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Season of birth, childhood asthma and allergy in a nationwide cohort – mediation through lower respiratory infections

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Season of birth and asthma or allergic rhinoconjunctivitis – mediation through respiratory infections

Key words: asthma, allergy, epidemiology, pollen, respiratory infectious disease, season, register

Abstract

Background

Previous studies have suggested an association between season of birth and risk of childhood asthma and allergic disease. The association may be modified by birth year and region, or mediated by respiratory tract infections.

Objective

We aimed to estimate the association between season of birth and risk of childhood asthma/wheeze or allergic rhinoconjunctivitis in a population-based setting, and the mediating effect of lower respiratory infections.

Methods

Two population-based cohorts were identified from the nationwide Swedish Medical Birth, Patient and Prescribed Drug Registers. The association between birth month/season and asthma/wheeze incidence was analysed using Cox proportional regression in the younger cohort born 2005-2010 (n=582,494) and asthma/allergic rhinoconjunctivitis prevalence during the 7th year of life using log-binomial models in the older cohort born 2001-2004 (n=367,583). Interactions were formally tested. Mediation analyses to address the effect of lower respiratory infections were performed in the older cohort using the R package 'medflex'.

Results

Children born during fall and winter had an increased risk of asthma/wheeze after 2 years of age in the younger cohort; hazard ratio 1.24 (95% confidence interval, CI 1.17, 1.33) for winter and risk of prevalent asthma during their 7th year of life in the older cohort; prevalence ratio (PR) 1.12 (95% CI 1.08, 1.16) for winter. These estimates were partly mediated by lower respiratory infections; the indirect effect for winter compared to summer was PR 1.03 (95%

CI 1.03, 1.04). The association was similar for allergic rhinoconjunctivitis in the 7th year of life, but not mediated by respiratory infections.

Conclusion

We found that the association between season of birth and risk of childhood asthma/wheeze, but not allergic rhinoconjunctivitis, is partly mediated through lower respiratory infections.

Clinical relevance

This has important implications for patient care, such as asthma management programs to notify timing of seasonality for viral respiratory tract infections.

Introduction

It has been suggested that season of birth is associated with risk of asthma and allergic disease in childhood, but results are contradictory. Children born to mothers exposed to high levels of birch pollen during pregnancy have been reported to have an increased risk of sensitisation[1] or asthma[2], and exposure to high levels of birch pollen in infancy has been found to increase the risk of sensitisation and allergic asthma.[3] Others have shown that children born in fall have a higher prevalence of asthma and higher levels of total IgE compared to those born in spring[4-8] and atopic dermatitis has been reported to be more prevalent in children born in fall than in spring,[9] yet others have found no consistent pattern.[10]

Early or fetal life exposure to allergens (during spring and early summer) or respiratory infections (during fall and early winter) has the potential to affect the immune system in young children and make them prone towards sensitisation and asthma. From clinical experience, it is clear that respiratory tract infections are also risk factors for subsequent asthma. Hence, the association between seasonality and asthma or allergies may in fact be mediated by respiratory tract infections. Such mediation could be studied using variation in birth year and geographical region, as pollen counts and respiratory infections vary across years and regions.[11,12]

Improved knowledge about the impact of birth season and seasonality on asthma or allergic rhinoconjunctivitis could inform future preventive measures to pregnant women and new parents to reduce the risk of childhood asthma and allergies. Thus, the aim of our study was 1) to assess if there is an association between season of birth and risk of childhood asthma or allergic rhinoconjunctivitis and 2) if the association is modified by birth year or geographical region (which mirrors different levels and timing of pollen exposure) or mediated by respiratory tract infections.

Methods

Study population & Study design

Two separate cohorts of children were identified through the Medical Birth Register (MBR), which includes data on more than 98% of all births in Sweden. The older cohort included all live-born children between January 1, 2001 and December 31, 2004 and the younger cohort included all children live-born between July 1, 2005 and December 31, 2010. Data from the two cohorts were linked, via individual personal identification numbers assigned to all residents in Sweden, to the Cause of Death register, the Migration Register, the National Patient Register (NPR) and the Swedish Prescribed Drug Register (SPDR). Parents were identified through the Multi-Generation Register.

In the present study, we accessed data from all registers until December 31, 2011. The reason why we chose two separate cohorts was due to data availability and completeness. The younger cohort was followed with complete data from birth until first asthma/wheeze onset date, death, emigration or December 31 2011 whichever occurred first. The older cohort was evaluated for prevalent and more established asthma and allergy during their 7th year of life. Children who died or emigrated before their 7th birthday were excluded.

Outcome definition

The nationwide SPDR was introduced in July 2005 and contains information on prescription- and dispense dates, number of packages and dosage of all prescribed medications dispensed in Swedish pharmacies, based on the Anatomical Therapeutic Chemical (ATC) classification system.

Asthma medication reported in the SPDR has been shown to be a suitable proxy for asthma in both children and adults.[13] The NPR has national coverage of hospitalisations in Sweden since

1987 and also includes ~80% of all outpatient specialist visits since 2001, including diagnosis codes, date of visit/admission/discharge and whether it was a planned or unplanned visit.

