

ORIGINAL ARTICLE

Adverse pregnancy outcomes and risk of later allergic rhinitis—Nationwide Swedish cohort study

Niki Mitselou¹  | Jenny Hallberg^{2,3,4}  | Olof Stephansson^{5,6} | Catarina Almqvist^{7,8}  | Erik Melén^{2,3,4}  | Jonas F. Ludvigsson^{1,7,9,10}

¹Department of Pediatrics, Örebro University Hospital, Örebro, Sweden

²Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

³Sachs' Children and Youth Hospital, Södersjukhuset, Stockholm, Sweden

⁴Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden

⁵Department of Medicine, Solna, Clinical Epidemiology Division, Karolinska Institutet, Stockholm, Sweden

⁶Department of Women's Health, Karolinska University Hospital, Stockholm, Sweden

⁷Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

⁸Pediatric Allergy and Pulmonology Unit, Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden

⁹Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Nottingham, UK

¹⁰Department of Medicine, Columbia University College of Physicians and Surgeons, New York, NY, USA

Correspondence

Niki Mitselou, Department of Pediatrics, Örebro University Hospital, Örebro, Sweden.

Email: niki.mitselou@oru.se

Funding information

Erik Melén and Catarina Almqvist are supported by grants from the Swedish Research Council, Stockholm County Council (ALF), and Swedish Lung-Heart Foundation. Niki Mitselou is supported by grants from the Swedish Research Council, Örebro County Council (ALF).

Editor: Jon Genuneit

Abstract

Background: Perinatal conditions may be associated with future allergic disease; however, data are conflicting and incomplete for childhood allergic rhinitis (AR). The aim of this study was to examine pregnancy outcome (cesarean delivery, preterm birth, low birthweight) and offspring AR as defined by national registers.

Methods: Nationwide longitudinal cohort study using prospectively recorded register data from 1 059 600 singleton livebirths born in Sweden in 2001–2012. Cox regression adjusted for infant sex and maternal factors (age at delivery, country of birth, parity, smoking, body mass index, and asthma/pulmonary disease) estimated hazard ratios (HRs) for AR during childhood.

Results: During the study period 2001–2013, 22 386 (2.11%) children were diagnosed with AR. AR was more common in infants born through cesarean delivery (2.34%) than in those born vaginally (2.10%) (HR = 1.12; 95% confidence interval [95% CI] = 1.08–1.16). This was equivalent to one extra case of AR in 383 children followed up in our study. AR was also associated with moderately preterm birth (≥ 32 –36 weeks of gestation: HR = 1.12, 95% CI = 1.04–1.20), large for gestational age (HR = 1.05, 95% CI = 1.01–1.10), and low (<7) 5-minute Apgar score (HR = 1.15, 95% CI = 1.02–1.30). Similar risk estimates were obtained when we restricted the outcome

Abbreviations: AR, allergic rhinitis; CI, confidence interval; HR, hazard ratio; ICD, International Classification of Diseases; LGA, large for gestational age; MBR, Medical Birth Register; NPR, National Patient Register; PAF, population-attributable fraction; SGA, small for gestational age.

The peer review history for this article is available at <https://publons.com/publon/10.1111/pai.13230>

© 2020 EAACI and John Wiley and Sons A/S. Published by John Wiley and Sons Ltd.

to ≥ 2 hospital-based records of AR. No association was observed between very preterm birth, post-term birth, low birthweight, or small for gestational age and AR.

Conclusion: Our study indicates an association between pregnancy outcomes and childhood AR, although observed effect sizes were generally modest.

KEYWORDS

allergic rhinitis, cesarean delivery, children, preterm birth

1 | INTRODUCTION

Allergic rhinitis (AR) is a common condition of the nasal mucosa characterized by immunoglobulin E (IgE)-mediated inflammation after allergen exposure.¹ Classical symptoms of AR include pruritus, rhinorrhea, sneezing, and nasal obstruction. AR often persists throughout life and tends to peak in adolescence and young adulthood. Today, the prevalence of AR in children ranges from 2% to 25%,^{2,3} but has increased globally in the past few decades. Although AR is not usually a severe disease, it is strongly associated with asthma^{4,5} and appears to have a significant impact on the quality of life of patients by affecting school performance as well as work productivity.^{2,3}

Previous research has linked adverse pregnancy outcomes and birth characteristics to a number of chronic disorders, including asthma.^{6–8} Evidence suggests that the risk of allergic disease is influenced by the early development of the immune system. However, the association between early-life factors and the risk of AR is not completely understood and little is known about the influence of perinatal conditions on the development of AR. Two meta-analyses reported a moderately increased risk of asthma and allergic disease in children born after cesarean delivery.^{9,10} A retrospective US study of 8953 children suggested that cesarean section increased the risk of AR. In that study, the risk of asthma was also greater after cesarean delivery, but the association was sex-specific and only held for girls.¹¹

Two apparent factors predisposing to asthma are preterm birth and low birthweight.^{8,12–14} Yet, asthma has several phenotypes and it is not clear whether pregnancy outcomes are linked specifically to allergic asthma and hence likely also to AR. Intriguingly, other studies indicate that preterm birth may be associated with a *lower* risk of allergic disease.^{15–18} Siltanen et al found that preterm birth reduces the long-term risk of atopy¹⁶ well into adulthood.¹⁷ Moreover, a Swedish cohort study reported that low gestational age decreased the risk of AR in young adulthood, implying that earlier exposure to environmental factors might protect against later allergic disease.¹⁸ Few studies have examined low birthweight and risk of allergic disease, including AR. The few studies that do exist have been negative, that is, reported a lack of association between low birthweight and subsequent development of AR.^{7,17,19–21} In contrast, AR may be more common in children with high birthweight or advanced gestational age.²¹

In this cohort study, we investigated the association between adverse pregnancy outcomes and the development of AR in over 1 million Swedish children born between 2001 and 2012.

