

Persistent pollen exposure during infancy is associated with increased risk of subsequent childhood asthma and hayfever

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Summary

Background Few studies have focused on pollen exposure and asthma in children. None have examined associations between persistent exposure to pollen in infancy and aeroallergen sensitisation and asthma in childhood.

Objectives To examine the association between higher ambient levels of pollen in the first 3–6 months of life and risk of eczema, sensitization to food and aeroallergens at 2 years and asthma or hayfever at age 6–7 years combined.

Methods Using a birth cohort of 620 infants with a family history of allergic disease born between 1990 and 1994, we examined risk of eczema or allergic sensitization (SPT > 3 mm to at least one of cow's milk, egg white, peanut, house dust-mite, rye grass, and cat dander) by age 2 and asthma or hayfever at age 6–7. Daily ambient levels of pollen were measured during this period.

Results Cumulative exposure to pollen concentrations up to 6 months was associated with aeroallergen sensitization with the highest risk occurring at 3 months (aOR = 1.34, 95% CI 1.06–1.72). Cumulative exposure to pollen up to 3 months was also associated with hayfever (aOR = 1.14, 95% CI 1.009–1.29) and between 4 and 6 months exposure with asthma only (aOR = 1.35, 95% CI 1.07–1.72).

Conclusion Persistent pollen exposure in infancy appears to increase the risk of asthma and hayfever in children. These results support the hypothesis that there is a critical window of opportunity in early development which may be important for modification of allergic outcomes.

Keywords aeroallergens, asthma, children, eczema, hayfever, pollen

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Introduction

Exposure to pollen grains, especially those of wind-pollinated species such as grasses, is known to be associated with the exacerbation of asthma especially in sensitized individuals [1]. However, there are many features of the relationship between pollen and asthma which we still do not fully understand. Various ecological studies, including our own, have confirmed that increasing level of pollen exposure is related to asthma hospital admissions both in adults and in children [2–4]. There is now increasing interest to investigate whether this impact of pollen on asthma morbidity is

independent of other established environmental exposures such as air pollutants and respiratory virus infections [5, 6]. More importantly, we know very little of the role of pollen as an early life exposure on the development of asthma and hayfever in children in later life.

The studies that have investigated the role of pollen exposure on subsequent development of allergies have examined the month of birth as an indicator of level of pollen exposure [7, 8] while only one published study has actually examined levels of ambient pollen exposure as a risk factor for wheeze at 24 months [9]. Harley and colleagues (2009) [9] reported increased odds of wheezing at

age 24 months when exposed to higher concentrations of cumulative pollen at 3 months, independent of the effects of lower respiratory infections. To the best of our knowledge, no study has examined the association between early life ambient pollen levels and asthma or hayfever after age 6 years. This is critical especially in the context of asthma as early life wheeze and asthma phenotypes before 6 years of age are mostly transient and related to respiratory viral infections [10] and therefore asthma phenotypes are better defined after this age. Also, no study has examined these associations with eczema and sensitization status.

In this study, we sought to examine the associations between birth during the pollen season and persistent exposure to ambient levels of cumulative pollen in the first 3, 4–6, and 6 months of life, eczema and sensitization at 2 years of age and asthma and hayfever later in childhood (6/7 years), as well as the way in which these associations may vary with a family history of asthma and hayfever. Although we have access to pollen data up to 12 months we chose 6 months as the cut-off because all children will be exposed to a pollen season at 12 months of life.

Methods

Study population

The Melbourne Atopy Cohort Study (MACS) is a longitudinal, birth cohort study that started as a randomised controlled trial (Australian and New Zealand Trials Registry ACTRN12609000734268) to investigate the effect of three infant formulas at weaning on subsequent allergies [11]. The cohort comprised 620 babies who were enrolled prior to birth by recruiting pregnant women living in Melbourne, Australia. Children were born between 24 March 1990 and 11 January 1994. Eligible babies had at least one first-degree family member with a history of eczema and/or asthma and/or hayfever and/or severe food allergy. This study was approved by the Mercy Maternity Hospital Ethics Committee (R07/20 and R88/06) and all mothers provided written informed consent.

Data collection methods

Methods of the MACS cohort have been described in detail elsewhere [12]. Briefly, an allergy-trained research nurse conducted telephone surveys with the babies' mothers every 4 weeks from birth to 15 months, at 18 months and annually from 2 to 7 years. Detailed demographic, environmental and familial allergy information was obtained at birth. The follow-up interviews included specific questions related to the development of allergic/atopic diseases and symptoms, other infant

illnesses or conditions, contact with health care professionals and medications used.