Asthma

Asthma/wheeze was assessed during the entire follow-up (0-6.5 years) for the younger cohort (children born between July 2005 and December 2010) and asthma during the 7th year of life for the older cohort (children born between January 2001 and December 2004).

Children were defined as being asthmatic according to the SPDR if having either:

- two or more dispensed prescriptions of glucocorticoids (R03BA), fixed combinations of β2-agonists and glucocorticoids (R03AK06 or R03AK07) and/or leukotriene receptor antagonists (R03DC03) with a time frame of 2 weeks or more between distributions for children aged 0-4.5 years and independent of time between distributions for children aged >4.5 years.
- alternatively three or more dispensed prescriptions of any of the medications listed above or inhalations of selective β2-adrenoreceptor agonists (R03AC02, R03AC03, R03AC12 or R03AC13) within a 12-months period.

To define prevalent asthma for the older children, at least one of the prescriptions had to be dispensed during the 7th year. To be defined as having asthma/wheeze, the younger children were also required to have an asthma diagnosis (J45) from the NPR while the older children were defined as asthmatic if having either a diagnosis from NPR or fulfilling the criteria from SPDR. Asthma/wheeze onset in the younger cohort was defined as the date of the first recording of either medication or specialist diagnosis.

Allergy

Allergy (allergic rhinonconjunctivitis) was assessed in the older cohort only and defined using the criteria described by Henriksen et al.[14] In brief, one of the following four criteria should be fulfilled from age 5.5-7. Criteria 1 (based on ICD-10): ≥1 hospital contact for J30. Criteria 2 (based on ATC and ICD-10): ≥ 2 filled prescriptions of R01AD and no hospital contact for (exclusions criteria): J33, J010, J019, J320 –J329. Criteria 3 (based on ICD-10 and ATC): ≥2 filled prescriptions of R06A and no hospital contact for L29 or DL50. Criteria 4 (based on ATC): ≥ 1 filled prescriptions of V01A and/or S01GX, Table S1.

Exposure classification

Date and month of birth were collapsed into seasons according to the Northern hemisphere as follows: spring (March-May), summer (June-August), fall (September-November) and winter (December-February).

Confounders, effect modifiers and mediators

Birth year, county of birth and family history of asthma/allergy were all considered as potential effect modifiers for the association between birth month/season of birth and asthma or allergy. Information on birth year and county of birth were collected from the Medical Birth Register. Family history of asthma and allergy was defined as having a biological mother or father who fulfilled the criteria for asthma/allergy defined for the older cohort between 2005 and 2011. Using a directed acyclic graph (DAG)[15] we did not identify any strict confounders for the association between birth month/season of birth and asthma or allergy, since confounders have to affect both the exposure (birth month) and outcome (Figure S1).

In- and outpatient diagnoses of lower respiratory infections pneumonia (ICD10: J12-J18) and respiratory syncytial virus (RSV) (ICD10: J12.1, J20.5 and J21.0) as potential mediators were identified from the NPR for all children prior to outcome or end of follow-up in the younger cohort and prior to the 6th birthday in the older cohort. Based on the DAG, gestational age (<

or >37 weeks) and sibling status (yes/no) retrieved from MBR were considered as potential confounders in the association between lower respiratory infections and asthma or allergic rhinoconjunctivitis and adjusted for in the mediator analysis (Figure S1).

Statistical analysis

Younger cohort

Incidence rates of asthma/wheeze were estimated as number of events per risk time in person-years. To investigate the association between birth month/season and asthma/wheeze, hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using Cox proportional hazard regression models with attained age (in days) as the underlying timescale. The proportional hazards assumption was formally assessed using the Therneau and Grambsch test of the Schoenfeld residuals. The test indicated non-proportional hazards with respect to birth month/season and attained age. We therefore modelled interactions between birth month/season and attained age by estimated separate effects of birth month and season of birth for the follow-up into two categories, 0-2 years and 2-6 years of age.

Older cohort

Log-binomial models were used to estimate prevalence ratios (PR) with 95% CIs as a measure of the association between birth month/season and prevalent asthma and allergic rhinoconjunctivitis during the 7th year of life. Date of birth was modelled as a continuous exposure, using restricted cubic splines with four degrees of freedom, in order to capture the non-linear effect.

Interactions between birth month/season of birth and the potential effect modifiers birth year, county and family history of asthma/allergy were formally tested in both cohorts using two-sided likelihood ratio (LR) tests with a 5% significance level.

