |
| Beclomethasone | Omalizumab |
| Budesonide | Salbutamol |
| Flutikasone | Salmeterol |
| Formoterol | Sodiumchromoglicate |
| Indakaterol | Terbutaline |
| Ipratroprium | Theophylline |
| Mometasone | Tiotropium bromide |
| Montelucast | |

**Table 2. Characteristics of the cohorts defined by respiratory infection during the first year of life**

| | Respiratory infection in first year<br><br>n= 42334<br>(16.7%) | No respiratory infection in first year<br><br>n= 211594<br>(83.3%) | Total<br><br>n= 253928<br>(100%) |
|---|---|---|---|
| Prescribed asthma medication* | 7485 (17.7) | 26591 (12.6) | 34076 (13.4) |
| Hospital asthma diagnosis* | 420 (1.0) | 761 (0.4) | 1181 (0.5) |
| No asthma* | 34749 (82.1) | 184775 (87.3) | 219524 (86.5) |
| Gestational age (weeks) | | | |
| ≤27 | 252 (0.6) | 1221 (0.6) | 1473 (0.6) |
| 28-31 | 723 (1.7) | 3578 (1.7) | 4301 (1.7) |
| 32-36 | 3906 (9.2) | 19528 (9.2) | 23434 (9.2) |
| 37- 41 | 34839 (82.3) | 174194 (82.3) | 209033 (82.3) |
| > 41 | 2507 (5.9) | 12535 (5.9) | 15042 (5.9) |
| Uncertain | 107 (0.3) | 538 (0.3) | 645 (0.3) |
| Birth weight | | | |
| <1000g | 241(0.6) | 1292 (0.6) | 1533 (0.6) |
| > 1000-1500g | 580 (1.4) | 2714 (1.3) | 3294 (1.3) |
| >1500-2000g | 953 (2.3) | 4300 (2.0) | 5253 (2.1) |
| >2000-2750g | 4099 (9.7) | 18815 (8.9) | 22914 (9.0) |
| >2750-3250g | 9727 (23.0) | 47617 (22.5) | 57344 (22.6) |
| >3250-4000g | 20178 (47.7) | 104693 (49.5) | 124871 (49.2) |
| > 4000g | 6426 (15.2) | 31524 (14.9) | 37950 (14.9) |
| Not recorded | 130 (0.3) | 639 (0.3) | 769 (0.3) |
| Maternal asthma | | | |
| Current | 721 (1.7) | 2754 (1.3) | 3475 (1.4) |
| Previous | 210 (0.5) | 749 (0.4) | 959 (0.4) |
| None | 41403 (97.8) | 208091 (98.3) | 249494 (98.3) |
| Maternal age at delivery | | | |
| 13-18 | 755 (1.8) | 2917 (1.4) | 3672 (1.5) |
| 19-25 | 14230 (33.6) | 66604 (31.5) | 80834 (31.8) |
| 26-30 | 15312 (36.2) | 76752 (36.3) | 92064 (36.3) |
| 31-35 | 8911 (21.0) | 46336 (21.9) | 55247 (21.8) |
| 36-40 | 2757 (6.5) | 16673 (7.9) | 19430 (7.7) |
| 41-54 | 369 (0.9) | 2312 (1.1) | 2681 (1.1) |
| Maternal smoking | | | |
| Non-smoker | 23871 (56.4) | 134802 (63.7) | 158673 (62.5) |
| Smoker | 12429 (29.4) | 46817 (22.1) | 59246 (23.3) |
| Not recorded | 6034 (14.3) | 29975 (14.2) | 36009 (14.2) |
| Child's sex | | | |
| Female | 17619 (41.6) | 103007 (48.7) | 120626 (47.5) |
| Male | 24715 (58.4) | 108587 (51.3) | 133302 (52.5) |
| Parity | | | |
| 1 | 12714 (30.0) | 87275 (41.2) | 99989 (39.4) |
| 2 | 17247 (40.7) | 74534 (35.2) | 91781 (36.1) |
| 3 | 8270 (19.5) | 34880 (16.5) | 43150 (17.0) |
| 4 or more | 4103 (9.7) | 14905 (7.0) | 19008 (7.5) |
| Chronic lung disease | | | |
| No | 42272 (99.9) | 211416 (99.9) | 253688 (99.9) |
| Yes | 62 (0.1) | 178 (0.1) | 240 (0.1) |

* These categories are not mutually exclusive.