Key Message

A Swedish cohort study of over 1 million children that examines the association between adverse pregnancy outcomes and risk of allergic rhinitis in offspring.

Caesarean delivery and preterm birth have been linked to asthma. There is evidence that the risk of allergic disease is influenced by the early development of the immune system. Yet, less is known about early-life risk factors for allergic rhinitis.

This large population-based cohort study suggests that caesarean delivery, moderately preterm birth, large for gestational age, and low 5-minute Apgar score are associated with an increased risk of allergic rhinitis in childhood, illustrating the impact of early-life influences on the development of allergic disease.

2 | METHODS

2.1 | Study design and population

This nationwide population-based cohort study used prospective data from nationwide healthcare registers in Sweden to investigate the association between adverse pregnancy outcomes and AR in childhood.

2.2 | Registers

Since 1973, virtually all births in Sweden have been registered in the Medical Birth Register (MBR).²² Using standardized medical records in prenatal, delivery, and neonatal care, data on pregnancy and birth are collected prospectively by healthcare providers.

The National Patient Register (NPR) was established in 1964 and has gradually expanded over the years to achieve nationwide coverage for inpatient diagnoses in 1987. Hospital-based outpatient visits have been recorded in the NPR since 2001, and therefore, we restricted our study sample to individuals born in that year or later. NPR diagnostic data are coded using the Swedish International Classification of Diseases (ICD) coding system.²³

Data between the MBR and NPR were linked through the unique personal identity number assigned to all Swedish residents.²⁴

2.3 | Study population

Through the MBR, we identified 1 232 739 consecutively born children between 2001 and 2012 in Sweden. We retrieved data on offspring sex, mode of delivery, gestational age, birthweight, and 5-minute Apgar score and examined the risk of developing AR in this population up to the year 2013. Our study population was restricted to 1 059 600 singletons (age range of 0 months to 13 years) who had complete data on all variables at the end of follow-up (Table 1). The end-point of our follow-up time was first diagnosis of AR, death, or December 31, 2013, whichever came first.

2.4 | Covariates

Information on maternal characteristics was retrieved from the MBR and included the following: age at delivery (≤ 24 , 25–29, 30–34, ≥ 35 years), country of birth (Sweden, any other Nordic country, or non-Nordic country), parity (nulliparous, 1–2 children, ≥ 3 children), smoking habits reported at first antenatal visit (non-smoker, 1–9 cigarettes per day, or ≥ 10 cigarettes per day), body mass index (BMI) in early pregnancy (≤ 18.49 , 18.5–24.99, 25–29.99, ≥ 30), and asthma/pulmonary disease (yes/no). Our data were divided into three calendar periods based on year of birth (2001–2004, 2005–2008, and 2009–2012).

2.5 | Exposures

We categorized mode of delivery into vaginal or cesarean. Cesarean delivery was categorized into elective (when performed before the onset of labor) vs. emergency. Gestational age was based on prenatal ultrasound examination (if available); otherwise, it was based on the date of the first day of the last menstrual period. We defined preterm birth as <37 weeks of gestation, very preterm as <32 completed weeks, moderately preterm as ≥ 32 – 36 weeks, and post-term birth as ≥ 42 weeks. Low birthweight was defined as a weight of <2500 g, moderately low as 1500–2499 g, and very low as <1500 g. Small for gestational age (SGA) was defined as birthweight less than the 10th percentile for children of similar sex and gestational age, according to the Swedish reference curve of estimated fetal growth.²⁵ Large for gestational age (LGA) was defined as birthweight above the 90th percentile. We defined low Apgar score as <7 at 5 minutes.

2.6 | Outcome—allergic rhinitis

During follow-up, we identified children in our cohort diagnosed with AR through the Swedish NPR. In this study, we defined allergic

rhinitis (AR) as having a relevant ICD-10 code (J30.0–4). We are not aware of any validation of the AR diagnosis in the NPR. However, the positive predictive values of most other disorders in this register range from 85% to 95%.^{23,26}

2.7 | Statistical analyses

Using Cox regression, we estimated hazard ratios (HRs) with 95% confidence intervals (CIs) for the association between cesarean delivery, preterm birth, low birthweight, SGA, LGA, low Apgar score, and AR diagnosis after adjusting for infant sex and maternal factors (age at delivery, country of birth, parity, early-pregnancy smoking, BMI, asthma/pulmonary disease; Tables 2 and 3). The proportional hazard assumption was tested through log-minus-log plots. We further studied the risk of having at least two hospital-based records of AR (Table 2). In an additional analysis, we stratified for years of follow-up (<1 , 1–4.99, ≥ 5 years; Table 3). Excess risks and population-attributable fractions (PAFs, %) for developing AR in children by pregnancy outcomes were calculated based on observed and expected incidence rates per 100 000 person-years standardized for covariates (Table 4).

