

# Analysis of the Relationship between Pollinosis and Date of Birth in Switzerland

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## Key Words

Rhinoconjunctivitis • Pollinosis • Grass pollen allergy • Birch pollen allergy

## Abstract

**Background:** The first months of life may represent a vulnerable period in the development of atopic diseases. The objective of this study was to examine the relationship between the month of birth and the development of birch and grass pollen allergy in the Swiss population. **Methods:** Data from the Swiss Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) as well as the Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution and Climate (SCARPOL) were used. A logistic regression was calculated with grass and birch pollen sensitisation (positive skin prick test) or allergy (positive skin prick test and allergic symptoms) as outcome variables and the season of birth as predictor variable. The contribution of the season of birth on pollinosis was further adjusted for well-known risk factors and potential confounding variables. **Results:** The logistic regression revealed a significant effect of the season of birth on birch pollen sensitisation and an effect of borderline significance on birch pollen allergy, i.e. subjects born in

the pollen season (March to April) showed an increased risk of being sensitised/allergic to birch pollen. The results also indicated a tendency towards an increased risk for subjects born in the grass pollen season (May to June) to develop grass pollen allergy. **Conclusion:** Our results support the hypothesis that the first few months of life constitute a sensitive period, during which inhalative exposure to certain allergens may predispose to the subsequent development of atopic respiratory disease.

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## Introduction

The prevalence of atopic diseases has dramatically increased over the last 30 years [1–3]. In Switzerland, two studies, the Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution and Climate (SCARPOL) and the Swiss Study on Air Pollution and Lung Diseases in Adults (SAPALDIA), allowed a thorough investigation of the prevalence of respiratory atopic diseases in Switzerland [4–7]. These studies revealed that in Switzerland, the prevalence of self-reported hay fever had increased from 0.82% in 1926 to 13.5% in

1991 [5]. In 1991, the prevalence of atopic sensitisation in adults was approximately 30%, predominantly caused by grass pollen (12.7%), followed by house dust mite (8.9%), silver birch pollen (7.9%), cat (3.8%) and dog epithelia (2.8%) [5]. In children, atopic sensitisation occurred in about 35%, caused by grass pollen (22.5%), house dust mite (12.4%), birch pollen (11.4%), dog (7.4%) and cat epithelia (6.4%) [4].

The development of atopic diseases depends on both genetic [8, 9] and environmental factors [10, 11], and sensitisation derives from the contact between a genetically predisposed individual and the environment. Early infancy is suggested to be a particularly vulnerable period in the development of atopic diseases. However, the relationship between allergen exposure and sensitisation is a controversial topic. While early exposure to cats or dogs appears to protect against allergic sensitisation [12], house dust mite exposure in infancy might be a risk factor for sensitisation [13]. Seasonal allergies such as pollen allergies are well suited to further examine the relationship between allergen exposure and sensitisation, as exposure is temporally limited to the pollen season. Therefore, many clinical trials have investigated the relationship between atopic diseases and the date of birth, of which some concluded that a positive relationship existed between pollinosis and the date of birth when birth coincided with [14–16] or was closely preceded [17–21] by the season of maximum allergen exposure. Other studies found no relationship between the date of birth and pollinosis [22, 23] or a negative relationship in that sensitisation to pollen and allergic rhinoconjunctivitis was least common in children born in the pollen season [24]. For Switzerland, no study has examined this relationship. Therefore, we analysed the relationship between the month of birth of subjects born in Switzerland and the development of two frequent causes of atopic allergy, i.e. allergy to grass pollen and birch pollen. Using the SAPALDIA as well as the SCARPOL data, we found an increased risk for subjects being born in the birch pollen season to develop birch pollen sensitisation/allergy and a tendency towards an increased risk for subjects born in the grass pollen season to develop grass pollen allergy.

## Methods

### Study Population

The Swiss SAPALDIA study represents a random sample of 9,651 adults (18–60 years old) from eight different regions of Switzerland (Aarau, Basel, Davos, Geneva, Lugano, Montana, Payerne and Wald). Details of the SAPALDIA study design have been de-

scribed elsewhere [5, 25]. In the present study, we included 7,435 (77%) subjects (49.4% males and 50.6% females) who were born in Switzerland. Skin prick test data were available of 96.9% of the subjects.