**Table 3. Early life characteristics and subsequent asthma risk after age 5 years**

| Characteristic | Asthma n (%) | No asthma n (%) | Unadjusted HR (95% CI) | P value | Adjusted[1] HR (95% CI) | P value |
|---|---|---|---|---|---|---|
| Respiratory infection in first year | | | | | | |
| Yes | 7585 (17.9) | 34749 (82.1) | 1.45 (1.41 to 1.49) | <0.001 | 1.51 (1.47 to 1.54) | <0.001 |
| No | 26819 (12.7) | 184775 (87.3) | Ref. | | Reference | |
| Maternal asthma | | | | | | |
| Current | 921 (26.5) | 2554 (73.5) | 3.86 (3.61 to 4.12) | <0.001 | 1.94 (1.82 to 2.08) | <0.001 |
| Previous | 222 (23.1) | 737 (76.9) | 3.05 (2.67 to 3.48) | <0.001 | 1.38 (1.21 to 1.58) | <0.001 |
| None | 33261 (13.3) | 216233 (86.7) | Ref. | | Ref. | |
| Maternal age at delivery (years) | | | | | | |
| 13-18 | 517 (14.1) | 3155 (85.9) | 0.96 (0.88 to 1.05) | 0.372 | 0.98 (0.90 to 1.07) | 0.625 |
| 19-25 | 11451 (14.2) | 69383 (85.8) | 1.02 (1.00 to 1.05) | 0.069 | 1.03 (1.00 to 1.06) | 0.026 |
| 26-30 | 12249 (13.3) | 79815 (86.7) | Ref. | | Ref. | |
| 31-35 | 7276 (13.2) | 47971 (86.8) | 0.99 (0.96 to 1.02) | 0.490 | 1.02 (0.99 to 1.05) | 0.140 |
| 36-40 | 2562 (13.2) | 16868 (86.8) | 1.00 (0.96 to 1.05) | 0.830 | 1.05(1.01 to 1.10) | 0.029 |
| 41-54 | 349 (13.0) | 2332 (87.0) | 1.00 (0.90 to 1.12) | 0.934 | 1.05(0.94 to 1.17) | 0.391 |
| Maternal smoking | | | | | | |
| Non-smoker | 21701 (13.7) | 136972 (86.3) | Ref. | | Ref. | |
| Smoker | 8278 (14.0) | 50968(86.0) | 0.93 (0.91 to 0.96) | <0.001 | 1.01 (0.99 to 1.04) | 0.380 |
| Not recorded | 4425 (12.3) | 31584 (87.7) | 0.59 (0.57 to 0.61) | <0.001 | 0.90 (0.87 to 0.93) | <0.001 |
| Child's sex | | | | | | |
| Female | 18150 (15.0) | 102476 (85.0) | 1.25 (1.22 to 1.27) | <0.001 | 1.27 (1.24 to 1.29) | <0.001 |
| Male | 16254 (12.2) | 117048 (87.8) | Ref. | | Ref. | |
| Parity | | | | | | |
| 1 | 14371 (14.4) | 85618 (85.6) | Ref. | | Ref. | |
| 2 | 12230 (13.3) | 79551 (86.7) | 0.93 (0.90 to 0.95) | <0.001 | 0.90 (0.88 to 0.93) | <0.001 |
| 3 | 5437 (12.6) | 37713 (87.4) | 0.87 (0.84 to 0.89) | <0.001 | 0.84 (0.82 to 0.87) | <0.001 |
| 4 or more | 2366 (12.4) | 16642 (87.6) | 0.88 (0.84 to 0.92) | <0.001 | 0.81 (0.78 to 0.85) | <0.001 |
| Chronic lung disease | | | | | | |
| No | 34360 | 219328 | Ref. | | Ref. | |
| Yes | 44 | 196 | 1.59 (1.18 to 2.14) | 0.002 | 1.44 (1.06 to 1.96) | 0.019 |

[1] Adjusted for child's sex, maternal asthma, maternal age at delivery, year of birth, maternal smoking, gestational age, infection during first year of life, parity, and chronic lung disease

**Table 4. Respiratory infection in the first year of life subsequent asthma risk after age 5 years, *stratified by gestational age***

| Infection stratified by gestational age | Asthma n (%) | No asthma n (%) | HR (95% CI) | P Value | HR[1] (95% CI) | P Value |
|---|---|---|---|---|---|---|
| **Week 0-27** | | | | | | |
| Infection | 52 (20.6) | 200 (79.4) | 2.03 (1.47 to 2.80) | < 0.001 | 2.22 (1.59 to 3.09) | < 0.001 |
| No infection | 130 (10.6) | 1091 (89.4) | Ref. | | Ref. | |
| **Week 28-31** | | | | | | |
| Infection | 132 (18.3) | 591 (81.7) | 1.47 (1.21 to 1.78) | < 0.001 | 1.57 (1.29 to 1.92) | < 0.001 |
| No infection | 458 (12.8) | 3130 (87.2) | Ref. | | Ref. | |
| **Week 32-36** | | | | | | |
| Infection | 738 (18.9) | 3168 (81.1) | 1.47 (1.35 to 1.59) | < 0.001 | 1.54 (1.42 to 1.68) | < 0.001 |
| No infection | 2588 (13.3) | 16940 (86.7) | Ref. | | Ref. | |
| **Week 37-41** | | | | | | |
| Infection | 6194 (17.8) | 28645 (82.2) | 1.44 (1.40 to 1.48) | < 0.001 | 1.49 (1.45 to 1.53) | < 0.001 |
| No infection | 22075 (12.7) | 152119 (87.3) | Ref. | | Ref. | |
| **Week > 41** | | | | | | |
| Infection | 446 (17.8) | 2061 (82.2) | 1.51 (1.36 to 1.68) | < 0.001 | 1.57 (1.41 to 1.75) | < 0.001 |
| No infection | 1512(12.1) | 11023 (87.9) | Ref. | | Ref. | |
| **Week uncertain** | | | | | | |
| Infection | 23 (21.5) | 84 (78.5) | 2.10 (1.29 to 3.42) | 0.003 | 2.21 (1.34 to 3.65) | 0.002 |
| No infection | 56 (10.4) | 482 (89.6) | Ref. | | Ref. | |

[1] Adjusted for child's sex, maternal asthma, maternal age at delivery, year of birth, birth weight, maternal smoking, infection during first year of life, parity, and chronic lung disease