Lower respiratory infections and mediation

To investigate whether the effect of birth month on asthma and allergic rhinoconjunctivitis was mediated by having a lower respiratory infection (i.e. pneumonia and RSV) during the first 3, 6, 12 months or any time before age 6, we performed mediation analyses in the older cohort. The R package "medflex" was used to fit natural effect models for nested counterfactuals.[16] This analysis decomposes the total effect of the exposure into estimates of the so-called natural direct and indirect effects. Indirect effects denotes the part of the total effect of birth month/season that is mediated via respiratory tract infections, while direct effects reflect the rest of the total effect, including mediation by exposures such as pollen concentration, time spent outdoors and physical activity. The natural effect models were adjusted for the potential mediator-outcome confounders sibling status (yes/no) and gestational age (<37 weeks) at birth and 95% confidence intervals were calculated using robust standard errors based on the sandwich estimator. We also investigated whether the effect of birth month on allergic rhinoconjunctivitis was mediated by having a lower respiratory infection during the first 6 or 12 months in the older cohort.

R 3.2.2[17] was used for the mediation analysis and Stata 14 software (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP) was used for all of the remaining statistical analyses.

The Regional Ethical Review Board in Stockholm, Sweden granted permission for the study and all individuals' information was de-identified prior to analyses.

Results

A total number of 582 494 live-born children were identified in the younger cohort (born between July 2005 and December 2010) (Table 1). Seven individuals were excluded from the

analysis because of apparent errors in prescription dates. The median follow-up time was 3.4 years, ranging from 0 to 6.5 years. The overall incidence rate of asthma/wheeze was 18.6 events (95 % CI: [18.4, 18.8]) per 1000 person-years and 6.5% of the individuals fulfilled the asthma/wheeze criteria during follow-up. The incidence rate of early-onset asthma/wheeze (0-2 years) was 28.3 and of later onset asthma/wheeze (2-6 years) 7.8 per 1000 person-years (Table 2).

A total number of 377 752 live-born children were identified in the older cohort (born between 2001 and 2004), among whom 367 583 (97.3%) had a complete follow-up during the 6th year of life; reasons for exclusion were emigration (n=8 629; 2.3%) and death (n=1 540; 0.4%) before the 7th birthday. The overall prevalence of asthma at age 7 was 5.9% and of allergic rhinoconjunctivitis 5.2%.

Background characteristics such as the month, season and year of birth, sex, birth county, lower respiratory infections and family history of asthma/allergy were similarly distributed in the two cohorts (Table 1).

Asthma

In the younger cohort, children born during fall and winter months (September-February) had a higher risk of developing later onset asthma/wheeze (after 2 years of age) compared to those born during summer; hazard ratio (HR) 1.19, and 95% confidence interval (CI) 1.12, 1.27 for fall and HR 1.24 (95% CI 1.17, 1.33) for winter. In contrast, early onset asthma/wheeze (0-2 years) was not associated with birth month or season of birth (Table 2). In the older cohort, children born during fall and winter months had higher prevalence of asthma during their 7th year of life; prevalence ratio (PR) 1.09 (95% CI 1.05, 1.13) for fall and 1.12 (95% CI 1.08, 1.16) for winter (Table 2). The association between date of birth as a continuous exposure and asthma showed a clear seasonal trend, Figure 1.

There was an interaction between birth month/season of birth and birth year in the younger cohort. Among children 2-6 years, estimates for spring and winter birth increased slightly over time, $p<0.01$ (Table S2). There was no interaction between birth month/season of birth and birth year for prevalent asthma during the 7th year of life. There was no significant interaction between birth month/season and county of birth or family history of allergy in either cohort (data not shown).

In the mediation analysis we found that the association between birth month/season of birth and asthma at 6 years of age was partly mediated through having a lower respiratory infection (Table 3). Overall there was a positive indirect effect going through lower respiratory infection. The direct effect of birth month/season of birth on asthma was higher than the indirect effect. For instance, the total effect of being born in the winter (December-February) compared to being born in the summer (June-August) was PR 1.12 (95% CI 1.08, 1.16) which decomposed into an direct effect PR 1.08 (95% CI 1.04, 1.12) and an indirect effect through lower respiratory infection within the first 6 months of PR 1.04 (95% CI 1.03, 1.04). Similar findings were shown for the first three months, first year and even year 0-6 (Table 3).

Allergic rhinoconjunctivitis

The effect of birth month on allergic rhinoconjunctivitis prevalence during the 7th year of life showed a pattern similar to the association between birth month and asthma. Children born during fall, winter and even spring had a higher risk of prevalent allergy at 6 years of age compared to children born in the summer (Table 4). The association between date of birth as a continuous exposure and allergic rhinoconjunctivitis showed a clear seasonal trend, Figure 2.

There was no statistically significant interaction between birth month/season of birth and birth year, county of birth or family history of allergy.

The association between birth month/season of birth and allergic rhinoconjunctivitis at 6 years of age was not mediated through lower respiratory infection; the total effect of being born in winter was PR 1.20 (95% CI 1.16, 1.25) which decomposed into direct effect PR 1.19 (95% CI 1.15, 1.24) and indirect effect PR 1.00 (95% CI 1.00, 1.01), Table S3.

Discussion

Principal findings

The main finding of this study was that after 2 years of age, children born during fall/winter were at increased risk of both asthma and allergic rhinoconjunctivitis compared to those born during spring/summer. For asthma, this seemed to be partly mediated through lower respiratory infections, indicating that some of the birth month effect was due to differences in exposure to respiratory infections related to seasons.

