

The interaction between early life upper respiratory tract infection and birth during the pollen season on rye-sensitized hay fever and ryegrass sensitization – a birth cohort study

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Studies on early life viral respiratory infection and subsequent atopic disease in childhood have conflicting findings. Animal models show that viral respiratory infection in conjunction with allergen presentation can enhance sensitization. This prospective study assesses the influence of an upper respiratory tract infection (URI) in the first month of life and the season of birth on the development of hay fever and ryegrass allergen sensitization in childhood. From a Tasmanian cohort born during 1988 and 1989, a group of 498 children were followed up at 8 yr and another different group of 415 children were followed up at 16 yr. The ryegrass pollen season in Tasmania occurs in November and December. Forty-four (9.6%) children in Follow-up sample 1 and 47 (12.5%) children in Follow-up sample 2 were born in the pollen season. The parental report of an early upper respiratory tract infection (EURI) was documented prospectively by a home interview at 1 month of age (median age 5.1 wk). Sensitization to ryegrass and house dust mite (HDM) was determined at 8 yr of age by skin prick testing and at 16 yr by ImmunoCap[®]. Ryegrass sensitized hay fever was defined as a positive response to a question on hay fever plus the presence of ryegrass allergy. For children tested at age 8 and born in the pollen season, a EURI by postnatal interview was associated with an increased risk of ryegrass sensitization (OR 5.80 95% CI 1.07, 31.31) but not for children with a EURI born outside the pollen season (OR 0.62 95% CI 0.35, 1.08). Similarly, EURI was significantly associated with early onset (≤ 8 yr) ryegrass sensitized hay fever for children born in the pollen season (AOR 4.78 95% CI 1.17, 19.47) but was not associated with early onset ryegrass sensitized hay fever for children born *outside* the pollen season (AOR 0.76 95% CI 0.43, 1.33). These findings suggest that early life viral URI interacts with ryegrass allergen exposure in the development of ryegrass allergen sensitization and ryegrass sensitized hay fever symptoms.

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Studies on the relation between an early life viral respiratory infection and subsequent child atopic disease have had conflicting findings. A cohort

study of German children showed that protection against asthma but not atopy at 7 yr of age was associated with two or more upper respiratory

tract infections (URI) in the first year (1). Ramsey et al. found that croup or having at least two ear infections in the first year of life was inversely associated with atopy at school age (2). However, in two separate Australian cohorts, an URI by 1 month of age was a positive risk factor for developing asthma at age 7 (3), and more than four URI in the first year of life were associated with a marginally increased risk of asthma at 6, and were not protective for atopy (4). The Oslo study showed that having more early life respiratory infections was positively associated with asthma and hay fever at age 10 (5). Respiratory Syncytial viral (RSV) infections have been associated with an increase in asthma but not allergen sensitization (2, 6) in later life.

The timing of viral infection in relation to allergen exposure may influence allergen sensitization. Animal models of influenza virus infection have demonstrated a biphasic effect with concurrent infection at the time of allergen exposure increasing (7) but infection prior to allergen exposure decreasing allergen sensitization (8). Studies from a number of countries have shown an association between time of birth and sensitization to seasonal pollen allergens, suggesting that there may be critical period in early life with regard to the development of inhaled allergen sensitization (9–12). There are few prospective studies from birth that examine these proposals and none have examined in a prospective fashion the interaction between respiratory infections and allergen exposure.

In this study, we have examined whether there is a demonstrable effect of an URI in early life on the development of hay fever or allergen sensitization in later childhood and, in view of the seasonal occurrence of ryegrass allergen, whether this differs by season of birth.