**Table 5. Respiratory infection in the first year of life subsequent asthma risk after age 10 years and after age 16 years, *stratified by gestational age***

| | Asthma n (%) | No asthma n (%) | HR (95% CI) | P Value | HR[1] (95% CI) | P Value |
|---|---|---|---|---|---|---|
| **≥ Age 10** | | | | | | |
| Gestational age (weeks) | | | | | | |
| ≤27 | | | | | | |
| Infection | 45 (17.9) | 207 (82.1) | 1.83 (1.30 to 2.57) | 0.001 | 1.99 (1.40 to 2.82) | < 0.001 |
| No infection | 123 (10.1) | 1098 (89.9) | Ref. | | Ref. | |
| 28-31 | | | | | | |
| Infection | 116 (16.0) | 607 (84.0) | 1.43 (1.17 to 1.76) | 0.001 | 1.52 (1.24 to 1.87) | < 0.001 |
| No infection | 411 (11.5) | 3167 (88.5) | Ref. | | Ref. | |
| 32-36 | | | | | | |
| Infection | 635 (16.3) | 3271 (83.7) | 1.39 (1.27 to 1.52) | < 0.001 | 1.46 (1.33 to 1.59) | < 0.001 |
| No infection | 2328 (11.) | 17200 (88.1) | Ref. | | Ref. | |
| 37- 41 | | | | | | |
| Infection | 5541 (15.9) | 29298 (84.1) | 1.44 (1.40 to 1.48) | < 0.001 | 1.49 (1.45 to 1.54) | < 0.001 |
| No infection | 19637 (11.3) | 154557 (88.7) | Ref. | | Ref. | |
| > 41 | | | | | | |
| Infection | 397 (15.8) | 2119 (84.2) | 1.51 (1.35 to 1.69) | < 0.001 | 1.57 (1.41 to 1.76) | < 0.001 |
| No infection | 1340 (10.7) | 11195 (89.3) | Ref. | | Ref. | |
| Uncertain | | | | | | |
| Infection | 19 (17.8) | 88 (82.2) | 1.93 (1.14 to 3.28) | 0.015 | 2.05 (1.19 to 3.55) | 0.010 |
| No infection | 50 (9.3) | 488 (90.7) | Ref. | | Ref. | |
| **≥ Age 16** | | | | | | |
| Gestational age (weeks) | | | | | | |
| ≤27 | | | | | | |
| Infection | 22 (8.8) | 227 (91.2) | 1.56 (0.96 to 2.52) | 0.071 | 1.65 (1.01 to 2.71) | 0.047 |
| No infection | 69 (5.7) | 1132 (94.3) | Ref. | | Ref. | |
| 28-31 | | | | | | |
| Infection | 65 (9.2) | 638 (90.8) | 1.41 (1.07 to 1.86) | 0.014 | 1.45 (1.10 to 1.91) | 0.009 |
| No infection | 233 (6.7) | 3249 (93.3) | Ref. | | Ref. | |
| 32-36 | | | | | | |
| Infection | 396 (10.5) | 3362 (89.5) | 1.43 (1.28 to 1.60) | < 0.001 | 1.49 (1.34 to 1.68) | < 0.001 |
| No infection | 1410 (7.5) | 17379 (92.5) | Ref. | | Ref. | |
| 37- 41 | | | | | | |
| Infection | 3227 (9.7) | 30040 (90.3) | 1.37 (1.32 to 1.42) | < 0.001 | 1.42 (1.37 to 1.48) | < 0.001 |
| No infection | 11987 (7.2) | 154347 (92.8) | Ref. | | Ref. | |
| > 41 | | | | | | |
| Infection | 248 (10.3) | 2161 (89.7) | 1.58 (1.37 to 1.82) | < 0.001 | 1.64 (1.42 to 1.90) | < 0.001 |
| No infection | 801 (6.7) | 11244 (93.3) | Ref. | | Ref. | |
| Uncertain | | | | | | |
| Infection | 16 (15.2) | 89 (84.8) | 2.48 (1.37 to 4.51) | 0.003 | 2.72 (1.47 to 5.04) | 0.002 |
| No infection | 33 (6.2) | 496 (93.8) | Ref. | | Ref. | |

[1] Adjusted for child's sex, maternal asthma, maternal age at delivery, year of birth, maternal smoking, birth weight, infection during first year of life, parity, and chronic lung disease.

# Respiratory infections in preterm infants and subsequent asthma

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**ABSTRACT**

**Objective** To investigate if gestational age modifies the association of airway infections, resulting in hospital admission during the first year after birth, with asthma risk after age 5 years.

**Patients** Swedish general population registers identified 42,334 children admitted to hospital for respiratory infection in their first year after birth during 1981-1995. They were individually matched with 211,594 children not admitted to hospital for infection.

**Methods** Cox regression analysis was used to estimate asthma risk after age 5 years (identified though diagnoses and prescribed treatments in registers), with adjustment for sex, gestational age, chronic lung disease, maternal asthma and smoking; and additionally for birth weight in models stratified for gestational age.

**Results** Hospital admission for airway infection in the first year is associated with an increased risk for subsequent asthma, producing an adjusted hazard ratio (and 95% confidence interval) of 1.51 (1.47 to 1.54). When stratified, the highest magnitude risk (statistically significant effect modification) was among those born with a gestational age of less than 28 weeks, producing an adjusted hazard ratio of 2.22 (1.59 to 3.09). This higher magnitude risk asthma persisted until after age 10 years. Early infection was statistically significantly associated with asthma after age 16 years for all gestational age groups, but the difference in risk magnitude between the extremely prematurely born and other children was reduced.

**Conclusions** Extremely preterm infants are most likely to have chronic respiratory sequelae following respiratory infections in early life.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

**Strengths**

- The vast majority of infants admitted to hospital with airway infections in their first year after birth in Sweden during the study period will have been identified.
- The use of prospectively recorded national register data allow for longitudinal analysis of asthma risk, with follow-up into early adulthood.

**Limitations**

- The infections are incompletely characterised, particularly during earlier years.
- Asthma was identified based on inpatient diagnoses and prescribed medication, but it was not possible to confirm the accuracy of diagnoses.

## INTRODUCTION

Respiratory infection in the first year after birth[1-3], and preterm birth[4-7] are both markers of subsequent asthma risk. How the interrelationship of these factors relates to persistent respiratory disease is incompletely understood.