SPSS version 25.0 (SPSS, Inc) was used for statistical analysis. HRs with 95% CIs that did not include 1.0 were considered statistically significant.

2.8 | Ethics

The study was approved by the Regional Ethical Review Board in Stockholm, Sweden (Dnr. 2008/1182-31/4).

3 | RESULTS

Our baseline cohort consisted of 1 232 739 consecutively born children between 2001 and 2012 in Sweden. Among these, 1 087 168 (88.19%) had complete data on all variables. Our study cohort was further restricted to singleton offspring. Final analyses were based on 1 059 600 (85.95%) singletons (Table 1). During the 2001–2013 study period, 22 386 (2.11%) of the 1 059 600 participating children developed AR; of these, 10 828 (1.02%) had at least two hospital-based diagnoses of AR. The median age at first diagnosis of AR was 5.7 years (range 0.2–12.9 years). The median follow-up was 6.7 years (range 0 months–13 years). Risk factors for AR included male sex, being born during the first calendar period (2001–2004), and having a Swedish-born mother, a nulliparous mother, or a mother with asthma/pulmonary disease (Table 1).

We calculated adjusted HRs (aHRs) to assess the link between perinatal characteristics and risk of AR (Tables 2 and 3). Some 2.34% of infants born through cesarean delivery vs 2.10% of those born vaginally developed AR. This corresponded to a 1.12-fold increased risk of AR (95% CI = 1.08–1.16), equivalent to one extra case of AR during

TABLE 1 Maternal and pregnancy characteristics

Characteristics	Children without allergic rhinitis N (%)	Children with allergic rhinitis N (%)
Total births	1 037 214 (97.9)	22 386 (2.1)
Infant sex		
Female	507 050 (48.9)	8044 (35.9)
Male	530 164 (51.1)	14 342 (64.1)
Calendar period of birth		
2001-2004	298 104 (28.7)	13 079 (58.4)
2005-2008	343 978 (33.2)	7521 (33.6)
2009-2012	395 132 (38.1)	1786 (8.0)
Maternal age at delivery (y)		
≤24	150 262 (14.5)	3259 (14.6)
25-29	310 111 (29.9)	7337 (32.8)
30-34	362 643 (35.0)	7779 (34.7)
≥35	214 198 (20.7)	4011 (17.9)
Country of birth		
Sweden	820 309 (79.1)	18 881 (84.3)
Other nordic (not Sweden)	17 002 (1.6)	397 (1.8)
Non-nordic	199 903 (19.3)	3108 (13.9)
Parity		
Nulliparous	462 165 (44.6)	11 246 (50.2)
1-2 children	516 601 (49.8)	10 205 (45.6)
≥3 children	58 448 (5.6)	935 (4.2)
Body mass index		
BMI ≤ 18.49	24 035 (2.3)	536 (2.4)
18.5 ≤ BMI ≤ 24.99	629 613 (60.7)	13 339 (59.6)
25 ≤ BMI ≤ 29.99	262 458 (25.3)	5752 (25.7)
BMI ≥ 30	121 108 (11.7)	2759 (12.3)
Early-pregnancy smoking habits		
Non-smoker	957 445 (92.3)	20 416 (91.2)
1-9 cigarettes/d	60 058 (5.8)	1495 (6.7)
≥10 cigarettes/d	19 711 (1.9)	475 (2.1)
Maternal asthma/pulmonary disease		
No	959 242 (92.5)	18 985 (84.8)
Yes	77 972 (7.5)	3 401 (15.2)

follow-up per 383 children born through cesarean delivery. AR was positively associated with both elective (HR = 1.10, 95% CI = 1.05-1.15) and emergency cesarean delivery (HR = 1.13, 95% CI = 1.08-1.19).

Allergic rhinitis was also associated with moderately preterm birth (HR = 1.12, 95% CI = 1.04-1.20), LGA (HR = 1.05, 95% CI = 1.01-1.10) and low 5-minute Apgar score (HR = 1.15, 95% CI = 1.02-1.30). We found no association between AR and very preterm birth, post-term birth, low birthweight, or SGA (Table 2).

Risk estimates did not differ when the outcome was defined as having ≥2 recorded hospital-based diagnoses of AR, except that the

association with elective cesarean delivery now failed to attain statistical significance (Table 2). Furthermore, when we stratified for years of follow-up (<1, 1-4.99, ≥5 years), the HRs for AR were similar for all the exposures in the three subgroups though they were no longer statistically significant and with wide CIs. Unfortunately, we did not have enough power in every subgroup. No difference was observed in risk estimates for AR between boys and girls (Table 3). HRs did not change significantly when the data were divided into three calendar periods of birth (2001-2004, 2005-2008, and 2009-2012; Table S1).