Definitions of outcomes

The outcomes of interest were presence of eczema by 2 years of age defined as parental report of either a doctor diagnosis of eczema or presence of any rash which was treated with a topical steroid-based preparation [13]. Sensitisation at 2 years of age was defined as a positive skin prick test with a mean weal diameter of 3 mm or greater to at least one of cow's milk, egg white, peanut, house dust-mite, rye grass, and cat dander (Bayer, Spokane, WA, USA). Histamine - 1 mg/mL was used as positive control, while a negative control was not used. Skin prick tests (SPTs) were performed at 6, 12, and 24 months according to a standard technique [14] by 1 of 3 allergy-trained research nurses. SPTs were read after 15–20 min intervals.

Food sensitisation was defined as positive to one of cow's milk, egg white, or peanut. Aeroallergen sensitisation was defined as positive to one of house dust mite or rye-grass. We considered asthma only, hayfever only, or having asthma and hayfever at age 6 and 7 years combined. These outcomes were derived from the following information collected from parents during telephone interviews conducted when children were aged 6 or 7 years:

- *Current childhood asthma*: asthma diagnosed by the family physician in the previous 12 months.
- *Current childhood hayfever*: one or more episodes of nasal discharge and/or congestion, in the absence of an upper respiratory tract infection in the previous 12 months, which either the GP or parent attributed to hayfever and which was treated with an antihistamine and/or nasal steroid.

Exposure definitions

We defined pollen exposure in two ways. We first defined as birth 'inside' or 'outside' the pollen season using a pollen season definition (between mid September to end of January) as defined by the Melbourne Pollen Collection laboratory [15]. The duration of the total pollen (including grass, tree, and other types of pollen) season varies from year to year, but generally occurs between September and end of January. The grass pollen season is usually 3 months. Secondly, we used daily measurements of 24-hour average pollen concentrations for grass and others (which include trees, weeds, and herbs) pollens in grains per m³ available from a Burkard volumetric trap located at the University of Melbourne [16] for the 495 MACS children born between October 1991 and January 1994. We were

unable to differentiate between different types of grass pollen using a Burkard trap and visual identification [17].

Pollen exposure was a binary variable to examine birth inside/outside the pollen season and as a continuous variable for the cumulative exposure to pollen in the first 6 months of life. We did not restrict the analysis to only the grass pollen (mid September to end of January) because we collected daily levels of pollen throughout the study period.

For each child, we calculated cumulative exposure to pollen over the first 3, between 4 and 6, and 6 months of their life as a summation of the daily pollen count during this period. We also considered lagged values of the pollen load at birth and 1 and 2 days after birth.

Statistical methods

We used logistic regression models to examine the associations between pollen exposure and eczema at 2 years of age, asthma only, hayfever, and having both asthma and hayfever at age 6–7 years. We used multinomial logistic regression models to model sensitisation as an outcome with 3 levels – no sensitisation (reference category), aeroallergen, and food sensitisation.

All models were adjusted for infant gender, family history of asthma, family history of hayfever if these variables changed the estimated associations between pollen exposure and the outcome by 10% or more or were significant at a 5% level in adjusted models [18]. We also examined the impact of upper and lower respiratory viral infections, otitis media, and gastrointestinal infections on the estimated effects using parent reported episodes in the first 2 months of life. We included variables for each infection type as presence/absence of an infection and number of episodes defined as none, 1, 2, 3, or more infections.

We conducted an interaction and a stratified analysis to determine whether the pollen and asthma or hayfever associations varied according to a parental history (in either the mother or the father) of asthma or hayfever or eczema when parental history was found to modify the associations. Interaction terms were included in the regression models if there was evidence of an effect modification from the family history. The results are presented in the tables as odds ratios (per grain increase in pollen) and 95% confidence intervals (CIs). All of the statistical analyses were performed using Stata release 10.1 (College Station, TX, USA).

Results

In Fig. 1 we show the dates of birth of the individual MACS study participants and the grass pollen concentrations during the pollen season(s) of 1991–1994. Of