The lungs of preterm infants are underdeveloped with immature airways and the association of prematurity with later respiratory disease indicates asthma's developmental origin[8-10]. Respiratory infections requiring hospital admission during the first year after birth may signal susceptibility to asthma or may be causally implicated in asthma aetiology; and these explanations are not necessarily mutually exclusive. Respiratory infection *epidemics* that produce infections among infants are associated with a raised risk of persistent respiratory disease[11], consistent with a causal explanation for at least a proportion of the association.

Earlier research has demonstrated that degree of prematurity is relevant to risk of persistent asthma and bronchiolitis in the first year[6]. This paper investigates whether the *combination* (interaction) of early respiratory infection with prematurity, when the immature lungs may

be particularly susceptible to long-term damage, represents a disproportionately raised risk for persistent respiratory disease. Swedish general population registers were used to identify a cohort of children who were admitted to hospital due to respiratory infection in their first year after birth and they were matched with a cohort of children not admitted to hospital for infection in their first year.



## METHODS

All children in Sweden admitted to hospital for severe infections that affect the airways in the 12 months following birth between 1981 and 1995 were identified (N=4233). They were individually matched with children who were not admitted to hospital for these infections in their first year (N=211594), with matching for gestational age, region of birth, and the month and year of their birth. Each exposed child was matched with five unexposed children, selected at random from among those with relevant characteristics. If fewer than five unexposed infants were available for matching with an exposed subject, all suitable children were selected. Follow-up to identify chronic airway disease (asthma) was up to 2010.

### Registers

This study utilised national Swedish register data that can be linked at the individual level using the unique personal identity number issued to all residents. Information on pregnancy and delivery, and other characteristics of mother and baby were obtained through the Medical Birth Register, which has recorded almost every delivery in Sweden since 1973. The Patient Register has had complete national coverage of inpatient diagnoses since 1987 and

included outpatient diagnoses since 2000. The Prescription Register has provided information on all prescribed medication since 2005.

**Measures**

The Patient Register was used to identify respiratory infections in the first year after birth that resulted in hospital admission; and these diagnoses are listed in Table 1. This register also identified diagnoses of lung disease through ICD codes consistent with asthma in children and young adults. To avoid surveillance bias (incidental reporting of asthma in children admitted or investigated for other diseases) asthma was only defined as the outcome here when it was the sole diagnosis made at the hospital visit. The Prescription Register – which records all treatments dispensed though pharmacies (including all prescriptions from primary care) was used to identify pharmaceutical treatments for asthma in children and young adults and the selected treatments are presented in table 1. The Medical Birth Register provided information on gestational age, birth weight, maternal age at delivery, maternal smoking during pregnancy, maternal asthma, sex of the child, parity and a diagnosis of neonatal chronic lung disease (CLD: ICD-8 776.6 and ICD-9 770H): these measures were categorised as presented in table 2.

**Statistical analysis**

Cox regression was used to estimate hazard ratios associated with asthma after 5 years of age (hospital diagnosis or treatment), with follow-up to first asthma event, exit from the study population or end of the study period, whichever came first. The following independent measures were also included in models individually, then mutually adjusted for each other: respiratory infection in the first year after birth, gestational age, sex, maternal

age at delivery, parity, maternal smoking, a maternal diagnosis of asthma, CLD and year of delivery (all modelled as series of binary dummy variables in the categories shown in tables 2 and 3). The non-stratified models (table 3) were not adjusted for birth weight, as it was collinear with gestational age while the stratified models (tables 4 and 5) and interaction tests were adjusted for a continuous measure of birth weight. Log-minus-log plots were used to assess whether the proportional hazards assumption was violated: the curves comparing the exposed and unexposed cohorts did not converge and proportionality was maintained.

The main analysis concerns the *combination* of early infection with gestational age and this was investigated in models for the association of first-year infection with asthma after age 5 years, stratified by gestational age, with adjustment for all of the potential confounding factors described above, with the addition of birth weight modelled as a continuous measure. To assess effect modification by gestational age for the association of early infection with asthma, interaction testing using the entire (non-stratified) study population was undertaken. The interaction terms for gestational age (categorical) by infection were adjusted for the main effect (gestational age and infection), as well as for all of the previously described potential confounding factors.

To assess whether the combination of prematurity with first year infection is a risk for asthma that persists beyond early childhood, the above analysis stratified for gestational age was repeated, but with truncated follow-up to identify asthma after age 10 years and after age 16 years.

SPSS software was used and statistical significance was defined as confidence intervals that do not include 1.00 and p values below 0.05.

**RESULTS**

As the two cohorts were matched, the distributions for gestational age and year of birth are almost identical (table 2). This matching is also reflected in the very similar distributions for birth weight. Children admitted to hospital with infections were more often male and their mothers were more likely to be younger, smokers, with a diagnosis of asthma and to have had a greater number of previous pregnancies. CLD was also more common in the infection cohort, particularly among the extremely preterm infants (12.3% compared with 7.9% among the extremely preterm).

Respiratory infection during the first year is statistically significantly associated with a raised risk of asthma after age 5 years, both before and after adjustment for potential confounding factors (table 3). Female sex, neonatal lung disease, maternal asthma, fewer previous pregnancies are associated with a statistically significant raised asthma risk in the adjusted model. Gestational age was a matching characteristic, so associations with this measure are not presented.

Table 4 shows the association of hospital admission for infection in the first year with asthma after age 5 years, *stratified by gestational age*. Infection is associated with asthma across all of the gestational age groups after adjustment for potential confounding factors. The highest magnitude association is among the most preterm infants. A notably raised risk was also observed among those with uncertain gestational age. Interaction testing among

the entire study population confirms statistically significant effect modification by the most premature gestational age group, at less than 28 weeks compared with the infants who were born at term. The interaction results were not statistically significant for the other gestational age groups, including where it was unspecified. After adjustment for the main effects the hazard ratio (and 95% confidence interval) is 1.41 (1.02 to 1.95; p for interaction=0.034) and with additional adjustment for the potential confounding factors it is 1.40 (1.01 to 1.93; p for interaction=0.042).