Finally, we estimated excess risks of AR per 100 000 person-years (adjusted for covariates) and PAFs (Table 4). The PAF was 11% for cesarean delivery, implying that 11% of all AR in children born after cesarean section may be linked to this delivery mode.

4 | DISCUSSION

In this large population-based cohort study of over 1 million Swedish children, cesarean delivery (elective and emergency) was associated with a modestly increased risk of AR in the offspring. Similarly, children born moderately preterm, LGA, or with a low 5-minute Apgar score were more likely to be diagnosed with AR during follow-up.

The positive association observed between cesarean delivery and AR is partly in line with the results of earlier research.^{9-11,27-29} Renz-Polster et al reported that children born by cesarean delivery had a significantly elevated risk of being diagnosed with AR (OR = 1.37, 95% CI = 1.14-1.63).¹¹ Another US study found that cesarean delivery was associated with increased odds of AR in a multivariate analysis in children with a parental history of atopy (odds ratio [OR] = 1.8, 95% CI = 1.0-3.1).²⁷ However, data are conflicting and inconclusive. In this respect, our findings diverge from the results of Pyrhonen et al³⁰ who did not find an association between cesarean delivery and AR. However, the confidence intervals in that study were wide and the follow-up lasted only up to the age of 4 years, which is too early to be fully informative for diagnosis of AR.

It has previously been suggested that the underlying maternal or fetal indications for cesarean delivery may account for the increased risk of allergic manifestations seen in offspring.⁶ Still, in our study, a higher risk of being diagnosed with AR was observed in children born after both elective and emergency cesarean deliveries. Similar findings were observed in our recent study on the association between perinatal characteristics and risk of later food allergy in offspring in which both elective and emergency cesarean deliveries were associated with increased risk.¹⁵ These observations strengthen the theory that labor per se functions as a regulator of the offspring immune system³¹ and are consistent with the hygiene hypothesis,^{32,33} illustrating the impact of the microbiota composition and early-life influences on the development of allergic disease.^{28,29}

Our findings also suggest that moderately preterm birth is associated with an increased risk of AR in offspring. This positive association was, however, not observed in children born very preterm (<32

TABLE 2 Perinatal characteristics and risk of allergic rhinitis

Characteristics	Exposed: observed events/total (%)	Unexposed: observed events/total (%)	Crude hazard ratio; 95% CI	Adjusted hazard ratio; 95% CI (model 1) ^a	Adjusted hazard ratio; 95% CI (model 2) ^b	Two recorded diagnoses Adjusted hazard ratio; 95% CI (model 2) ^c
Cesarean delivery	4000/170 499 (2.3)	18 386/889 101 (2.1)	1.18; 1.14-1.22	1.12; 1.08-1.16	1.12; 1.08-1.16	1.08; 1.02-1.13
Elective	1907/86 576 (2.2)		1.10; 1.05-1.16	1.10; 1.05-1.15	1.10; 1.05-1.15	1.06; 0.99-1.14
Emergency	2093/83 923 (2.5)		1.25; 1.20-1.31	1.14; 1.08-1.19	1.13; 1.08-1.19	1.09; 1.02-1.17
Gestational age						
Very preterm birth < 32 wk	116/6240 (1.9)	19 395/933 593 (2.1)	0.98; 0.81-1.17	0.91; 0.76-1.10	1.10; 0.80-1.51	0.82; 0.48-1.39
Moderately preterm ≥ 32-36 wk	1057/42 975 (2.5)		1.19; 1.11-1.26	1.12; 1.06-1.20	1.12; 1.04-1.20	1.13; 1.02-1.24
Post-term ≥ 42 wk	1818/76 792 (2.4)		1.07; 1.02-1.12	1.00; 0.95-1.05	1.00; 0.95-1.05	1.02; 0.95-1.09
Low birthweight						
Very low ≤ 1499 g	79/4992 (1.6)	21 721/1 028 589 (2.1)	0.84; 0.67-1.05	0.81; 0.65-1.01	0.71; 0.42-1.22	0.52; 0.22-1.21
Moderately low 1500-2499 g	589/26 146 (2.3)		1.10; 1.02-1.20	1.08; 1.00-1.18	0.99; 0.90-1.08	0.96; 0.84-1.10
Fetal growth						
Small for gestational age	2011/99 161 (2.0)	17 678/841 953 (2.1)	0.98; 0.94-1.03	0.96; 0.92-1.01	0.96; 0.91-1.00	0.97; 0.91-1.04
Large for gestational age	2683/117 936 (2.3)		1.05; 1.01-1.09	1.07; 1.02-1.11	1.05; 1.01-1.10	1.10; 1.04-1.17
Low Apgar score (<7) at 5 min	270/11 106 (2.4)	22 043/1 044 036 (2.1)	1.30; 1.16-1.47	1.18; 1.04-1.33	1.15; 1.02-1.30	1.31; 1.11-1.54

Statistically significant findings are presented in italics.

^aModel 1: adjustment for sex, maternal age at delivery, country of birth, parity, body mass index, early-pregnancy smoking, and maternal asthma/pulmonary disease.

^bModel 2: adjustment for all variables in model 1 plus cesarean delivery, gestational age, and birthweight.