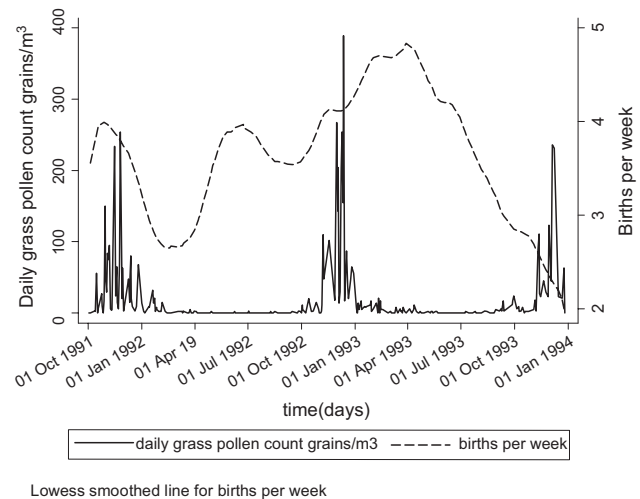


Fig. 1. Daily levels of grass pollen grains per m^3 and a loess smooth function of total weekly births for the MACS cohort during the study period.

the MACS cohort, 336 (54.2%) were born in the pollen season (which varies from year to year but always falls between Sept and Jan in Australia).

At age 2 years, 113 (18%) of infants were reported as having eczema, 220 (37%) were positive (skin prick test ≥ 3 mm) to at least one allergen. Of these, 76 (13%) were sensitized to only food allergens, 105 (18%) were sensitized to only aeroallergens. In adjusted analyses, birth during the pollen season was not associated with eczema or sensitization to aeroallergen or food at 2 years of age (Table 1). A greater cumulative exposure to pollen by 3 months (aOR = 1.34, 95% CI 1.06–1.72), between 4 and 6 months (aOR = 1.19, 95% CI 0.99–1.48, a trend towards statistical significance $P = 0.09$), and by 6 months (aOR = 1.04, 95% CI 1.02–1.07) were associated with an increased odds of aeroallergen sensitization only. Cumulative exposure to pollen in the first 6 months of life was not associated with eczema.

At age 6 and 7 years combined, 117 (22%) children were reported as having hayfever, 85 (16%) as having asthma only, and 62 (12%) as having both asthma and hayfever. 376 (62%) of children had at least one parent with a history of asthma. In adjusted logistic regression models, we observed an interaction between birth during pollen season and parental history of asthma in relation to the allergic outcomes of interest (Table 2). Only among those without a parental history of asthma, being born during the pollen season was related to childhood hayfever (aOR = 3.35, 95% CI 1.31–8.57) and having both asthma and hayfever in childhood (aOR = 4.99, 95% CI 1.08–23.01, P for interaction = 0.02 and 0.04 respectively). Inclusion of parental history of hayfever or eczema did not change the estimated effect sizes.

Table 1. Adjusted associations between birth during the pollen season, cumulative exposure to pollen by 3, 4–6, and 6 months and eczema and sensitisation at 2 years of age

	Adjusted OR (95% CI)		
	Eczema (<i>n</i> = 113, 18%)	Aeroallergen sensitisation [†] (<i>n</i> = 105, 18%)	Food sensitisation [†] (<i>n</i> = 76, 13%)
Birth during the Pollen Season (<i>n</i> = 336, 54.2%) [‡]	1.09 (0.73–1.66)	0.83 (0.54–1.29)	0.76 (0.47–1.25)
Cumulative exposure by 3 months [§]	1.09 (0.86–1.39)	1.34 (1.06–1.72)*	1.03 (0.77–1.39)
Cumulative exposure between 4 and 6 months	0.94 (0.77–1.17)	1.19 (0.98–1.48)	1.07 (0.84–1.37)
Cumulative exposure by 6 months	1.008 (0.98–1.03)	1.04 (1.02–1.07)**	1.007 (0.97–1.04)

P* value < 0.05; *P* value < 0.001.[†]From a multinomial logistic regression with no sensitisation as the reference category. All models were adjusted for infant gender and parental history.[‡]Dichotomized variable.[§]Cumulative exposures expressed as effect per grain increase in pollen exposure during each period.**Table 2.** Adjusted associations between birth during the pollen season, cumulative exposure to pollen by 3, 4–6, and 6 months and hayfever, asthma only, and having both asthma and hayfever at age 6–7 years

	Adjusted OR (95% CI)		
	Hayfever	Having both hayfever and asthma	Asthma only
Birth during the pollen season			
All children	1.48 (0.98–2.26)	1.51 (0.87–2.59)	0.76 (0.48–1.22)
No parental history of asthma [†] (<i>n</i> = 239, 38%)	3.35 (1.31–8.57)*	4.99 (1.08–23.01)*	0.59 (0.27–1.31)
Parental history of asthma (<i>n</i> = 376, 62%)	1.14 (0.69–1.88)	1.08 (0.57–2.03)	0.87 (0.49–1.57)
Cumulative exposure by 3 months [‡]	1.14 (1.009–1.29)*	1.11 (0.95–1.31)	0.96 (0.72–1.27)
Cumulative exposure between 4 and 6 months	1.001 (0.89–1.12)	1.04 (0.91–1.22)	1.35 (1.07–1.72)*
Cumulative exposure by 6 months	1.11 (1.01–1.21)*	1.13 (1.01–1.26)*	1.04 (1.001–1.08)*

**P* < 0.05.[†]The estimate for no parental history and parental history is a stratification variable. An interaction term was significant for both outcomes – *P* value for interaction = 0.02 and 0.04 respectively.[‡]Cumulative exposures are continuous variables expressed as effect per grain increase in pollen exposure during each period.