Methods

Tasmanian Infant Health Survey

The cohort study was conducted 1988–1995 and operated through the six major obstetric hospitals in the state, representing 93% of live births. Singleton infants born at these hospitals were scored to assess the risk of SIDS, based on their perinatal profile (13). The cohort entry score was based on a composite score of maternal age, birth weight, infant sex, duration of second stage of labor, infant feeding intention and period of birth. Infants born March–April were more likely to develop SIDS and thus were given a higher score than those born June–July (inter-

mediate risk) or August–February (lower risk) (13). Infants with a composite score over the cut-off and all multiplets were eligible to join the study (13). From January 1988 to December 1995, 11,055 live births were eligible and 9826 (89%) participated in a hospital interview scheduled 4 days after birth and a home interview scheduled during the fifth postnatal week (14).

At a home interview, a verbal questionnaire, and infant and home observations were made. A positive history of an infant cold at the home interview is termed an early URI (EURI). The report of a EURI in this cohort shows high construct validity in relation to previously reported correlates of early infection. That is, positive predictors ($p < 0.05$) of a EURI included increasing household resident number, sleeping in shared room, winter birth, maternal postnatal smoking, infant bottle feeding at 1 month, but not family history of asthma (3).

Pollen season

In Southern Australia the grass pollen season occurs principally in November and December (15). Ryegrass pollination extends for around 6 wk. The timing can be calculated with some precision from the level of the preceding July rainfall. Utilizing the July 1988 and July 1989 rainfall in Launceston, Northern Tasmania for Follow-up sample 1 and Hobart, Southern Tasmania for Follow-up sample 2, indicated a ryegrass season commencing in November for each year of birth by region. We thus designated birth in November or December as birth in the pollen season.

Follow-up samples

Follow-up sample 1. In 1997, the Childhood Allergy and Respiratory Health Survey was conducted in Northern Tasmania, involving children who had participated in the Tasmanian Infant Health Survey (TIHS) in 1988 or 1989 and were residing in Northern Tasmania in 1997. A parental questionnaire included questions on asthma from the International Study of Asthma and Allergy in Childhood (16) and a question on whether the child had attacks of hay fever (sneezing, running or blocked nose, sometimes with itchy eyes). The age (in completed years) of hay fever onset was obtained. Skin prick tests (SPT) to ryegrass, *Alternaria*, *Dermatophagoides pteronyssinus* (Der p 1), *Dermatophagoides farinae* (Der f 1), cat, dog, cow's milk, egg and peanut (Hollister-Stier allergen extracts,

Spokane, WA, USA) and positive (histamine 10 and 1 mg/ml) and negative (glycerine) controls were performed. Wheal sizes of 3 mm or greater at 15 min were classified as positive. Of 596 eligible children, 499 (84%) agreed to participate, hospital interview data were available on 497 and SPT and infant postnatal home interview data were available on 459. The mean age at follow-up was 8.7 yr (Table 1) (17).

Follow-up sample 2. In 2004/5, the T Bone study (a study of bone health) was conducted in Southern Tasmania (18). The subjects who resided in Southern Tasmania were part of an original cohort of 1443 individuals enrolled in 1988–1989 as part of an investigation into sudden infant death syndrome. A total of 730 were traced and approached to participate in a study of bone health (18). Of these 139 failed to respond to the first or subsequent contacts, 129 responded but declined, 38 failed to attend for assessment and nine were not included for other reasons. Of these 415 participants, 374 also agreed to ImmunoCap® testing.

The questionnaire contained the ISAAC module on rhinitis for 14–15 yr olds (19) and included the questions:

- “Have you ever had a problem with sneezing or a runny nose when you did not have the cold or flu?”