Early Infection is associated with asthma after age 10 and after age 16 years for all gestational age groups, but although still statistically significant, the notably increased magnitude for the most premature is somewhat reduced after age 16 years (table 5).

The analysis was repeated excluding those with missing maternal smoking information and the results were not notably altered (data not shown).

**DISCUSSION**

In this register-based cohort study, hospital admission for respiratory infection in the 12 months following birth was associated with an increased risk of asthma after age 5 years, particularly among those born extremely prematurely.

Another study using Swedish register data found that early infection and prematurity were independently associated with later increased corticosteroid use[6]. While the results between the earlier study and ours are similar for associations with infection, the cohorts in our study were matched for gestational age, which was considered as a potential modifying

factor for the effect of early infections. Here, asthma after age 5 years was identified through prescribed corticosteroids and other asthma medication, as well as inpatient or outpatient hospital diagnoses. We used several strategies to ensure that the associations are with asthma rather than other comorbidity associated with prematurity and early infection. Only diagnoses of asthma made after age 5 years were included, as these are more likely to represent persistent asthma. We limited diagnoses to instances where asthma was the sole diagnosis recorded by the outpatient or inpatient discharge summary to minimise surveillance bias, where admission for another condition results in an incidental diagnosis of asthma: this can produce a conservative estimate of association. While it can be difficult to differentiate between the effects of infection and susceptibility to infection, we attempted to tackle this through adjustment for a variety of potential confounding factors, including birth weight within gestational age categories to provide fine-grain control for foetal development. The extremely preterm infants more often had CLD, possibly signalling to both susceptibly to early infection and also asthma: we therefore adjusted for neonatal CLD.

This study has some potential limitations. Identification of asthma through registers does not provide information about disease phenotype, including whether allergic sensitisation is implicated and confirmation of individual diagnoses is not possible. The infections defining the exposed cohort are not always well characterised (particularly from the earlier periods), but all will affect the lungs and were sufficiently serious to result in hospital admission. Prior to 1990, respiratory syncytial virus (RSV) was often diagnosed as an unspecified viral infection, so we included some non-specific infections. Earlier studies found that RSV was responsible for the majority of bronchiolitis diagnoses during the first year after birth[12 13], while rhinovirus was associated with 18% of bronchiolitis diagnoses, although hospital

admission was less common[14]. It is possible that use of more specific diagnoses, not available through the Patient Register, would result in higher magnitude associations. We were unable to examine delivery mode as a potential confounding factor as this was not available in our data set: caesarean section has been linked with an increased asthma risk in term infants[15]. Number of older siblings is an important indicator of asthma risk. While this was not measured directly, we adjusted for parity as a reliable indicator of number of older siblings. Also, it has been hypothesised that previous pregnancies – directly measured by parity - may influence immune-mediated disease risk through changes in the mother's immune profile[16]. The measure of maternal smoking was incomplete as it was not always included in the Medical Birth Register. The proportions without smoking data were almost identical in both the exposed and unexposed cohorts. When the analysis was restricted to mothers with complete smoking data, the results were not materially altered. Our study will have underestimated the total number of asthma diagnoses, as we did not have data from primary care, and because we excluded asthma with comorbid diagnoses to avoid confounding by comorbidity. The use of prescribed medication will have improved our ability to identify chronic asthma as this will identify those diagnosed and treated in primary care. The two strategies to identify asthma were combined to maximise reliable asthma identification and statistical power. Unavoidably, gestational age was unavailable for some infants: the higher magnitude asthma risk associated with infections in this group may be due to a proportion who were also very premature, and possibly other risks. As interaction testing by gestational age was undertaken, adjustment rather than internal stratification for this factor was performed. Despite this, use of a matching characteristic may still have resulted in underestimation of interaction effects between infection and gestational age.

Both RSV and rhinovirus infections in infancy have been linked with subsequent childhood wheezing[1 3], but the association of early life infections with allergy and possible asthma risk has a complicated pattern. While some markers of infection, such as positive serology for Epstein-Barr virus (EBV) and cytomegalovirus (CMV) are associated with a reduced risk of allergic sensitisation[17], there is evidence that early infection with RSV may increase the risk of allergic asthma through its influence on regulatory T-cell function[18]. However, pre-existing atopy – or associated characteristics - may also influence subsequent infection risk, as rhinovirus bronchiolitis has been found to occur more frequently in infants who had prior allergic sensitization[19]. Whether or not allergy is implicated, respiratory infections in infancy, both RSV and non-RSV infections, are thought to contribute to airway impairment[3 20-23]. The possible non-mutually exclusive mechanisms include through structural damage[24], modification of the mucosal immunology of the lungs[25] or through epigenetic changes[26]. Treatment of infections by antibiotics has been suggested as a risk for asthma, but the evidence is weak; and reviews suggest that the association is due to confounding by indication.

Lung development continues throughout foetal life and babies who are born prematurely have developmental deficits of airway[27-30] and may result in chronic asthma[8], which can diminish with increasing age as lung function improves[31 32]. Atopic sensitization – and thus allergic asthma that may be more persistent in adulthood - is less common in those born preterm compared with term deliveries[33]. Thus, the combination of early infection and prematurity may conspire to increase both allergic and non-allergic risks for asthma, helping to explain the multiplicative effect of this combination of exposures for the risk of subsequent asthma. The notably higher risk of asthma associated with this exposure

combination continues throughout childhood, but appears to be less profound after age 16 years, possibly reflecting age-associated changes.

This study provides evidence that respiratory infections resulting in hospital admission during the first year after birth are a risk for subsequent asthma after age 5 years. The increase in childhood asthma risk is particularly high among extremely preterm infants.

**What is already known on this subject**

- Infants born preterm have an increased risk of airway disease and subsequent childhood asthma.