Interpretation

Our results confirm most previous studies showing that children born during fall/winter have a higher prevalence of asthma and allergic rhinoconjunctivitis compared to those born in spring.[4-7] We extend previous findings further by showing that some of this effect is partly mediated by lower respiratory infections for asthma but not allergic rhinoconjunctivitis. This is a novel finding and interesting from a mechanistic point of view. There could however be many other mediators such as pollen counts, time spent indoor, physical activity and daylight. Also, since there is a strong collinearity between trimester and pollen exposure, we cannot confirm whether differences in asthma and allergic rhinoconjunctivitis are due to exposure to pollen levels during pregnancy or the first year of life.[1,3] In Sweden, levels of birch pollen allergens were extremely high in 2006, so a difference in the effect by birth year could imply that pollen exposure is of importance.[11,18] There was however no interaction by birth year for

any of the outcomes except for the younger cohort in which estimates increased over time for winter births. Time trends of asthma and allergic rhinoconjunctivitis incidence rates have recently been reported[14,19] and our findings imply that the role of actual pollen counts should be explored in future studies.

It may, to a certain extent, be difficult to differ between the effect of respiratory infections and pollen exposure. A child born during winter when respiratory tract infections are common will also experience a full pollen season early on while a child born during summer will be much less exposed to respiratory tract infections during the first months and will be less exposed to pollen until after half a year of age. Thus, the overall environment of the newborns differs by birth month for items such as hours spent indoors and microbial exposure, but also timing of day care start and residual confounding.[20-22] However, Wu et al reported that children born approximately four months before the peak of the annual winter virus season had the highest risk for subsequent asthma over five consecutive seasons despite yearly shifts in the timing of the winter virus peak with up to six weeks.[23]

Strengths of the study

This study is the largest to date with several strengths. It is a population-based, longitudinal register-based study in a unified health care environment and thus the results are generalisable to the total population. Information on exposure and outcomes was prospectively collected so recall bias is avoided. We included two separate cohorts to be able to address both new onset (younger cohort) and prevalent asthma (older cohort).The asthma outcome definitions have been previously validated in medical records based on the SPDR and found to be good proxies for asthma.[13] Background characteristics such as perinatal factors, socioeconomic status or air pollution are not likely to affect birth month and be confounders[24-26] and were therefore not included. Finally, the large sample gave us high statistical power.

Limitations of the data

There are also inherent limitations to the study. We estimated exposure to lower respiratory infections only through unplanned hospital visits for pneumonia and RSV which may be more severe than those diagnosed in primary health care, potentially resulting in an underestimation of the mediating effect of respiratory tract infections. We also found that the associations were different for asthma before and after 2 years of life, which may be due to diagnostic uncertainty and transient wheezing or asthma phenotypes among very young children.

Conclusion

In conclusion, we found that there is clear association between season of birth and risk of childhood asthma and allergic rhinoconjunctivitis, and that some of this association is mediated through lower respiratory infections. These findings have important implications for patient care, such as asthma management programs to notify timing of seasonality for viral respiratory tract infections.

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Conflict of interest: None of the authors have a conflict of interest.

Data sharing: Data available on request due to privacy/ethical restrictions.

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Figure legends

Figure 1. The association between date of birth as a continuous exposure and asthma.

Figure 2. The association between date of birth as a continuous exposure and allergic rhinoconjunctivitis.

Figure S1. Simplified directed acyclic graph (DAG) to illustrate confounders for the association between birth month/season of birth and asthma or allergic rhinoconjunctivitis as well as the mediation for lower respiratory infections (siblings and low gestational age).

Tables

Table 1. Cohort characteristics

		Younger cohort (children born 2005-2010	Older cohort (children born 2001-2004)
	Total	582 487	367 583
	N Asthma (%)	37 778 (6.5)	21 719 (5.9)
	N Allergy (%)	---	19 095 (5.2)
Birth month	**January**	43 621 (7.5)	30 222 (8.2)
	February	42 223 (7.2)	29 134 (7.9)
	March	47 497 (8.2)	32 479 (8.8)
	April	46 809 (8.0)	32 939 (9.0)
	May	47 606 (8.2)	32 817 (8.9)
	June	46 461 (8.0)	31 597 (8.6)
	July	57 370 (9.8)	33 063 (9.0)
	August	55 440 (9.5)	31 792 (8.6)
	September	52 303 (9.0)	30 540 (8.3)
	October	51 546 (8.8)	30 135 (8.2)
	November	46 114 (7.9)	26 553 (7.2)
	December	45 497 (7.8)	26 312 (7.2)
Season	**Spring**	141 912 (24.4)	98 235 (26.7)
	Summer	159 271 (27.3)	96 452 (26.2)
	Fall	149 963 (25.7)	87 228 (23.7)
	Winter	131 341 (22.5)	85 668 (23.3)
Sex	**Boy**	299 503 (51.4)	189 068 (51.4)
	Girl	282 984 (48.6)	178 515 (48.6)
Birth year	**2001**		86 527 (23.5)
	2002		90 732 (24.7)
	2003		94 011 (25.6)
	2004		96 313 (26.2)
	2005	47 993 (8.2)	
	2006	102 943 (17.7)	
	2007	104 216 (17.9)	
	2008	106 409 (18.3)	
	2009	107 819 (18.5)	
	2010	113 107 (19.4)	
County of birth*	**Stockholm**	148 484 (25.5)	91 504 (24.9)
	Uppsala-Örebro	111 830 (19.2)	72 780 (19.8)
	South-East	58 290 (10.0)	37 869 (10.3)
	West	100 497 (17.3)	62 550 (17.0)
	South	115 012 (19.7)	70 088 (19.1)
	North	48 372 (8.3)	32 792 (8.9)
Respiratory infection	**Yes**	25 997 (4.5)	21 855 (6.0)
Family history of asthma	**Any parent**	89 422 (15.4)	61 585 (16.8)
Family history of allergy	**Any parent**	---	155 526 (42.3)