The SCARPOL study included 4,470 children from 10 different Swiss towns (Anières, Berne, Biel, Geneva, Langnau, Lugano, Montana, Payerne, Rheintal and Zurich) and from three age groups (1st, 4th and 8th school grade). The age of the children ranged between 5 and 16 years, with a mean of 10 years. Skin prick test data were available of 2,879 (64.4%) children (50.2% girls and 49.8% boys). Details of the SCARPOL study design have been described elsewhere [26].

### Definitions

Grass and birch pollen sensitisations were defined positive based on a positive result in the skin prick tests to grass and birch pollen, respectively (adjusted wheal diameter  $\geq 3$  mm). Mite sensitisation was similarly defined based on a positive result in the skin prick test to house dust mite (*Dermatophagoides pteronyssinus*). Grass pollen allergy was defined as a positive skin prick test to grass pollen combined with self-assessed rhinitis or conjunctivitis occurring during natural pollen exposure in spring/summer (SAPALDIA) or in May, June or July (SCARPOL). Birch pollen allergy was defined as a positive skin prick test to birch pollen combined with self-assessed rhinitis or conjunctivitis occurring during natural pollen exposure in spring (SAPALDIA) or in March/April (SCARPOL).

### Statistical Analysis

The statistical analysis was performed by means of logistic regression, which is suited to model effects on dichotomous outcome variables. It is especially useful when multiple predictors are being considered [27]. Analyses were performed with respect to pollen sensitisation and pollen allergy. Three different selection criteria were applied in order to control for possible confounding by multiple sensitisation or allergy. Firstly, no subjects were excluded. Secondly, subjects sensitised or allergic to grass or birch pollen were excluded. Thirdly, subjects sensitised/allergic to grass pollen and mites or birch pollen and mites were excluded (fig. 1, 2). Beside the season of birth, the predictor of primary interest, we included other important risk factors for pollinosis as well as potential confounding variables. The odds ratios (ORs) for the season of birth were thus adjusted for the presence of other predictor variables. Nine independent variables were included in the final model for the SAPALDIA data: season of birth, sex, age, education, maternal atopy or asthma, paternal atopy or asthma, number of older siblings, study area and date of interview. The following variables entered the final model for the SCARPOL data: season of birth, sex, age, social status, maternal hay fever, paternal hay fever, farming as a family occupation, study area and date of interview. The pollen season was defined as the months with symptom-triggering concentrations of pollen, i.e. May to June for the grass pollen season and March to April for the birch pollen season. As there were too few cases of birch pollen-allergic subjects in the SCARPOL data set, we confined the analysis for the SCARPOL data to grass pollen sensitisation or allergy and to birch pollen sensitisation.

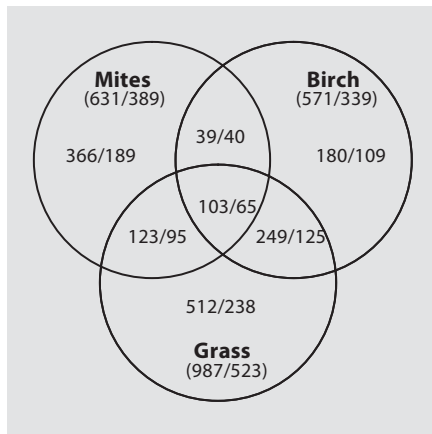


**Fig. 1.** Numbers of house dust mite, grass and birch pollen sensitisations for the SAPALDIA and the SCARPOL study, respectively (total numbers in parentheses).

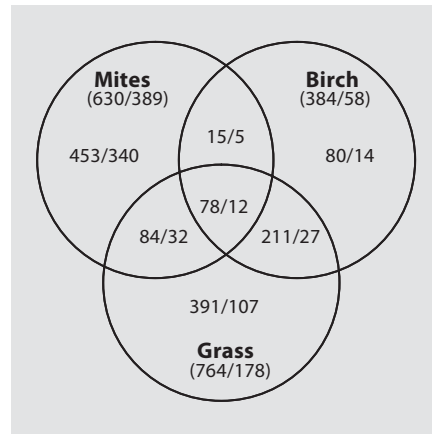


**Fig. 2.** Numbers of house dust mite sensitisation and grass and birch pollen allergies for the SAPALDIA and the SCARPOL study, respectively (total numbers in parentheses). As the questionnaire did not contain questions that would have allowed the definition of allergic symptoms due to mite allergy, we used mite sensitisation as selection criterion.