Table 1. Characteristics of the child Study Samples born 1988 to 1989 on whom prospective data on month of birth and an early upper respiratory tract infection were available

	Child Follow-up sample 1	Child Follow-up sample 2
Year of follow-up	1997	2004/2005
Age at follow-up	Mean = 8.71 s.d. = 0.59	Mean = 16.30 s.d. = 0.44
Year of birth	1988–1989	1988–1989
Region of birth (Tasmania)	North: 94.6% (434/459), South: 5.4% (25/459)	South: 97.1% (365/376) North: 2.9% (11/376)
Postnatal age (weeks) at home interview	Mean = 6.0 s.d. = 2.2	Mean = 6.1 s.d. = 2.6
Season of birth Nov–Dec	9.6% (44/459)	12.5% (47/376)
EURI by home interview	38.3% (176/459)	32.5% (122/376)
Gastrointestinal infection by home interview	19.2% (88/459)	14.6% (55/376)
Antibiotic use by home interview	17.5% (80/458)	14.4% (54/374)
Rye sensitization	17.3% (79/458)‡	36.0% (121/336)†
HDM sensitization	23.4% (107/458)‡	41.8% (141/337)†
Hay fever ever	24.7% (113/457)	30.6% (115/376)

†ImmunoCap® test of ≥ 0.35 kU_A/l units at age 16.

‡Skin prick test of ≥ 3 mm at age 8.

- In the past 12 months (recent) have you had a problem with sneezing, or a runny or blocked nose when you did not have a cold or flu? In the last 12 months, has this been accompanied by itchy watery eyes?
- Have you ever had hayfever? If yes, at what age did it first occur?”

ImmunoCap® (Pharmacia Diagnostics AB, Uppsala, Sweden) tests were conducted for specific IgE to ryegrass, *Alternaria*, *D. pteronyssinus* (Der p 1), *D. farinae* (Der f 1), cat, dog, cow's milk, egg and peanut allergens. An ImmunoCap® test result ≥ 0.35 kU_A/l was regarded as positive.

We examined the characteristics of those eligible and followed up for each study compared to those eligible but not seen subsequently. For Follow-up sample 1 those participating did not differ to non-participants with regard to at-birth family history of asthma, prematurity, birth weight, birth during the pollen season, a EURI, and postnatal smoke exposure at 1 month. Participants were, however more likely to be infants having some breastfeeds at 1 month (46.6% vs. 33.7%; $p = 0.03$). For Follow-up sample 2 participants did not differ from non-participants with regard to family history of asthma or season of birth but were less likely to have had a EURI (32.5% vs. 42.5%; $p = 0.004$) than those not followed up.

Pooled sample

The pooled sample consisted of the 791 children from either study from whom data were available on aeroallergen sensitization, hay fever and if, from Follow-up sample 2, who also had data on the age of hay fever onset.

Outcomes

The main outcome measures were as follows:

Follow-up sample 1: Positive SPT to ryegrass (≥ 3 mm) or hay fever. Rye-sensitized hay fever was defined as a positive response to the question on hay fever plus the presence of a positive skin test to ryegrass.

In Follow-up sample 2 the outcomes were a positive ImmunoCap® test (≥ 0.35 kU_A/l) to ryegrass and hay fever. Rye-sensitized hay fever was defined as a positive response to the question on hay fever plus the presence of a positive ImmunoCap® test to ryegrass.

For the pooled group we examined children with rye-sensitized hay fever with an onset of the hay fever before or at age 8, to provide a comparable outcome for hay fever in Follow-up

sample 1. This was termed ‘early onset’ rye-sensitized hay fever.

Statistical methods

We examined the distribution of relevant variables as outlined in Table 1. The data were stratified by pollen season at birth to examine whether the association for a EURI with ryegrass sensitization differed by this factor (Table 2). In Table 2, logistic regression was used with exposure terms for birth in pollen season (January–October vs. November–December = 1), EURI (yes vs. no) and postnatal age at interview. This model was used to look at outcomes including: any ryegrass sensitization (yes = 1, no = 0), or an allergen-specific comparison where sensitization to ryegrass was present but not sensitization to other allergens. To assess for interaction between EURI and pollen season, a product term between a EURI and Nov–Dec birth was added to the model. Testing of trend with ordered categorical variables were undertaken by testing the statistical significance of the coefficient of a linear predictor formed by assigning consecutive integer scores to the categories in ascending or descending order. Potential confounders were added as covariates to this model (20). Routinely, we adjusted for postnatal age at interview, infant’s sex and perinatal entry score. Additionally infant or other characteristics that were significantly associated ($p < 0.05$) with allergic hay fever or associated with an odds ratio less than 0.67 or more than 1.5 were examined. Factors from past studies which were implicated as determinants of rye sensitization or hay fever, were also considered as confounders. Analyses that pooled the two cohorts included a term for cohort in the model. To assess