*2 children missing information on county.

Table 2. The association between birth month/season and asthma, crude

		Children born 2005-2010				Children born 2001-2004	
		0-2 years		2-6 years		6 years	
		IR*(95% CI)	HR (95% CI)	IR* (95% CI)	HR (95% CI)	N (%)	PR (95% CI)
Birth month	**January**	29 (28-30)	1.01 (0.96, 1.07)	9 (8-9)	1.28 (1.15, 1.43)	1910 (6.3)	1.13 [1.07,1.21]
	February	27 (26-28)	0.95 (0.90, 1.01)	8 (8-9)	1.22 (1.09, 1.36)	1825 (6.3)	1.12 [1.06,1.20]
	March	27 (26-28)	0.94 (0.89, 0.99)	8 (7-8)	1.11 (0.99, 1.23)	1955 (6.0)	1.08 [1.02,1.15]
	April	28 (27-29)	0.99 (0.94, 1.04)	8 (7-8)	1.07 (0.96, 1.20)	1920 (5.8)	1.05 [0.98,1.11]
	May	28 (27-29)	0.99 (0.93, 1.04)	7 (7-8)	1.03 (0.92, 1.16)	1731 (5.3)	0.95 [0.89,1.01]
	June	29 (27-30)	1.00 (0.95, 1.05)	7 (7-8)	0.96 (0.96, 1.08)	1709 (5.4)	0.97 [0.91,1.04]
	July	29 (28-30)	1.00 (Reference	7 (6-7)	1.00 (Reference	1842 (5.6)	1.00 (Reference)
	August	28 (27-29)	0.98 (0.93, 1.03)	7 (7-8)	1.07 (0.96, 1.19)	1846 (5.8)	1.04 [0.98,1.11]
	September	29 (28-30)	1.00 (0.95, 1.06)	8 (7-8)	1.13 (1.02, 1.26)	1846 (6.0)	1.08 [1.02,1.16]
	October	30 (29-31)	1.04 (0.98, 1.09)	8 (7-9)	1.20 (1.08, 1.33)	1828 (6.1)	1.09 [1.02,1.16]
	November	28 (27-29)	0.97 (0.92, 1.03)	9 (8-10)	1.31 (1.17, 1.46)	1665 (6.3)	1.13 [1.06,1.20]
	December	28 (27-30)	0.99 (0.94, 1.05)	9 (8-9)	1.29 (1.15, 1.44)	1642 (6.2)	1.12 [1.05,1.19]
Season of birth	**Spring**	28 (27-28)	0.98 (0.95, 1.01)	8 (7-8)	1.06 (0.99, 1.13)	5606 (5.7)	1.02 [0.98,1.06]
	Summer	28 (28-29)	1.00 (Reference	7 (7-8)	1.00 (Reference	5397 (5.6)	1.00 (Reference)
	Fall	29 (28-29)	1.01 (0.98, 1.04)	8 (8-8)	1.19 (1.12, 1.27)	5339 (6.1)	1.09 [1.05,1.13]
	Winter	28 (28-29)	0.99 (0.96, 1.03)	9 (8-9)	1.24 (1.17, 1.33)	5377 (6.3)	1.12 [1.08,1.16]

* per 1000 person-years
IR - incidence rate
HR - hazard ratio
PR - prevalence ratio
CI - confidence interval

Table 3. Mediation analysis with the total, natural direct (NDE) and indirect effect (NIE) of respiratory tract infection in the first 3, 6, 12 months and first 6 years on the association between birth month/season and asthma at age 6 years.