**Table 1.** Adjusted ORs and 95% CI (in parentheses) for grass or birch pollen sensitisation and allergy associated with birth in the grass (May to June) or birch pollen season (March to April)

| Data set                    | Grass pollen     |                  |                  | Birch pollen     |                  |                  |
|-----------------------------|------------------|------------------|------------------|------------------|------------------|------------------|
|                             | total            | birch            | birch/mites      | total            | grass            | grass/mites      |
| <i>Sensitisation and OR</i> |                  |                  |                  |                  |                  |                  |
| SAPALDIA                    | 1.02 (0.85–1.22) | 1.10 (0.89–1.37) | 1.18 (0.93–1.49) | 1.19 (0.96–1.47) | 1.48 (1.08–2.04) | 1.68 (1.19–2.36) |
| SCARPOL                     | 0.97 (0.73–1.30) | 1.11 (0.79–1.55) | 1.14 (0.77–1.67) | 1.07 (0.77–1.48) | 1.07 (0.67–1.70) | 1.27 (0.76–2.12) |
| <i>Allergy and OR</i>       |                  |                  |                  |                  |                  |                  |
| SAPALDIA                    | 1.07 (0.88–1.31) | 1.12 (0.88–1.43) | 1.25 (0.97–1.63) | 1.07 (0.82–1.40) | 1.55 (0.97–2.48) | 1.66 (1.00–2.75) |
| SCARPOL                     | 1.07 (0.70–1.66) | 1.34 (0.86–2.10) | 1.59 (0.97–2.62) |                  |                  |                  |

The reference categories with an OR of 1 were defined as July through April for regression analysis with grass pollen sensitisation/allergy and May through February for regression analysis with birch pollen sensitization/allergy. ORs were adjusted for sex, age, education, maternal atopy/asthma, paternal atopy/asthma, number of older siblings, study area and date of interview (SAPALDIA), as well as for sex, age, social status, maternal hay fever,

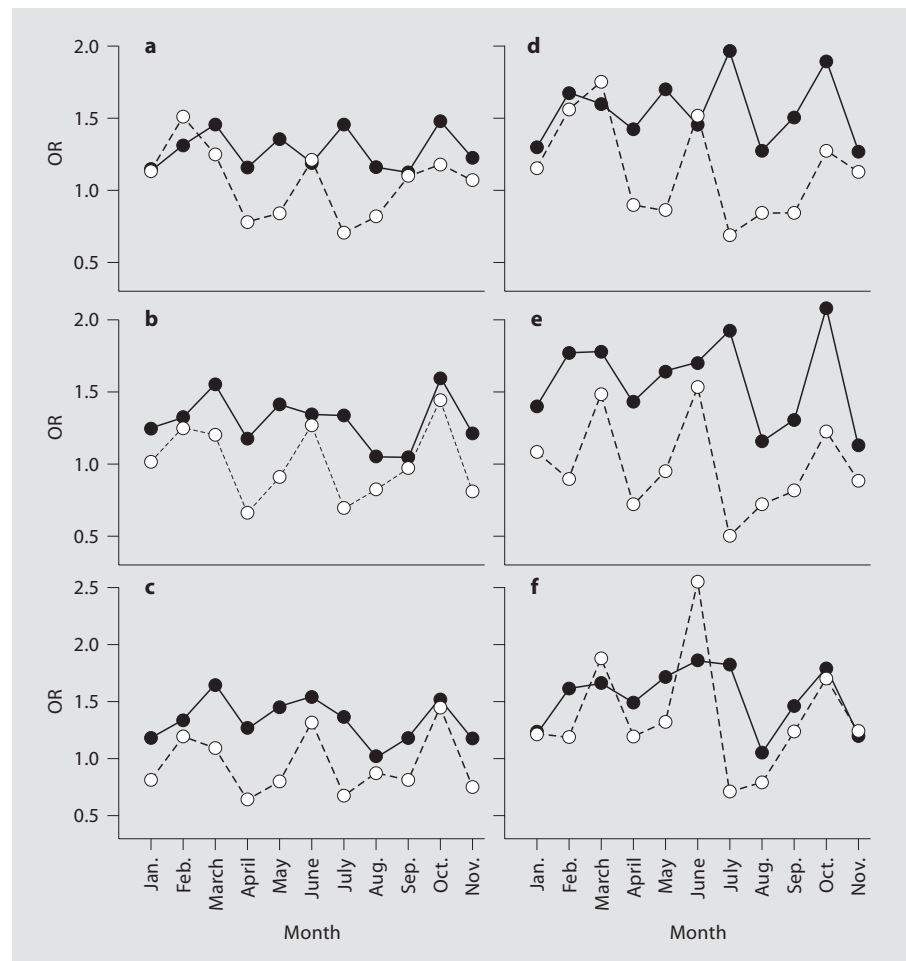
paternal hay fever, farming as a family occupation, study area and date of interview (SCARPOL). Odds are computed as the probability of an event divided by the complementary probability that the event does not occur. ORs are ratios of odds between two groups or populations. The statistical significance is indicated when the 95% CI excludes 1.