whether the association between birth in the pollen season, a EURI and ryegrass sensitization was specific to ryegrass sensitization only or also for sensitization to other allergens, we examined the association between these factors and the likelihood of being sensitized to ryegrass compared to the other aeroallergens tested. Analyses were conducted using STATA 9.2 (Stata Corporation, College Station, TX, USA, 2007), with confidence intervals and p values obtained using standard Wald-type statistics. p values less than 0.05 were generally regarded as statistically significant but the interpretation of findings is based on the precise p values and confidence intervals reported.

Ethics

Ethics approval was granted by the Southern Tasmania Health and Medical Human Research Ethics Committee and the Ethics Committee of the Children’s Hospital at Westmead.

Results

General

Table 1 shows approximately one-third of infants had a EURI by the 1 month interview. Forty four (9.6%) children in Follow-up sample 1 and 47 (12.5%) children in Follow-up sample 2 were born in the pollen season. As would be expected the proportion of children with rye and HDM allergen sensitization was higher in the adolescent cohort (Follow-up sample 2). A history of EURI was if anything less common for children born in the pollen season than children born in the non-pollen season [Follow-up sample

Table 2. Adjusted odds ratios and 95% confidence intervals for an early upper respiratory tract infection and subsequent aeroallergen sensitization by pollen season of birth in the Tasmanian Infant Cohort

Study	Outcome	If born outside pollen season, % (n/N) with outcome			If born in pollen season, % (n/N) with outcome			Interaction p value for difference in effect by season of birth
		No EURI (%)	EURI (%)	Adjusted odds ratio (95% CI) for EURI and outcome	No EURI (%)	EURI (%)	Adjusted odds ratio (95% CI) for EURI and outcome	
Follow-up sample 1	Ryegrass sensitization	19.4 (48/248)	13.9 (23/166)	0.62 (0.35, 1.08)	11.4 (4/35)	44.4 (4/9)	5.80 (1.07, 31.31)	0.01
Follow-up sample 2	Ryegrass sensitization	38.0 (76/200)	32.4 (33/102)	0.74 (0.44, 1.25)	34.6 (9/26)	37.5 (3/8)	1.07 (0.20, 5.58)	0.69
Follow-up sample 1	Any aeroallergen sensitization	34.7 (86/248)	29.5 (49/166)	0.80 (0.52, 1.22)	22.9 (8/35)	55.6 (5/9)	4.27 (0.92, 19.83)	0.04
Follow-up sample 2	Any aeroallergen sensitization	51.0 (102/200)	55.9 (57/102)	1.19 (0.73, 1.95)	57.7 (15/26)	50.0 (4/8)	0.71 (0.14, 3.51)	0.54

Adjusted for sex, postnatal age at home visit and perinatal cohort entry score.

1; OR 0.38 (0.16, 0.84), Follow-up sample 2; OR 0.68 (0.31, 1.41)].

The association between EURI (early upper respiratory infection), and ryegrass sensitization and birth in the pollen season

In Follow-up sample 1, a EURI was not associated with ryegrass sensitization for children born outside the pollen season [AOR 0.62 (0.35, 1.08) but a EURI was associated with ryegrass sensitization for children born in the pollen season (AOR 5.80 (1.07, 31.31)] (Table 2); $p = 0.01$ for interaction (difference in the association according to the season of birth). In adolescence (Follow-up sample 2) no significant season-of-birth differences in the association between a EURI and ryegrass sensitization were observed ($p = 0.69$) (Table 2). This difference in the effect of a EURI by season of birth was also evident for any aeroallergen sensitization (Follow-up sample 1, Table 2). This effect appeared to be predominantly influenced by ryegrass sensitization because there was no difference in EURI effect by season of birth for early non-rye aeroallergen sensitization ($p = 0.97$).