^cModel 2. The outcome in this analysis is having at least two recorded diagnoses of food allergy.

TABLE 3 Perinatal characteristics and risk of allergic rhinitis according to follow-up and sex

Characteristics	<1 y HR; 95% CI	1-4.99 y HR; 95% CI	≥5 y HR; 95% CI	Boys HR; 95% CI	Girls HR; 95% CI
Cesarean delivery	1.13; 0.85-1.46	1.02; 0.97-1.08	1.04; 0.99-1.08	1.10; 1.06-1.15	1.14; 1.08-1.21
Elective	1.38; 0.94-2.02	1.04; 0.96-1.12	1.04; 0.98-1.11	1.09; 1.03-1.16	1.10; 1.02-1.19
Emergency	0.99; 0.70-1.41	1.01; 0.93-1.08	1.03; 0.97-1.10	1.11; 1.04-1.17	1.19; 1.10-1.29
Gestational age					
Very preterm birth < 32 wk	0.45; 0.04-4.64	1.19; 0.72-1.97	0.91; 0.60-1.40	0.93; 0.62-1.39	1.52; 0.92-2.51
Moderately preterm ≥ 32-36 wk	1.20; 0.66-2.20	0.98; 0.88-1.09	0.95; 0.87-1.05	1.11; 1.02-1.21	1.13; 1.00-1.27
Post-term ≥ 42 wk	0.67; 0.42-1.08	0.96; 0.88-1.04	0.96; 0.90-1.02	1.02; 0.97-1.08	0.93; 0.85-1.02
Low birthweight					
Very low ≤ 1499 g	0.76; 0.10-5.70	0.58; 0.22-1.56	0.91; 0.39-2.08	0.83; 0.42-1.61	0.57; 0.24-1.36
Moderately low 1500-2499 g	1.03; 0.46-2.30	1.03; 0.88-1.20	1.10; 0.97-1.25	1.00; 0.89-1.13	0.96; 0.83-1.12
Fetal growth					
Small for gestational age	1.11; 0.68-1.80	1.02; 0.94-1.10	1.00; 0.94-1.07	0.98; 0.93-1.05	0.92; 0.84-1.00
Large for gestational age	0.90; 0.66-1.22	1.01; 0.95-1.08	0.99; 0.94-1.04	1.08; 1.02-1.13	1.04; 0.97-1.12
Low Apgar score (<7) at 5 min	1.45; 0.60-3.52	0.91; 0.75-1.11	0.95; 0.81-1.11	1.23; 1.07-1.42	1.32; 1.06-1.63

Note: Statistically significant findings are presented in *italics*.

All models were adjusted for sex, maternal age at delivery, country of birth, parity, body mass index, early-pregnancy smoking, maternal asthma/pulmonary disease plus cesarean delivery, gestational age, and birthweight.

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio.

TABLE 4 Excess risks and population-attributable fractions for developing allergic rhinitis in children by adverse pregnancy outcomes

Perinatal characteristics	Observed number of events	Expected number of events ^a	Excess risk/100 000 person-years	Attributable fraction (%)
Cesarean delivery	4000	3571	39	11
Elective	1907	1734	31	9
Emergency	2093	1852	45	12
Gestational age				
Very preterm < 32 wk	116	105	19	9
Moderately preterm ≥ 32-36 wk	1057	944	33	11
Post-term ≥ 42 wk	1818	1818	0	0
Low birthweight				
Very low ≤ 1499 g	79	111	-127	-41
Moderately low 1500-2499 g	589	595	-7	-1
Fetal growth				
Small for gestational age	2011	2095	-16	-4
Large for gestational age	2683	2555	16	5
Low Apgar score (<7) at 5 min	270	235	78	13

Note: Attributable fraction is the proportion of all cases of allergic rhinitis exposed to a risk factor that could be prevented if the exposure was eliminated (eg, % of all allergic rhinitis in children exposed to cesarean delivery may be due to mode of delivery).

^aExpected number of events was standardized as regards covariates.

gestational weeks), for whom inverse associations were observed in two of our models. Whether this observation is a result of different neonatal care practices received by very preterm infants compared with moderately preterm infants or is due to different stages of immune system development between the two groups remains to be examined.

Previous research suggests that preterm birth reduces the risk of later allergic disease.¹⁵⁻¹⁸ A Finnish study reported a decrease in the risk of allergic disease in adulthood after preterm birth (mean gestational age 29.2 weeks, range 24.0-35.6).¹⁷ That study examined 166 adults who were born preterm and at very low birthweight between 1978 and 1985. Thus, the results may not be valid any longer because neonatal care in the 1970s and 1980s differs from that of today. Another study from Finland found a lower risk of atopy in 72 10-year-old children born preterm in 1987-1988 and of very low birthweight.¹⁶ In our nationwide cohort study of over 1 million Swedish children born until 2012, we found a negative association between very preterm birth (<32 weeks) and risk of food allergy.¹⁵ Finally, another Swedish cohort study found a lower risk of AR in young adults who were born preterm (<37 gestational weeks) from 1973 to 1979.¹⁸ In that study, the adjusted ORs for nasal corticosteroid prescription decreased by earlier preterm gestational ages. Again, we need to consider that neonatal care in the 1970s differs from present-day neonatal care and also that mild or self-treated AR may have been missed in that study because of their use of medication prescription as a proxy for AR.