## Results

As illustrated in figure 1, 987 (13.7%) of all included SAPALDIA subjects had a positive skin prick test to grass pollen and 571 (7.9%) to birch pollen, while in the SCARPOL data set, 523 children (18.2%) had a positive skin prick test to grass pollen and 339 (11.8%) to birch pollen.

Figure 2 shows the corresponding frequencies for grass and birch pollen allergy. Of all included SAPALDIA subjects, 764 (10.6%) could be defined as allergic to grass pollen and 384 (5.3%) to birch pollen, while 178 children (6.2%) of the SCARPOL data set could be defined as allergic to grass pollen and 58 (2.0%) to birch pollen. In both cohorts, a relatively large proportion of subjects

**Fig. 3.** Adjusted ORs for grass pollen sensitisation (**a–c**) and grass pollen allergy (**d–f**) with exclusion criteria: none (**a, d**), birch pollen sensitisation (**b**) or allergy (**e**), birch pollen and mite sensitisation (**c**), and birch pollen allergy and mite sensitisation (**f**) analysed for the SAPALDIA (●) and the SCARPOL (○) data. ORs were adjusted for sex, age, education, maternal atopy/asthma, paternal atopy/asthma, number of older siblings, study area and date of interview (SAPALDIA), as well as for sex, age, social status, maternal hay fever, paternal hay fever, farming as a family occupation, study area and date of interview (SCARPOL). December was defined as the reference month with an OR of 1.



showed a combined grass and birch pollen sensitisation or allergy.

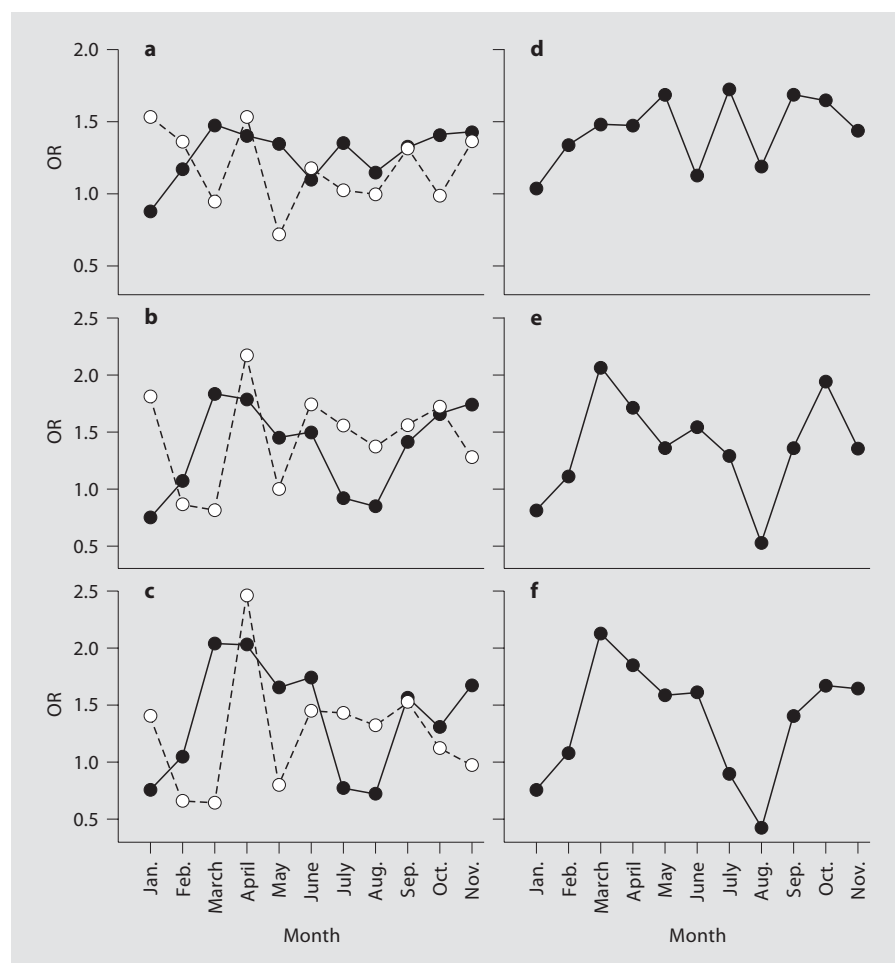
The logistic regression analysis of the SAPALDIA data indicated that being born in the grass pollen season (May through June) was not associated with significantly increased risks of grass pollen sensitisation or allergy (table 1). However, the ORs increased when subjects with multiple sensitisation or allergy were excluded. The logistic regression analysis of the SCARPOL data showed a similar result. While the ORs were not significantly increased for grass pollen sensitisation or allergy, they steadily increased when subjects with multiple sensitisation or allergy were excluded (table 1). Furthermore, the analysis of the SCARPOL data revealed that being born in June was associated with a significantly increased risk of grass pollen allergy (fig. 3).