Additional confirmatory analysis was conducted among infants with a EURI only.

Among this group with early infection, infants born in the pollen season did not have an increased risk of sensitization to HDM alone [AOR 1.44 (0.33, 6.26)], or non-rye aeroallergens [AOR 1.22 (0.13, 11.46)] but were fivefold more likely to be ryegrass sensitized [AOR 5.58 (1.31, 23.86)] compared to infants with a EURI outside

the pollen season. Thus, the season of birth effect among children with a EURI was demonstrated for ryegrass sensitization but not for HDM sensitization.

The association between EURI (early upper respiratory infection), hay fever and birth in the pollen season

As there was an association between birth in the pollen season and rye sensitization in early childhood but not in adolescence, we also examined whether there was any association with hay fever symptoms in either cohort or in the pooled group with subjects consisting of those presenting by the age of 8 yr (early onset hay fever).

In the pooled group there was a tendency for a EURI to be more likely to be associated with early onset hay fever for infants born in (AOR = 2.95) but not those born outside (AOR = 1.14), the pollen season but the difference in effect was not marked ($p = 0.11$) (Table 3). However, in the pooled group ($n = 791$) when this was restricted to ryegrass sensitized hay fever, clearer patterns were evident with an adverse effect for a EURI for those born in the pollen season (AOR = 4.78) but not those born outside (AOR = 0.76), difference in effect, $p = 0.02$ (Table 3).

Further analysis in the pooled data set

We examined other potential confounders further in the pooled data set with regard to early onset rye-sensitized hay fever. In general, adjustment for additional confounders slightly

Table 3. Adjusted odds ratios and 95% confidence intervals for an early upper respiratory tract infection and subsequent hay fever by pollen season of birth in the Tasmanian Infant Cohort

Study	Outcome	If born outside pollen season, % (n/N) with outcome			If born in pollen season, % (n/N) with outcome			Adjusted odds ratio (95% CI) for EURI and outcome	Interaction p value for difference in effect by season of birth
		No EURI	EURI	Adjusted odds ratio (95% CI) for EURI and outcome	No EURI	EURI			
Follow-up sample 1	Hay fever by follow-up	23.6% (58/246)	26.9% (45/166)	1.19 (0.76, 1.88)	20.0% (7/35)	33.3% (3/9)	2.08 (0.41, 10.48)		0.52
Follow-up sample 2	Hay fever by follow-up	31.1% (68/219)	28.2% (31/110)	0.84 (0.50, 1.40)	31.4% (11/35)	41.7% (5/12)	1.51 (0.39, 5.86)		0.43
Pooled samples	Hay fever (≤ 8 yr)†	18.2 (84/461)	20.7 (57/275)	1.14 (0.77, 1.68)	17.1 (12/70)	38.1 (8/21)	2.95 (0.99, 8.77)		0.11
Pooled samples	Ryegrass sensitized hay fever (≤ 8 yr)†	9.9% (44/445)	7.8% (21/268)	0.76 (0.43, 1.33)	8.2% (5/61)	29.4% (5/17)	4.78 (1.17, 19.47)		0.02

Adjusted for sex, postnatal age at home visit and perinatal cohort entry score.

†Additionally adjusted for household resident density at 1 month of age, antibiotic use, infant postnatal smoke exposure to active smoking in the same room at 1 month, and gas used for cooking and family history of asthma.

increased the univariate associations shown in Table 3. Breastfeeding at 1 month was not associated with hay fever and further adjustment did not alter the results in Table 3. Further individual adjustment for maternal smoking during pregnancy, prematurity, low birth weight, first-born, teenage motherhood, paternal unemployment, maternal education, multiple birth, birth length or head circumference, cat or dog as family pet at 1 month, child sleeping in bedroom alone, first immunization by 12 wk or early introduction of solids did not alter the findings in Table 3. Adjusting for the perinatal scoring system did not appear important either.