		Infection first 3 months			Infection first 6 months		
		Total effect PR (95%CI)	**NDE PR (95% CI)**	**NIE PR (95% CI)**	**Total effect PR (95%CI)**	**NDE PR (95% CI)**	**NIE PR (95% CI)**
Birth month	**January**	1.12 (1.05, 1.20)	1.08 (1.01, 1.16)	1.04 (1.03, 1.06)	1.13 (1.06, 1.21)	1.08 (1.01, 1.15)	1.05 (1.04, 1.06)
	February	1.12 (1.05, 1.20)	1.09 (1.02, 1.17)	1.03 (1.02, 1.04)	1.12 (1.05, 1.20)	1.09 (1.03, 1.17)	1.03 (1.02, 1.03)
	March	1.07 (1.00, 1.15)	1.06 (0.99, 1.13)	1.01 (1.01, 1.02)	1.08 (1.01, 1.15)	1.07 (1.00, 1.14)	1.01 (1.01, 1.01)
	April	1.04 (0.97, 1.11)	1.03 (0.96, 1.11)	1.00 (1.00, 1.01)	1.04 (0.98, 1.11)	1.04 (0.98, 1.11)	1.00 (1.00, 1.00)
	May	0.94 (0.87, 1.00)	0.94 (0.87, 1.01)	1.00 (1.00, 1.00)	0.96 (0.89, 1.02)	0.96 (0.89, 1.02)	1.00 (1.00, 1.00)
	June	0.95 (0.89, 1.03)	0.95 (0.89, 1.03)	1.00 (1.00, 1.00)	0.96 (0.90, 1.03)	0.96 (0.90, 1.03)	1.00 (1.00, 1.00)
	July	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	August	1.04 (0.96, 1.11)	1.03 (0.96, 1.11)	1.00 (1.00, 1.00)	1.05 (0.98, 1.11)	1.04 (0.97, 1.11)	1.01 (1.01, 1.01)
	September	1.09 (1.02, 1.17)	1.09 (1.02, 1.17)	1.00 (1.00, 1.00)	1.08 (1.02, 1.16)	1.07 (1.00, 1.14)	1.02 (1.01, 1.02)
	October	1.08 (1.01, 1.15)	1.07 (1.00, 1.15)	1.01 (1.00, 1.01)	1.09 (1.02, 1.16)	1.06 (0.99, 1.13)	1.03 (1.02, 1.03)
	November	1.11 (1.04, 1.19)	1.09 (1.02, 1.17)	1.02 (1.01, 1.02)	1.12 (1.05, 1.19)	1.08 (1.01, 1.15)	1.03 (1.03, 1.04)
	December	1.10 (1.03, 1.18)	1.07 (1.00, 1.15)	1.03 (1.02, 1.04)	1.11 (1.04, 1.19)	1.07 (1.00, 1.14)	1.04 (1.03, 1.05)
Season of birth	**Spring**	1.02 (0.98, 1.06)	1.02 (0.98, 1.05)	1.01 (1.00, 1.01)	1.02 (0.98, 1.06)	1.02 (0.98, 1.06)	1.00 (1.00, 1.00)
	Summer	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Autumn	1.09 (1.05, 1.13)	1.08 (1.04, 1.13)	1.01 (1.00, 1.01)	1.09 (1.05, 1.13)	1.06 (1.02, 1.11)	1.02 (1.02, 1.03)
	Winter	1.12 (1.08, 1.16)	1.08 (1.04, 1.13)	1.03 (1.02, 1.04)	1.12 (1.08, 1.16)	1.08 (1.04, 1.12)	1.04 (1.03, 1.04)
		Infection first year			**Infection first 0-6 years**		
		Total effect PR (95%CI)	**NDE PR (95% CI)**	**NIE PR (95% CI)**	**Total effect PR (95%CI)**	**NDE PR (95% CI)**	**NIE PR (95% CI)**
Birth month	**January**	1.13 (1.06, 1.20)	1.09 (1.02, 1.16)	1.04 (1.03, 1.04)	1.13 (1.06, 1.20)	1.06 (1.00, 1.13)	1.06 (1.05, 1.07)
	February	1.12 (1.05, 1.19)	1.10 (1.03, 1.17)	1.02 (1.01, 1.02)	1.12 (1.05, 1.19)	1.08 (1.02, 1.15)	1.03 (1.03, 1.04)
	March	1.08 (1.01, 1.15)	1.07 (1.01, 1.14)	1.00 (1.00, 1.01)	1.08 (1.01, 1.14)	1.06 (1.00, 1.13)	1.01 (1.01, 1.02)
	April	1.05 (0.98, 1.11)	1.05 (0.99, 1.12)	1.00 (0.99, 1.00)	1.05 (0.98, 1.11)	1.05 (0.99, 1.11)	1.00 (0.99, 1.01)
	May	0.95 (0.89, 1.01)	0.95 (0.89, 1.01)	1.00 (0.99, 1.00)	0.95 (0.89, 1.01)	0.95 (0.89, 1.01)	1.00 (0.99, 1.00)
	June	0.97 (0.91, 1.03)	0.97 (0.91, 1.03)	1.00 (1.00, 1.00)	0.97 (0.91, 1.03)	0.96 (0.91, 1.03)	1.00 (1.00, 1.01)
	July	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	August	1.04 (0.98, 1.11)	1.04 (0.97, 1.10)	1.01 (1.00, 1.01)	1.04 (0.98, 1.11)	1.03 (0.96, 1.09)	1.01 (1.01, 1.02)
	September	1.08 (1.02, 1.15)	1.07 (1.01, 1.14)	1.01 (1.00, 1.01)	1.08 (1.02, 1.15)	1.06 (1.00, 1.13)	1.02 (1.01, 1.02)
	October	1.08 (1.02, 1.15)	1.07 (1.00, 1.14)	1.01 (1.01, 1.02)	1.08 (1.02, 1.15)	1.05 (0.99, 1.12)	1.03 (1.02, 1.03)
	November	1.11 (1.05, 1.19)	1.09 (1.02, 1.16)	1.02 (1.02, 1.03)	1.12 (1.05, 1.19)	1.07 (1.01, 1.14)	1.04 (1.04, 1.05)
	December	1.11 (1.04, 1.18)	1.08 (1.01, 1.15)	1.03 (1.02, 1.03)	1.11 (1.04, 1.18)	1.06 (0.99, 1.13)	1.05 (1.04, 1.06)
Season of birth	**Spring**	1.02 (0.98, 1.06)	1.02 (0.99, 1.06)	1.00 (1.00, 1.00)	1.02 (0.98, 1.06)	1.02 (0.99, 1.06)	1.00 (0.99, 1.00)
	Summer	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Autumn	1.09 (1.05, 1.13)	1.08 (1.04, 1.12)	1.01 (1.01, 1.02)	1.09 (1.05, 1.13)	1.06 (1.03, 1.10)	1.02 (1.02, 1.03)
	Winter	1.12 (1.08, 1.16)	1.09 (1.05, 1.13)	1.03 (1.02, 1.03)	1.11 (1.07, 1.16)	1.07 (1.03, 1.11)	1.04 (1.04, 1.05)