The regression analysis with birch pollen sensitisation or allergy as outcome variable also indicated a rise in the ORs as multiple sensitisation or allergy was excluded (ta-

ble 1). In the SAPALDIA cohort, subjects born in March through April had a 68% increased risk of being sensitised (likelihood ratio test,  $p < 0.01$ ) and a 66% increased risk of being allergic ( $p = 0.062$ ) to birch pollen (table 1). While the ORs for birch pollen sensitisation were not significantly increased for the SCARPOL subjects born in March through April, they were significantly higher for children born in April as compared with children not born in April (fig. 4).

In order to visualise the course of risk of pollinosis over the year, we performed a second analysis with the month of birth instead of the season of birth as predictor variable. For both grass and birch pollinosis, the peak in the pollen season got more pronounced when multiple sensitisation or allergy was excluded (fig. 3, 4). In the SCARPOL data, the peaks appeared to be more strongly confined to the months of June (grass pollen) and April (birch pollen), respectively. The course of risk over the year for grass pollinosis appeared to be similar for the

**Fig. 4.** Adjusted ORs for birch pollen sensitisation (**a–c**) and birch pollen allergy (**d–f**) with exclusion criteria: none (**a, d**), grass pollen sensitisation (**b**) or allergy (**e**), grass pollen and mite sensitisation (**c**), and grass pollen allergy and mite sensitisation (**f**) analysed for the SAPALDIA (●) and the SCARPOL (○) data. ORs were adjusted for sex, age, education, maternal atopy/asthma, paternal atopy/asthma, number of older siblings, study area and date of interview (SAPALDIA), as well as for sex, age, social status, maternal hay fever, paternal hay fever, farming as a family occupation, study area and date of interview (SCARPOL). December was defined as the reference month with an OR of 1.



SAPALDIA and the SCARPOL data with two additional peaks in March and October.

Interestingly, not all the risk factors showed similar associations with grass and birch pollen sensitisation or allergy. Male sex, higher education, having an atopic or asthmatic mother or father, or having at most one older sibling were all positively associated with the risk of grass pollen sensitisation and allergy (results not shown). In the adult sample (SAPALDIA), younger age was positively associated with the risk of grass pollen allergy, while within the juvenile sample (SCARPOL), younger age was negatively associated with grass pollen allergy (results not shown). For birch pollen sensitisation or allergy, no correlation with sex, age, education, family history of atopy or asthma and older siblings was determined.