We then restricted the pooled cohort to those born between August and February, when the cohort entry criteria did not change for any month of birth, to confirm that alterations in the scoring system by month of birth had not contributed to the results. After adjustment for infant age at interview and sex, the adjusted odds ratio for a EURI and rye-sensitized hay fever by age 8 or before was 1.51 (95% CI 0.58, 3.89) for those born August, September, October, January or February, and 4.90 (1.21, 19.86) for those born in November or December. Again, there was a marked adverse effect of EURI among those born in the pollen season, but not for those born August to February.

In the pooled group, we also examined how other infections were associated with rye-sensitized hay fever by birth during the pollen season. Table 1 shows that reported gastrointestinal infection and antibiotic use were reported for under one-fifth of the sample in early infancy. A history of gastroenteritis by 1 month was not associated with rye-sensitized hay fever [OR 1.18 (0.60, 2.19)] with no difference by season of birth (interaction $p = 0.16$). Thus the associations observed in Table 3 for a EURI were not evident for another type of early life infection.

Discussion

Unique features of this study are the documentation in a prospective fashion of the interaction of a respiratory tract infection within the first 6 wk of life with birth in the pollen season and follow up in childhood. The intermittent nature of ryegrass pollen exposure allows examination of the interaction between a EURI and season of birth with subsequent allergen sensitization and hay fever symptoms. Ryegrass exposure provides a unique model to study interactions between allergen exposure, the time of birth and EURI due to the limited exposure (around 6 wk) in Southern Australia. There was a more than

fivefold risk for ryegrass sensitization by age 8 for those children born in the ryegrass season but this association was not present for those born outside the pollen season. In the pooled group comprising a total of 791 children, a EURI was positively associated with an almost fivefold risk of ryegrass sensitized hay fever. Thus the apparent enhancing effect of a EURI on the development of ryegrass sensitized hay fever by age 8 was only observed if the EURI occurred in conjunction with pollen season. These findings suggest that in humans the timing of an URI in early life relative to allergen exposure influences subsequent allergen sensitization, and are consistent with results from animal models where concurrent viral infection at the time of allergen exposure enhanced the development of IgE to inhaled allergens (7, 8, 21). In animal models respiratory virus infections can enhance aeroallergen sensitization at the time of aeroallergen exposure possibly by increased permeability of the airway mucosa to allergens and/or recruitment of antigen presenting dendritic cells to the respiratory epithelium.

The occurrence of a EURI is based on parental report, which was also used for the Oslo birth cohort (5). A history of EURI is positively associated with winter, resident density, maternal smoking and bottle feeding in the Tasmanian cohort (3), suggesting that the parental report reflects a EURI. In addition, the prevalence of a EURI in our population of 38% is consistent with the finding that 40% of infants had been exposed to common respiratory viruses when examined by reverse transcription-polymerase chain reaction at 2 wk of age (22). As the history of a EURI was documented close to the event it is unlikely to be affected by recall bias.

The strengths of this study include the fact that data has been prospectively collected from birth, that allergy or family history of allergic disease were not criteria for inclusion and that the two follow-up studies were from the same birth cohort, facilitating pooling. In the larger pooled sample, it was possible to conduct a careful evaluation of potential confounding factors such as household resident density. Although the numbers of infants born in the pollen season were relatively small, the statistical evidence for an interaction effect was strong when the two separate cohorts were analyzed together. In addition, the interaction of ryegrass with season of birth was apparent for ryegrass but not HDM sensitization, indicating specificity. In contrast to ryegrass HDM provides a perennial source of allergen where the timing of birth would not be expected to be critical. For Follow-up sample 1,

the only characteristic where responders differed from non-responders was the breastfeeding history. However, breastfeeding history was not associated with rye sensitization or hay fever in Follow-up sample 1 and we concluded that the results for Follow-up sample 1 are unlikely to be influenced by a bias due to attrition of subjects. For Follow-up sample 2, responders did differ to non-responders on several characteristics. However, follow-up did not vary by season of birth, so it is unlikely that the differences in the effect of a EURI by birth in pollen season reflects differential follow-up and the findings for Follow-up sample 2 were similar to Follow-up sample 1, where attrition bias was minimal.