- Respiratory infection in infancy is also associated with an increased risk of childhood asthma, independent of gestational age.

**What this study adds**

- Extremely premature infants who experience respiratory infections before one year of age have an even higher increase in risk of subsequent asthma than term infants.

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## Table 1. Respiratory infections and prescribed asthma treatments

| **Respiratory infections during the first year of life** | |
|---|---|
| Adenovirus infection | Pneumococcal pneumonia |
| Other specified Adenovirus infection | Pneumonia |
| Bordetella Pertussis | Pneumonia due to streptococcus |
| Bronchitis | Pneumonia due to Haemophilus influenzae |
| Bronchiolitis | Pneumonia due to respiratory syncytial virus |
| Bronchopneumonia organism unspecified | Other unspecified pneumonia |
| Coxsackie virus infection | Bacterial pneumonia unspecified |
| Cytomegalovirus | Other specified viral pneumonia |
| Echo virus infection | Pneumonia in other infectious diseases classified elsewhere |
| Influenza | Rhinovirus infection |
| Influenza with other respiratory manifestations | Other specified viral infections |
| Influenza unspecified | Suspected viral infections |
| Influenza with pleuropneumonia | Unspecified viral infections |
| **Prescribed treatments** | |
| Beclomethasone | Omalizumab |
| Budesonide | Salbutamol |
| Flutikasone | Salmeterol |
| Formoterol | Sodiumchromoglicate |
| Indakaterol | Terbutaline |
| Ipratroprium | Theophylline |
| Mometasone | Tiotropium bromide |
| Montelucast | |

**Table 2. Characteristics of the cohorts defined by respiratory infection during the first year of life**

| | Respiratory infection in first year<br><br>n= 42334<br>(16.7%) | No respiratory infection in first year<br><br>n= 211594<br>(83.3%) | Total<br><br>n= 253928<br>(100%) |
|---|---|---|---|
| Prescribed asthma medication* | 7485 (17.7) | 26591 (12.6) | 34076 (13.4) |
| Hospital asthma diagnosis* | 420 (1.0) | 761 (0.4) | 1181 (0.5) |
| No asthma* | 34749 (82.1) | 184775 (87.3) | 219524 (86.5) |
| Gestational age (weeks) | | | |
| ≤27 | 252 (0.6) | 1221 (0.6) | 1473 (0.6) |
| 28-31 | 723 (1.7) | 3578 (1.7) | 4301 (1.7) |
| 32-36 | 3906 (9.2) | 19528 (9.2) | 23434 (9.2) |
| 37- 41 | 34839 (82.3) | 174194 (82.3) | 209033 (82.3) |
| > 41 | 2507 (5.9) | 12535 (5.9) | 15042 (5.9) |
| Uncertain | 107 (0.3) | 538 (0.3) | 645 (0.3) |
| Birth weight | | | |
| <1000g | 241(0.6) | 1292 (0.6) | 1533 (0.6) |
| > 1000-1500g | 580 (1.4) | 2714 (1.3) | 3294 (1.3) |
| >1500-2000g | 953 (2.3) | 4300 (2.0) | 5253 (2.1) |
| >2000-2750g | 4099 (9.7) | 18815 (8.9) | 22914 (9.0) |
| >2750-3250g | 9727 (23.0) | 47617 (22.5) | 57344 (22.6) |
| >3250-4000g | 20178 (47.7) | 104693 (49.5) | 124871 (49.2) |
| > 4000g | 6426 (15.2) | 31524 (14.9) | 37950 (14.9) |
| Not recorded | 130 (0.3) | 639 (0.3) | 769 (0.3) |
| Maternal asthma | | | |
| Current | 721 (1.7) | 2754 (1.3) | 3475 (1.4) |
| Previous | 210 (0.5) | 749 (0.4) | 959 (0.4) |
| None | 41403 (97.8) | 208091 (98.3) | 249494 (98.3) |
| Maternal age at delivery | | | |
| 13-18 | 755 (1.8) | 2917 (1.4) | 3672 (1.5) |
| 19-25 | 14230 (33.6) | 66604 (31.5) | 80834 (31.8) |
| 26-30 | 15312 (36.2) | 76752 (36.3) | 92064 (36.3) |
| 31-35 | 8911 (21.0) | 46336 (21.9) | 55247 (21.8) |
| 36-40 | 2757 (6.5) | 16673 (7.9) | 19430 (7.7) |
| 41-54 | 369 (0.9) | 2312 (1.1) | 2681 (1.1) |
| Maternal smoking | | | |
| Non-smoker | 23871 (56.4) | 134802 (63.7) | 158673 (62.5) |
| Smoker | 12429 (29.4) | 46817 (22.1) | 59246 (23.3) |
| Not recorded | 6034 (14.3) | 29975 (14.2) | 36009 (14.2) |
| Child's sex | | | |
| Female | 17619 (41.6) | 103007 (48.7) | 120626 (47.5) |
| Male | 24715 (58.4) | 108587 (51.3) | 133302 (52.5) |
| Parity | | | |
| 1 | 12714 (30.0) | 87275 (41.2) | 99989 (39.4) |
| 2 | 17247 (40.7) | 74534 (35.2) | 91781 (36.1) |
| 3 | 8270 (19.5) | 34880 (16.5) | 43150 (17.0) |
| 4 or more | 4103 (9.7) | 14905 (7.0) | 19008 (7.5) |
| Chronic lung disease | | | |
| No | 42272 (99.9) | 211416 (99.9) | 253688 (99.9) |
| Yes | 62 (0.1) | 178 (0.1) | 240 (0.1) |

* These categories are not mutually exclusive.