## Discussion

It is generally understood that environmental factors are of major importance regarding the onset of allergic diseases, and it is suggested that the neonate with an atopic predisposition (parental or sibling atopy) is especially vulnerable with respect to the development of allergies. The relationship between pollen exposure during early infancy and the development of allergies has been thoroughly studied [14–23]. However, the exact time period that is most significantly associated with the risk of allergic development is ill defined. Some studies, for instance, showed that the higher risk of pollinosis applies to subjects born during the pollen season [14–16], while others suggested that subjects born a few months before the peak of the pollen season have a higher risk of pollinosis [17–21]. A 3-month lag between the months with the highest prevalence of pollinosis and the peak of environmental pollen antigens has been explained by the fact

that the age of 3 months corresponds to a physiological low in maternal immunoglobulin levels [19]. As these immunoglobulins decline and the child's production of own serum antibodies has not yet matured, the infant is more vulnerable to environmental antigenic stimulation.

Our study is the first to investigate the relationship between pollinosis and the date of birth in Switzerland. The results demonstrated that being born in seasons of birch (March–April) or grass (May–June) pollen was associated with an increased risk of developing birch or grass pollinosis, respectively. Especially when cases with multiple sensitisation or allergy were excluded, it could be shown that those born in the pollen seasons were more likely to develop pollinosis than those born during the rest of the year. In the SCARPOL cohort, the month of birth effect was more strongly confined to the month with the highest pollen count, i.e. June (grass pollinosis) and April (birch pollinosis). By demonstrating an increased risk of pollinosis for subjects born in the pollen seasons, our results generally supported the hypothesis that the risk is at its highest when the child is exposed to pollen allergens at the time of birth and not the hypothesis of the 3-month lag between the months with the highest prevalence of pollinosis and the peak of the pollen season. Only for grass pollen allergy, a slight peak in March suggested such a 3-month lag relationship.

The effect of the month of birth on pollinosis was expected to be even greater, if not a second peak in October was surprisingly detected. This was first observed in the adult population (SAPALDIA) and was interpreted as a coincidence or only a result of cumulative environmental experiences. However, the subsequent analysis of the juvenile population (SCARPOL) showed an almost identical pattern, with three peaks in March, June and October. Prospective analyses of other cohorts in Switzerland or neighbouring countries are required to verify this pattern, and experimental studies are needed to elucidate its causes.

The close relationship between the month of birth and the development of allergy or atopy might go back to events taking place even before the time of birth. An indication of immunological memory being established before birth is the delay in the onset of disease rather than its prevention as a consequence of interventions to reduce allergen exposure immediately after birth [28, 29]. Evidence that children are more likely to inherit allergic diseases from the mother than the father further supports the importance of prenatal influence [30]. Despite the fact that the prenatal environment plays an important and decisive role in the development of allergy later in life, the effects of prenatal immunological experiences have been less studied.

In mice, the fetoplacental unit produces interleukin (IL)-4, IL-5 and IL-10 [31], and the fetal cytokine production itself reaches a peak of T helper cell 2 (Th2) bias shortly before the time of birth. The latter might explain why exposure at the time of birth is associated with such a high risk of allergy against the immediate allergen. IL-4 and IL-5 are crucial for immunoglobulin E isotype switching and production in B cells, whereas both IL-4 and IL-10 can turn off the cytokine synthesis of Th1 cells. Therefore, irrespective of whether or not the mother is allergic herself, the foetus is exposed to conditions that would favour the development of Th2-like responses. Hence, upon this background of heightened Th2-like activity shortly before birth, a high load of environmental pollen allergens may lead to sensitisation in the neonate. It has also been suggested that maternal allergen exposure beyond the 22nd week of pregnancy may play an important role in fetal T cell priming [32]. The immune response of infants with an inherited tendency to a reduced interferon- $\gamma$  production may be influenced still further by maternal allergen exposure and immune response to that allergen during pregnancy. Therefore, maternal allergen exposure during pregnancy may contribute to the development of allergic-type responses already in the infant. These responses may then be reinforced by the exposure of the infant to the same or other antigens in the first months of life, leading to persistent immunoglobulin E responses and allergy.

In conclusion, the present study of a Swiss adult (SAPALDIA) and children (SCARPOL) population showed that subjects born in the birch or grass pollen season had an increased risk of developing pollen sensitisation or allergy. The comparison of the results from the SAPALDIA and the SCARPOL data indicated that there might be a typical annual course of risk of grass pollinosis that goes beyond the pollen season. However, the reasons for this regularity would need further studies for verification and explanation.

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