Pooling of data from observational studies allows a reduction in potential sources of heterogeneity across studies, such as the modelling of exposure and confounding and provides greater statistical power (23). We pooled the data from the two studies to demonstrate an interaction between early onset of rye-sensitized hay fever by 8 yr of age and the time of birth. This allowed a similar period of the life course (up to 8 yr of age) to be examined in both studies.

Potential limitations of this study are that the main findings are based on post-stratification data, with small total numbers born in the pollen season. However, the findings of a similar season of birth-EURI interaction for both ryegrass sensitization and hay fever by age 8, the specificity of the season of birth effect for ryegrass rather than HDM allergen among those with a EURI and the lack of an interaction with season of birth for other infections are all consistent with an interaction between a EURI and pollen season of birth on ryegrass sensitization in early life.

It should be considered that children destined to develop hay fever or ryegrass sensitization may be more likely to develop upper airway symptoms which could be misclassified as a EURI. However, if this were so the association with the birth in the ryegrass pollen season would imply sensitization to ryegrass whilst prospective studies indicate rye sensitization is detected in later childhood and not in the newborn period (24). In addition the lack of an increased risk of a EURI for children born in the pollen season indicates that reverse causality (with pollen-provoking URI-like symptoms among susceptible infants or increased reporting by atopic parents) was not a problem.

The interaction between a EURI and season of birth for ryegrass sensitization was seen at 8 yr of age but not in adolescence. Sensitization to ryegrass is antecedent to the development of

hay fever and develops progressively throughout childhood and the teenage years (24). One possible explanation is that although early life events might determine the onset of sensitization, as the child gets older the relative influence of these events may wane compared to other life environmental influences. Similar observations of early life environmental influences which diminish in later life have been made with regard to food (25), inhalant allergen sensitization (1) and the effects of infant feeding (26) and RSV infection on asthma (27). Further work is required to exclude chance and confirm the apparent difference in age specific sensitization.

An increased exposure to viral respiratory infections has been suggested as a possible mechanism to explain the hygiene hypothesis, which has developed from the observation that exposure to siblings in early life, is associated with reduced atopic disease (28). However, the originator of the hygiene hypothesis (29) and others (30) have expressed doubts whether the differences in early life viral respiratory infections provide an adequate explanation for the consistent reduction in atopic disease associated with increased sibling exposure. The present study does not provide support for the hypothesis that early life viral respiratory infection is protective for allergen sensitization or allergic disease but is in line with experimental models where concomitant viral infections at the time of allergen exposure have been associated with increased allergen sensitization (7, 8, 21). It may also help explain human population studies where early life viral infections were associated with increased allergic disease (3–5, 31). In the study of Benn et al., a cold in the first 6 months of life did not reduce atopic dermatitis before 18 months and in fact was a positive risk factor in girls (31). The present study has only examined the occurrence of a viral infection in very early life and thus does not exclude the possibility that repeated upper respiratory infections may be protective against subsequent atopy.

The results suggest that for ryegrass allergen sensitization there may be a window of susceptibility in early life and are consistent with a number of studies showing a relationship between time of birth and sensitization to grass pollen allergens. The effect of an early life infection on allergen sensitization and hay fever was related only to URI but not to gastroenteritis suggesting, if not due to the lower prevalence of gastrointestinal infection as compared to respiratory infection, that any immunomodulatory effect may be infection or site-specific. Our findings are consistent with suggestions that early

life viral respiratory infections may in some situations enhance the development of atopy and atopic disease.

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