**Table 3. Early life characteristics and subsequent asthma risk after age 5 years**

| Characteristic | Asthma n (%) | No asthma n (%) | Unadjusted HR (95% CI) | P value | Adjusted[1] HR (95% CI) | P value |
|---|---|---|---|---|---|---|
| Respiratory infection in first year | | | | | | |
| Yes | 7585 (17.9) | 34749 (82.1) | 1.45 (1.41 to 1.49) | <0.001 | 1.51 (1.47 to 1.54) | <0.001 |
| No | 26819 (12.7) | 184775 (87.3) | Ref. | | Reference | |
| Maternal asthma | | | | | | |
| Current | 921 (26.5) | 2554 (73.5) | 3.86 (3.61 to 4.12) | <0.001 | 1.94 (1.82 to 2.08) | <0.001 |
| Previous | 222 (23.1) | 737 (76.9) | 3.05 (2.67 to 3.48) | <0.001 | 1.38 (1.21 to 1.58) | <0.001 |
| None | 33261 (13.3) | 216233 (86.7) | Ref. | | Ref. | |
| Maternal age at delivery (years) | | | | | | |
| 13-18 | 517 (14.1) | 3155 (85.9) | 0.96 (0.88 to 1.05) | 0.372 | 0.98 (0.90 to 1.07) | 0.625 |
| 19-25 | 11451 (14.2) | 69383 (85.8) | 1.02 (1.00 to 1.05) | 0.069 | 1.03 (1.00 to 1.06) | 0.026 |
| 26-30 | 12249 (13.3) | 79815 (86.7) | Ref. | | Ref. | |
| 31-35 | 7276 (13.2) | 47971 (86.8) | 0.99 (0.96 to 1.02) | 0.490 | 1.02 (0.99 to 1.05) | 0.140 |
| 36-40 | 2562 (13.2) | 16868 (86.8) | 1.00 (0.96 to 1.05) | 0.830 | 1.05(1.01 to 1.10) | 0.029 |
| 41-54 | 349 (13.0) | 2332 (87.0) | 1.00 (0.90 to 1.12) | 0.934 | 1.05(0.94 to 1.17) | 0.391 |
| Maternal smoking | | | | | | |
| Non-smoker | 21701 (13.7) | 136972 (86.3) | Ref. | | Ref. | |
| Smoker | 8278 (14.0) | 50968(86.0) | 0.93 (0.91 to 0.96) | <0.001 | 1.01 (0.99 to 1.04) | 0.380 |
| Not recorded | 4425 (12.3) | 31584 (87.7) | 0.59 (0.57 to 0.61) | <0.001 | 0.90 (0.87 to 0.93) | <0.001 |
| Child's sex | | | | | | |
| Female | 18150 (15.0) | 102476 (85.0) | 1.25 (1.22 to 1.27) | <0.001 | 1.27 (1.24 to 1.29) | <0.001 |
| Male | 16254 (12.2) | 117048 (87.8) | Ref. | | Ref. | |
| Parity | | | | | | |
| 1 | 14371 (14.4) | 85618 (85.6) | Ref. | | Ref. | |
| 2 | 12230 (13.3) | 79551 (86.7) | 0.93 (0.90 to 0.95) | <0.001 | 0.90 (0.88 to 0.93) | <0.001 |
| 3 | 5437 (12.6) | 37713 (87.4) | 0.87 (0.84 to 0.89) | <0.001 | 0.84 (0.82 to 0.87) | <0.001 |
| 4 or more | 2366 (12.4) | 16642 (87.6) | 0.88 (0.84 to 0.92) | <0.001 | 0.81 (0.78 to 0.85) | <0.001 |
| Chronic lung disease | | | | | | |
| No | 34360 | 219328 | Ref. | | Ref. | |
| Yes | 44 | 196 | 1.59 (1.18 to 2.14) | 0.002 | 1.44 (1.06 to 1.96) | 0.019 |

[1] Adjusted for child's sex, maternal asthma, maternal age at delivery, year of birth, maternal smoking, gestational age, infection during first year of life, parity, and chronic lung disease

**Table 4. Respiratory infection in the first year of life subsequent asthma risk after age 5 years, *stratified by gestational age***

| Infection stratified by gestational age | Asthma n (%) | No asthma n (%) | HR (95% CI) | P Value | HR[1] (95% CI) | P Value |
|---|---|---|---|---|---|---|
| **Week 0-27** | | | | | | |
| Infection | 52 (20.6) | 200 (79.4) | 2.03 (1.47 to 2.80) | < 0.001 | 2.22 (1.59 to 3.09) | < 0.001 |
| No infection | 130 (10.6) | 1091 (89.4) | Ref. | | Ref. | |
| **Week 28-31** | | | | | | |
| Infection | 132 (18.3) | 591 (81.7) | 1.47 (1.21 to 1.78) | < 0.001 | 1.57 (1.29 to 1.92) | < 0.001 |
| No infection | 458 (12.8) | 3130 (87.2) | Ref. | | Ref. | |
| **Week 32-36** | | | | | | |
| Infection | 738 (18.9) | 3168 (81.1) | 1.47 (1.35 to 1.59) | < 0.001 | 1.54 (1.42 to 1.68) | < 0.001 |
| No infection | 2588 (13.3) | 16940 (86.7) | Ref. | | Ref. | |
| **Week 37-41** | | | | | | |
| Infection | 6194 (17.8) | 28645 (82.2) | 1.44 (1.40 to 1.48) | < 0.001 | 1.49 (1.45 to 1.53) | < 0.001 |
| No infection | 22075 (12.7) | 152119 (87.3) | Ref. | | Ref. | |
| **Week > 41** | | | | | | |
| Infection | 446 (17.8) | 2061 (82.2) | 1.51 (1.36 to 1.68) | < 0.001 | 1.57 (1.41 to 1.75) | < 0.001 |
| No infection | 1512(12.1) | 11023 (87.9) | Ref. | | Ref. | |
| **Week uncertain** | | | | | | |
| Infection | 23 (21.5) | 84 (78.5) | 2.10 (1.29 to 3.42) | 0.003 | 2.21 (1.34 to 3.65) | 0.002 |
| No infection | 56 (10.4) | 482 (89.6) | Ref. | | Ref. | |