All models for cumulative exposure to pollen were adjusted for infant gender and parental history.

We examined possible confounding effects of birth during the winter months as a marker of respiratory viruses for models where pollen exposure was significantly associated with hayfever and having both hayfever and asthma. The adjusted OR for both hayfever and having both hayfever and asthma declined slightly (2.97, 95% CI 1.13–7.81, *P* = 0.03 and (4.67, 95% CI 0.99–22.4, *P* = 0.05). The interaction term for birth during the pollen season and parental history of asthma remained significant for both outcomes.

Cumulative exposure to pollen during the first 3 months of life was associated with hayfever at 6/7 years combined (aOR = 1.14, 95% CI 1.009–1.29), cumulative exposure to pollen between 4 and 6 months of life was associated with increased odds of asthma only (aOR = 1.35, 95% CI 1.07–1.72). A greater cumulative exposure to pollen in the first 6 months of life was associated with increased odds of hayfever (aOR = 1.11, 95% CI 1.01–1.21), asthma only (aOR = 1.04, 95% CI 1.001–1.08), and having both hayfever and asthma (aOR = 1.13, 95% CI 1.01–1.26 per 1 grain/m³ increase).

We also examined these associations adjusting for sensitization to determine whether these relationships with asthma and hayfever are mediated by early life sensitization. For hayfever, there was little change in the estimated effects of cumulative exposure to pollen both at 3 and 6 months (aOR = 1.15, 95% CI 1.01–1.31, *P* = 0.03 and aOR = 1.09, 95% CI 1.00–1.19, *P* = 0.05 respectively). The association between cumulative exposure to pollen by 6 months and having both asthma and hayfever slightly declined and became borderline significant after adjusting for sensitization status (aOR = 1.11, 95% CI 0.99–1.24, *P* = 0.07). Cumulative exposure to pollen between 4 and 6 and up to 6 months was still associated with increased odds of asthma only after adjusting for sensitization status (aOR = 1.38, 95% CI 1.08–1.76, *P* = 0.009 and aOR = 1.04, 95% CI 1.006–1.07, *P* = 0.02 respectively).

None of these estimated associations changed when we included presence of upper and lower respiratory infections, otitis media, and gastrointestinal infections. Furthermore, none of these estimated associations chan-

ged when we conducted a subgroup analyses by family history of asthma and hayfever (all *P* values for interaction > 0.10).

Discussion

Our study is the first to show an association between continual exposure to ambient pollen in the first 6 months of life, and aeroallergen sensitization at 2 years and asthma and hayfever in later childhood. Furthermore, birth during the pollen season resulted in a risk of allergic disease in later childhood in children without a parental history of asthma. Few studies have had access to daily measures of the ambient levels of pollen collected through the year. This was a major strength of this study, as we were able to link the daily measure of pollen to the date of birth of the MACS participants and calculate the cumulative exposure for the first 6 months of life.

Our findings on the increased odds of hayfever for those born during the pollen season are consistent with many other studies [8, 19]. None of these studies has examined the effect of family history by season of birth. It appears that birth in the pollen season places low-risk children (based on a negative history of parental asthma) into a high-risk group. Season of birth is only a very crude marker of pollen exposure. Actual exposures vary based on intensity, duration, and timing of pollen season.

It is widely agreed that a parental history of asthma is an important risk factor for the development of childhood asthma and allergies [5, 20, 21]. Furthermore, studies have shown that a maternal history of asthma is a stronger predictor of the incidence of asthma compared with maternal hayfever [20, 21]. To the best of our knowledge, this is the first study to show differences in the influence of pollen exposure at birth on allergic diseases based on a parental history of asthma. It is possible that children with a parental history of asthma are already susceptible, and therefore respond differently to allergen exposure, and thus the impact of being born during the pollen season is less pronounced. By being genetically predisposed, they may respond to other early life exposures such as respiratory viral infections. However, we do not know this for certain, as few studies have examined the interactions between parental history and early life exposure.