Large for gestational age and low 5-minute Apgar score (representing fetal distress during labor) were also associated with a significantly increased risk of AR in childhood. These results agree with the observations of our recent cohort study showing that the risk of food allergy is higher in children born LGA or with a low 5-minute Apgar score,¹⁵ and also support the hypothesis that early growth conditions and factors operating during early stages of development may influence a predisposition to the inception of non-communicable diseases, including the subsequent risk of allergic disease.³⁴

The longitudinal population-based design and large sample size are two strengths of this study. We had access to data on more than one million births. Using nationwide healthcare registers, we were able to examine the risk of developing AR in nearly all children born in Sweden in 2001-2012. Moreover, selection bias should be minimal given that virtually complete ascertainment of children and cases was possible.³⁵ In addition, the free-of-charge healthcare system for children in Sweden guarantees equal access to pediatric health care independent of socioeconomic status.³⁶ Consequently, this study likely includes an unbiased, generalizable proportion of children with mild, moderate, and severe AR representative of the general population.

There are several limitations related to this study, including the risk of residual confounding. Although we controlled for a broad range of covariates, we were not able to examine the role of breast-feeding, antibiotic use, or underlying indications for cesarean delivery. Yet, a 2014 systematic review reported there is no strong evidence to support breast-feeding to prevent later allergy.³⁷ Also,

a study by Ortqvist et al³⁸ including sibling analyses suggested that positive associations between exposure to antibiotics in intrauterine and early life and one atopic disease (childhood asthma) could have been due to confounding by shared factors within families, in addition to confounding by respiratory infections. Previous research has underlined the influence of environmental factors related to urban living on the development of allergic disease, and a reduced prevalence of AR in children of farming families has been suggested.³³ In this paper, though, we were unable to perform stratified analysis to examine the risk of AR by urban versus rural residence, as we lacked data on these demographic characteristics.

Data on maternal or paternal AR diagnoses are not registered in the MBR. During the first antenatal visit, all pregnant women are asked by midwives about a number of specific diseases, including asthma for which we have adjusted in our models. As opposed to children, only a small proportion of adults are likely to be referred to a hospital-based specialist for AR. We do not have access to primary care data and, as visits to general practitioners are not recorded in the NPR, we were unable to adjust for this potential confounder.

The diagnosis of AR in this study was based on relevant Swedish ICD-10 codes. We are not aware of any validation of AR in the NPR, and it is likely that cases of mild-to-moderate AR that are primarily treated in the primary care have been missed, since other Swedish studies report higher childhood AR prevalences.³⁹ In general, the positive predictive values for most disorders in the NPR range between 85% and 95%.^{23,26} Yet, this high validity cannot uncritically apply to other diseases. In Sweden, general practitioners often investigate and treat AR in children. A large proportion of children (especially those with moderate-to-severe AR), though, are referred to a hospital-based specialist for second opinion and confirmation of diagnosis. Cases of moderate-to-severe AR, patients with comorbidities (asthma, eczema, or other chronic disease), or children who receive allergen-specific immunotherapy (or being evaluated for potential treatment) are being followed by hospital-based pediatricians or pediatric allergists. Thus, it is likely that the structure of the NPR may have contributed to somewhat lower coverage in this study, in particular of mild AR. A cross-national population-based study from Denmark and Sweden based on information on disease-specific dispensed prescribed medication, specific hospital contacts, or both reported an 11% lifetime prevalence of AR at age 5 years in Swedish children and 7% in Danish.⁴⁰ Regrettably, we did not have access to data on AR-specific prescribed medications. Hence, our observations of a positive association with several birth characteristics may relate to moderate-to-severe childhood AR that has been diagnosed in a hospital-based inpatient or outpatient setting. While diagnoses assigned by pediatricians or pediatric allergists are likely to have a high specificity, we carried out a sensitivity analysis where we examined the risk of having ≥ 2 recorded diagnoses of AR (to further increase specificity). This analysis showed similar risk estimates, except that the association between *elective* cesarean delivery and AR no longer attained statistical significance.

In conclusion, this large nationwide cohort study found an increased risk of childhood AR in offspring born by cesarean delivery.

In addition, children born moderately preterm, LGA, or with low Apgar score were at a higher risk of AR.

CONFLICT OF INTEREST

Dr Ludvigsson coordinates a study on behalf of the Swedish IBD quality register (SWIBREG). This study has received funding from Janssen Corporation. The other authors have no conflicts of interest to disclose.