Adjusted for siblings (yes/no) and gestational age <37 weeks

NDE - Natural direct effect
NIE - Natural indirect effect
PR - prevalence ratio
CI - confidence interval

Table 4. The association between birth month/season and allergic rhinoconjunctivis at 6 years of age

		Children born 2001-2004 6 years	
		N (%)	PR (95% CI)
Birth month	**January**	1 741 (5.8)	1.17 (1.10,1.25)
	February	1 715 (5.9)	1.20 (1.12,1.28)
	March	1 835 (5.7)	1.15 (1.08,1.23)
	April	1 729 (5.3)	1.07 (1.00,1.14)
	May	1 517 (4.6)	0.94 (0.88,1.01)
	June	1 435 (4.5)	0.93 (0.86,0.99)
	July	1 622 (4.9)	1.00 (Reference)
	August	1 523 (4.8)	0.98 (0.91,1.05)
	September	1 642 (5.1)	1.03 (0.96,1.10)
	October	1 591 (5.3)	1.08 (1.01,1.15)
	November	1 392 (5.2)	1.07 (1.00,1.15)
	December	1 453 (5.5)	1.13 (1.05,1.21)
Season of birth	**Spring**	5 081 (5.2)	1.09 (1.05,1.13)
	Summer	4 580 (4.8)	1.00 (Reference)
	Fall	4 525 (5.2)	1.09 (1.05,1.14)
	Winter	4 909 (5.7)	1.21 (1.16,1.26)

PR - prevalence ratio
CI - confidence interval

Table S1. Algorithm to define children with allergic rhinoconjunctivitis according to Henriksen et al (19)
Children with allergic rhinoconjunctivitis fulfilled either criterion 1 – 4 below

CRITERIA 1 (based on ICD-10):
≥1 hospital contact for:
J30 “hay fever and allergic rhinitis”
J30.0 ”vasomotor rhinitis”
J30.1 “allergic rhinitis due to pollen”
J30.2 “other seasonal allergic rhinitis”
J30.3 “other allergic rhinitis”
J30.4 “allergic rhinitis, unspecified”
J31.0 “chronic rhinitis”

CRITERIA 2 (based on ATC and ICD-10):
≥ 2 filled prescriptions of:
R01AD01 – R01AD60 “inhaled corticosteroids for rhinitis”
And no hospital contact for (exclusions criteria):
J33 “nasal polyps”
J330 ”polyps in nasal cavity”
J331 “polyp related sinus degeneration”
J331A “woakes' ethmoiditis”
J338” nasal polyps, other”
J338A “polypus sinus sphenoidalis”
J339 “nasal polyps, unspecified”
J010- J019 ”acute sinusitis”
J320 –J329 ”chronic sinusitis”

CRITERIA 3 (based on ICD-10 and ATC)
≥2 filled prescriptions of:
R06A “antihistamines for systemic use”
And no hospital contact for:
L29 “pruritus” or
DL50 “allergic urticaria”

CRITERIA 4 (based on ATC)
≥ 1 filled prescriptions of:
V01A “specific immune therapy, allergen substract therapy” or/and
S01GX “medication for allergic conjunctivitis”

Table S2. Analysis of interaction between birth month/ season of birth and birth year, using two-sided likelihood ratio test.