To our knowledge no study examined persistent exposure to pollen in early life and eczema and allergen sensitization in infants. However, our findings on pollen exposure in early life are similar to those of two previously published studies for our asthma outcomes [7, 9]. Our study confirms and extends these two studies which assessed asthma at age 4–5 years and provides new insights into the mechanisms of allergen exposure

and childhood allergic disease by showing: (1) strong associations between higher concentrations of pollen at birth and childhood allergic disease, and a novel finding that this association continued to 6 months; and (2) that an early life exposure to pollen is associated not only with an increased risk of a wheeze in toddlers and infants but also with allergen sensitization in toddlers and allergic disease in later childhood.

Our finding on cumulative pollen exposure in the first 6 months of life may suggest that persistent aeroallergen exposure increases risk of asthma and hayfever in all children – irrespective of family history and that the timing of the process is also very important. The first 6 months may be the ‘critical period’ of early life exposure, after which other lifestyle and environmental factors come into play and alter the mechanisms for the subsequent development of asthma and hayfever. This line of thinking is not inconsistent with studies which suggest that birth and the subsequent months – while the immune system develops – are an important period of exposure, impacting the risk of asthma and allergic disease [22]. We could have examined continual pollen exposure up to 12 months of life. However, all children would then be exposed to a ‘pollen season’ in the first 12 months of life and it would have been difficult to unravel the effects of early life exposure.

We did not see much change in the association between pollen exposure and asthma and hayfever when adjusted for sensitisation status, which is somewhat surprising. This can be interpreted as that the mechanism behind the association of early life pollen exposure and increased risk of asthma and hayfever is not related to increased risk of pollen sensitization. However, in the MACS cohort we had very few children who were sensitized to rye grass pollen and therefore any sub-analysis would not be reliable. As we don’t have sensitisation data at 6/7 years, we were unable to fully tease out the possible mechanisms for the allergy exposure-sensitisation-clinical outcomes pathways. Furthermore, we were unable to determine the grass species for grass pollen exposure to fully understand whether the associations are mediated by rye grass pollen sensitisation.

We are not surprised that our findings suggest that pollen exposure in the first 6 months of life is not associated with eczema or sensitization to food. Biologically, we would expect pollen exposure to lead to both hayfever and asthma, but would not expect it to impact on the skin or gut and therefore eczema or food allergy. This may add further evidence to suggest that there may be an underlying genetic or familial component for the development of allergic disease in early life that interacts with different environmental exposures that determine the direction in risk that will lead to different phenotypic outcomes. However, it is important to highlight that in this cohort the numbers for food sensitization by 2 years

were low and that more studies are required to address these important issues.

A major strength of this study is its prospective design. Although we assessed children at age 6/7 year the exposure was measured prospectively prior to the outcome. Furthermore, 6/7 years is a much better age to be looking at the outcomes of asthma (viral wheeze has largely resolved) and hayfever (low prevalence in earlier age groups) than previous studies that have assessed asthma outcomes at age 4–5 years [6, 23]. We also have a high rate of follow-up with ~80% of the original sample completing the survey at 6/7 years.

Some limitations should be considered when interpreting the results. The MACS study is a birth cohort study of high-risk children (either parent or a sibling has a history of asthma and/or allergies) and therefore the findings may not apply to the general population. A further limitation of this study is that no negative (saline) control was used for SPT, which raises the possibility that some of the positive SPT results may have been due to dermatographism. However, we have found that the prevalence of possible dermatographism to be very low in this study group [24].

We were unable to differentiate between different grass species using a Burkard trap and therefore were unable to correlate rye grass sensitization with rye grass pollen exposure. Pollen was measured at only one site. This may pose an issue of misclassification of exposure. Although there are marked daily fluctuations in air-

borne grass pollen levels over Melbourne during the grass pollen season, the majority of this pollen comes from grasslands to Melbourne's north and is distributed over the city by winds blowing from this region. Thus, all subjects living in Melbourne during the study period should receive similar exposures to grass pollen [17].

A possible limitation in this study is the survey definitions of current asthma and hayfever, although they are fairly consistent with those used in the validated ISAAC questionnaires [25]. It is also possible that the null result we observed for eczema may be due to the definition used in this study.

Conclusion

There is an increased risk of aeroallergen sensitisation in infants, and asthma and hay fever in later childhood when exposed to ambient levels of pollen in the first 6 months of life. These results support the hypothesis that there is a critical window of opportunity in early development which may be important for modification of allergic outcomes. Further birth cohort studies with low risk children and with individual measurements are required to confirm our findings and to determine whether these early life environmental exposures such as ambient levels of pollen are causal.

Conflict of interest: The authors declare no conflicts of interest.

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