[1] Adjusted for child's sex, maternal asthma, maternal age at delivery, year of birth, birth weight, maternal smoking, infection during first year of life, parity, and chronic lung disease

**Table 5. Respiratory infection in the first year of life subsequent asthma risk after age 10 years and after age 16 years, *stratified by gestational age***

| | Asthma n (%) | No asthma n (%) | HR (95% CI) | P Value | HR[1] (95% CI) | P Value |
|---|---|---|---|---|---|---|
| **≥ Age 10** | | | | | | |
| Gestational age (weeks) | | | | | | |
| ≤27 | | | | | | |
| Infection | 45 (17.9) | 207 (82.1) | 1.83 (1.30 to 2.57) | 0.001 | 1.99 (1.40 to 2.82) | < 0.001 |
| No infection | 123 (10.1) | 1098 (89.9) | Ref. | | Ref. | |
| 28-31 | | | | | | |
| Infection | 116 (16.0) | 607 (84.0) | 1.43 (1.17 to 1.76) | 0.001 | 1.52 (1.24 to 1.87) | < 0.001 |
| No infection | 411 (11.5) | 3167 (88.5) | Ref. | | Ref. | |
| 32-36 | | | | | | |
| Infection | 635 (16.3) | 3271 (83.7) | 1.39 (1.27 to 1.52) | < 0.001 | 1.46 (1.33 to 1.59) | < 0.001 |
| No infection | 2328 (11.) | 17200 (88.1) | Ref. | | Ref. | |
| 37- 41 | | | | | | |
| Infection | 5541 (15.9) | 29298 (84.1) | 1.44 (1.40 to 1.48) | < 0.001 | 1.49 (1.45 to 1.54) | < 0.001 |
| No infection | 19637 (11.3) | 154557 (88.7) | Ref. | | Ref. | |
| > 41 | | | | | | |
| Infection | 397 (15.8) | 2119 (84.2) | 1.51 (1.35 to 1.69) | < 0.001 | 1.57 (1.41 to 1.76) | < 0.001 |
| No infection | 1340 (10.7) | 11195 (89.3) | Ref. | | Ref. | |
| Uncertain | | | | | | |
| Infection | 19 (17.8) | 88 (82.2) | 1.93 (1.14 to 3.28) | 0.015 | 2.05 (1.19 to 3.55) | 0.010 |
| No infection | 50 (9.3) | 488 (90.7) | Ref. | | Ref. | |
| **≥ Age 16** | | | | | | |
| Gestational age (weeks) | | | | | | |
| ≤27 | | | | | | |
| Infection | 22 (8.8) | 227 (91.2) | 1.56 (0.96 to 2.52) | 0.071 | 1.65 (1.01 to 2.71) | 0.047 |
| No infection | 69 (5.7) | 1132 (94.3) | Ref. | | Ref. | |
| 28-31 | | | | | | |
| Infection | 65 (9.2) | 638 (90.8) | 1.41 (1.07 to 1.86) | 0.014 | 1.45 (1.10 to 1.91) | 0.009 |
| No infection | 233 (6.7) | 3249 (93.3) | Ref. | | Ref. | |
| 32-36 | | | | | | |
| Infection | 396 (10.5) | 3362 (89.5) | 1.43 (1.28 to 1.60) | < 0.001 | 1.49 (1.34 to 1.68) | < 0.001 |
| No infection | 1410 (7.5) | 17379 (92.5) | Ref. | | Ref. | |
| 37- 41 | | | | | | |
| Infection | 3227 (9.7) | 30040 (90.3) | 1.37 (1.32 to 1.42) | < 0.001 | 1.42 (1.37 to 1.48) | < 0.001 |
| No infection | 11987 (7.2) | 154347 (92.8) | Ref. | | Ref. | |
| > 41 | | | | | | |
| Infection | 248 (10.3) | 2161 (89.7) | 1.58 (1.37 to 1.82) | < 0.001 | 1.64 (1.42 to 1.90) | < 0.001 |
| No infection | 801 (6.7) | 11244 (93.3) | Ref. | | Ref. | |
| Uncertain | | | | | | |
| Infection | 16 (15.2) | 89 (84.8) | 2.48 (1.37 to 4.51) | 0.003 | 2.72 (1.47 to 5.04) | 0.002 |
| No infection | 33 (6.2) | 496 (93.8) | Ref. | | Ref. | |

[1] Adjusted for child's sex, maternal asthma, maternal age at delivery, year of birth, maternal smoking, birth weight, infection during first year of life, parity, and chronic lung disease.

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies***

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 3 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 3 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 4 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 4-5 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 4-5 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | 4 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 4-6 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 4-5 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 4-6 |
| Study size | 10 | Explain how the study size was arrived at | 4 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 5-6, 16 |

| | | | |
|---|---|---|---|
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 5-6 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 5-6 |
| | | (*c*) Explain how missing data were addressed | 7 |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | 5-6 |
| | | (*e*) Describe any sensitivity analyses | 6-7 |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 4 |
| | | (b) Give reasons for non-participation at each stage | 4 |
| | | (c) Consider use of a flow diagram | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 6-7, 16 |
| | | (b) Indicate number of participants with missing data for each variable of interest | 5-7, 16 |
| | | (c) Summarise follow-up time (eg, average and total amount) | 4 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 6-7, 16-19 |
| | | (*b*) Report category boundaries when continuous variables were categorized | 16-17 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 5-7, 17-19 |

| | | | |
|---|---|---|---|
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 7-8 |
| **Limitations** | | | |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 8-11 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 11 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 1 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.