	Asthma 0-2 years						p-value for interaction between birth season and birth year
Season	**2005** HR(95%CI)	**2006** HR(95%CI)	**2007** HR(95%CI)	**2008** HR(95%CI)	**2009** HR(95%CI)	**2010** HR(95%CI)	
Spring	No obs	0.95 (0.88, 1.02)	0.95 (0.88, 1.01)	1.00 (0.94, 1.08)	1.00 (0.93, 1.07)	1.04 (0.95, 1.14)	
Summer	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	<0.01
Fall	1.02 (0.94, 1.11)	1.03 (0.96, 1.11)	1.01 (0.94, 1.08)	1.03 (0.96, 1.10)	0.97 (0.90, 1.04)	0.93 (0.84, 1.02)	
Winter	1.06 (0.94, 1.19)	0.99 (0.92, 1.06)	0.98 (0.91, 1.05)	0.96 (0.90, 1.03)	1.02 (0.95, 1.09)	1.08 (0.99, 1.18)	

	Asthma 2-6 years						p-value for interaction between birth season and birth year
Season	**2005** HR(95%CI)	**2006** HR(95%CI)	**2007** HR(95%CI)	**2008** HR(95%CI)	**2009** HR(95%CI)	**2010** HR(95%CI)	
Spring	No obs	1.00 (0.89, 1.13)	1.14 (1.01, 1.29)	1.26 (1.09, 1.46)	1.31 (1.02, 1.68)	**No observations**	
Summer	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)		<0.01
Fall	1.13 (0.99, 1.28)	1.24 (1.11, 1.40)	1.15 (1.02, 1.31)	0.98 (0.83, 1.15)	0.82 (0.58, 1.17)		
Winter	1.16 (0.98, 1.39)	1.24 (1.10, 1.39)	1.27 (1.12, 1.44)	1.41 (1.22, 1.64)	1.54 (1.18, 2.00)		

	Asthma at 6 years of age				p-value for interaction between birth season and birth year
Season	**2001** PR(95%CI)	**2002** PR(95%CI)	**2003** PR(95%CI)	**2004** PR(95%CI)	
Spring	1.04 (0.96, 1.12)	1.05 (0.97, 1.13)	0.96 (0.89,1.03)	1.04 (0.96, 1.11)	
Summer	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	0.5230
Fall	1.09 (1.01, 1.18)	1.11 (1.03, 1.19)	1.06 (0.99, 1.14)	1.12 (1.04, 1.20)	
Winter	1.18 (1.09, 1.27)	1.14 (1.06, 1.23)	1.04 (0.96, 1.12)	1.14 (1.06, 1.23)	

HR hazard ratio
PR - prevalence ratio
CI - confidence interval

Table S3. Mediation analysis with the total, natural direct (NDE) and indirect effect (NIE) of lower respiratory infection in the first 6 and 12 months on the association between birth month/season and allergic rhinoconunctivitis at age 6 years.

		Infection first year		
		Total effect PR (95%CI)	**NDE PR (95% CI)**	**NIE PR (95% CI)**
Birth month	January	1.16 (1.10, 1.25)	1.20 (1.09, 1.24)	1.01 (1.01, 1.01)
	February	1.20 (1.12, 1.28)	1.15 (1.12, 1.28)	1.00 (1.00, 1.01)
	March	1.15 (1.08, 1.23)	1.15 (1.08, 1.23)	1.00 (1.00, 1.00)
	April	1.07 (1.01, 1.15)	1.07 (1.01, 1.15)	1.00 (1.00, 1.00)
	May	0.94 (0.88, 1.01)	0.94 (0.88, 1.01)	1.00 (1.00, 1.00)
	June	0.93 (0.87, 0.99)	0.93 (0.87, 0.99)	1.00 (1.00, 1.00)
	July	1.00	1.00	1.00
	August	0.97 (0.91, 1.04)	0.97 (0.91, 1.04)	1.00 (1.00, 1.00)
	September	1.03 (0.96, 1.10)	1.03 (0.96, 1.10)	1.00 (1.00, 1.00)
	October	1.07 (1.00, 1.14)	1.07 (1.00, 1.14)	1.00 (1.00, 1.00)
	November	1.06 (0.99, 1.14)	1.06 (0.98, 1.13)	1.01 (1.00, 1.01)
	December	1.11 (1.04, 1.19)	1.10 (1.03, 1.18)	1.01 (1.00, 1.01)
Season of birth	Spring	1.09 (1.05, 1.13)	1.09 (1.05, 1.14)	1.00 (1.00, 1.00)
	Summer	1.00	1.00	1.00
	Autumn	1.09 (1.04, 1.13)	1.08 (1.04, 1.13)	1.00 (1.00, 1.00)
	Winter	1.20 (1.16, 1.25)	1.19 (1.15, 1.24)	1.01 (1.00, 1.01)

NDE - Natural direct effect
NIE - Natural indirect effect
PR - prevalence ratio
CI - confidence interval