ORCID

Niki Mitselou  <https://orcid.org/0000-0001-8056-9915>
 Jenny Hallberg  <https://orcid.org/0000-0003-4960-692X>
 Catarina Almqvist  <https://orcid.org/0000-0002-1045-1898>
 Erik Melén  <https://orcid.org/0000-0002-8248-0663>

REFERENCES

- Wise SK, Lin SY, Toskala E, et al. International consensus statement on allergy and rhinology: allergic rhinitis. *Int Forum Allergy Rhinol*. 2018;8(2):108-352.
- Greiner AN, Hellings PW, Rotiroti G, Scadding GK. Allergic rhinitis. *Lancet*. 2011;378(9809):2112-2122.
- Brozek JL, Bousquet J, Agache I, et al. Allergic rhinitis and its impact on asthma (ARIA) guidelines-2016 revision. *J Allergy Clin Immunol*. 2017;140(4):950-958.
- Simons FE. Allergic rhinobronchitis: the asthma-allergic rhinitis link. *J Allergy Clin Immunol*. 1999;104(3 Pt 1):534-540.
- Leynaert B, Neukirch F, Demoly P, Bousquet J. Epidemiologic evidence for asthma and rhinitis comorbidity. *J Allergy Clin Immunol*. 2000;106(5 Suppl):S201-S205.
- Almqvist C, Cnattingius S, Lichtenstein P, Lundholm C. The impact of birth mode of delivery on childhood asthma and allergic diseases—a sibling study. *Clin Exp Allergy*. 2012;42(9):1369-1376.
- Lundholm C, Ortqvist AK, Lichtenstein P, Cnattingius S, Almqvist C. Impaired fetal growth decreases the risk of childhood atopic eczema: a Swedish twin study. *Clin Exp Allergy*. 2010;40(7):1044-1053.
- Ortqvist AK, Lundholm C, Carlstrom E, Lichtenstein P, Cnattingius S, Almqvist C. Familial factors do not confound the association between birth weight and childhood asthma. *Pediatrics*. 2009;124(4):e737-e743.
- Bager P, Wohlfahrt J, Westergaard T. Caesarean delivery and risk of atopy and allergic disease: meta-analyses. *Clin Exp Allergy*. 2008;38(4):634-642.
- Thavagnanam S, Fleming J, Bromley A, Shields MD, Cardwell CR. A meta-analysis of the association between Caesarean section and childhood asthma. *Clin Exp Allergy*. 2008;38(4):629-633.
- Renz-Polster H, David MR, Buist AS, et al. Caesarean section delivery and the risk of allergic disorders in childhood. *Clin Exp Allergy*. 2005;35(11):1466-1472.
- Jaakkola JJ, Ahmed P, Ieromnimon A, et al. Preterm delivery and asthma: a systematic review and meta-analysis. *J Allergy Clin Immunol*. 2006;118(4):823-830.
- Sonnenschein-van der Voort AM, Arends LR, de Jongste JC, et al. Preterm birth, infant weight gain, and childhood asthma risk: a meta-analysis of 147,000 European children. *J Allergy Clin Immunol*. 2014;133(5):1317-1329.
- Castro-Rodriguez JA, Forno E, Rodriguez-Martinez CE, Celedon JC. Risk and protective factors for childhood asthma: What is the evidence? *J Allergy Clin Immunol Pract*. 2016;4(6):1111-1122.
- Mitselou N, Hallberg J, Stephansson O, Almqvist C, Melen E, Ludvigsson JF. Caesarean delivery, preterm birth, and risk of food allergy: Nationwide Swedish cohort study of more than 1 million children. *J Allergy Clin Immunol*. 2018;142(5):1510-1514.e2.
- Siltanen M, Kajosaari M, Pohjavuori M, Savilahti E. Prematurity at birth reduces the long-term risk of atopy. *J Allergy Clin Immunol*. 2001;107(2):229-234.
- Siltanen M, Wehkalampi K, Hovi P, et al. Preterm birth reduces the incidence of atopy in adulthood. *J Allergy Clin Immunol*. 2011;127(4):935-942.
- Crump C, Sundquist K, Sundquist J, Winkleby MA. Gestational age at birth and risk of allergic rhinitis in young adulthood. *J Allergy Clin Immunol*. 2011;127(5):1173-1179.
- Mitchell EA, Clayton T, Garcia-Marcos L, Pearce N, Foliaki S, Wong G. Birthweight and the risk of atopic diseases: the ISAAC Phase III study. *Pediatr Allergy Immunol*. 2014;25(3):264-270.
- Fergusson DM, Crane J, Beasley R, Horwood LJ. Perinatal factors and atopic disease in childhood. *Clin Exp Allergy*. 1997;27(12):1394-1401.
- Katz KA, Pocock SJ, Strachan DP. Neonatal head circumference, neonatal weight, and risk of hayfever, asthma and eczema in a large cohort of adolescents from Sheffield, England. *Clin Exp Allergy*. 2003;33(6):737-745.
- Cnattingius S, Ericson A, Gunnarskog J, Kallen B. A quality study of a medical birth registry. *Scand J Soc Med*. 1990;18(2):143-148.
- Ludvigsson JF, Andersson E, Ekblom A, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health*. 2011;11:450.
- Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekblom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol*. 2009;24(11):659-667.
- Marsal K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. *Acta Paediatr*. 1996;85(7):843-848.
- Ortqvist AK, Lundholm C, Wettermark B, Ludvigsson JF, Ye W, Almqvist C. Validation of asthma and eczema in population-based Swedish drug and patient registers. *Pharmacoepidemiol Drug Saf*. 2013;22(8):850-860.
- Pistiner M, Gold DR, Abdulkarim H, Hoffman E, Celedon JC. Birth by cesarean section, allergic rhinitis, and allergic sensitization among children with a parental history of atopy. *J Allergy Clin Immunol*. 2008;122(2):274-279.
- van Nimwegen FA, Penders J, Stobberingh EE, et al. Mode and place of delivery, gastrointestinal microbiota, and their influence on asthma and atopy. *J Allergy Clin Immunol*. 2011;128(5):pp. 948-55.e1-3.
- Salam MT, Margolis HG, McConnell R, McGregor JA, Avol EL, Gilliland FD. Mode of delivery is associated with asthma and allergy occurrences in children. *Ann Epidemiol*. 2006;16(5):341-346.
- Pyrhonen K, Nayha S, Hiltunen L, Laara E. Caesarean section and allergic manifestations: insufficient evidence of association found in population-based study of children aged 1 to 4 years. *Acta Paediatr*. 2013;102(10):982-989.
- Schlinzig T, Johansson S, Stephansson O, et al. Surge of immune cell formation at birth differs by mode of delivery and infant characteristics—A population-based cohort study. *PLoS ONE*. 2017;12(9):e0184748.
- Strachan DP. Hay fever, hygiene, and household size. *BMJ*. 1989;299(6710):1259-1260.
- Strachan DP. Family size, infection and atopy: the first decade of the "hygiene hypothesis". *Thorax*. 2000;55(Suppl 1):S2-S10.
- Hanson M, Gluckman P. Developmental origins of noncommunicable disease: population and public health implications. *Am J Clin Nutr*. 2011;94(6 Suppl):1754S-1758S.
- Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.

36. Wettergren B, Blennow M, Hjern A, et al. Child health systems in Sweden. *J Pediatr*. 2016;177:S187-S202.
37. de Silva D, Geromi M, Halken S, et al. Primary prevention of food allergy in children and adults: systematic review. *Allergy*. 2014;69(5):581-589.
38. Ortqvist AK, Lundholm C, Kieler H, et al. Antibiotics in fetal and early life and subsequent childhood asthma: nationwide population based study with sibling analysis. *BMJ*. 2014;349:g6979.
39. Westman M, Kull I, Lind T, et al. The link between parental allergy and offspring allergic and nonallergic rhinitis. *Allergy*. 2013;68(12):1571-1578.
40. Henriksen L, Simonsen J, Haerskjold A, et al. Incidence rates of atopic dermatitis, asthma, and allergic rhinoconjunctivitis in Danish and Swedish children. *J Allergy Clin Immunol*. 2015;136(2):360-366.e2.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Mitselou N, Hallberg J, Stephansson O, Almqvist C, Melén E, Ludvigsson JF. Adverse pregnancy outcomes and risk of later allergic rhinitis—Nationwide Swedish cohort study. *Pediatr Allergy Immunol*. 2020;00:1–9. <https://doi.org/10.1111/pai.13230>

eTable 1. Perinatal characteristics and risk of allergic rhinitis according to calendar period of birth

Characteristics	2001-2004 HR; 95%CI	2005-2008 HR; 95%CI	2009-2012 HR; 95%CI
Caesarean delivery	<i>1.19; 1.14-1.24</i>	<i>1.15; 1.08-1.22</i>	<i>1.22; 1.09-1.37</i>
Elective	<i>1.10; 1.04-1.18</i>	<i>1.09; 1.01-1.18</i>	<i>1.14; 0.97-1.34</i>
Emergency	<i>1.27; 1.20-1.35</i>	<i>1.21; 1.12-1.30</i>	<i>1.31; 1.12-1.52</i>
Gestational age			
Very preterm birth <32 weeks	1.05; 0.83-1.32	0.78; 0.55-1.10	1.35; 0.76-2.38
Moderately preterm ≥32-36 weeks	<i>1.15; 1.05-1.24</i>	<i>1.26; 1.33-1.39</i>	1.19; 0.95-1.48
Post term ≥42 weeks	1.04; 0.97-1.10	<i>1.13; 1.04-1.23</i>	1.14; 0.96-1.35
Low Birth weight			
Very low ≤1499g	0.95; 0.72-1.25	<i>0.64; 0.41-0.98</i>	0.99; 0.48-2.09
Moderately low 1500-2499g	<i>1.12; 1.01-1.25</i>	1.03; 0.89-1.19	1.24; 0.95-1.63
Fetal growth			
<i>Small</i> for gestational age	0.99; 0.93-1.05	1.02; 0.94-1.10	1.02; 0.87-1.19
<i>Large</i> for gestational age	1.04; 0.99-1.10	1.06; 0.99-1.14	1.09; 0.94-1.26
Low Apgar score (<7) at 5 minutes	<i>1.35; 1.15-1.56</i>	<i>1.30; 1.06-1.56</i>	1.00; 0.48-2.09

HR, hazard ratio. 95%CI=95% confidence interval.

All models were adjusted for sex, maternal age at delivery, country of birth, parity, body mass index, early pregnancy smoking, maternal asthma/pulmonary disease plus caesarean delivery, gestational age and birth weight.