

The influence of gender and atopy on the natural history of rhinitis in the first 18 years of life

R. J. Kurukulaaratchy^{1,2}, W. Karmaus³, A. Raza¹, S. Matthews¹, G. Roberts^{1,4} and S. H. Arshad^{1,2}

¹The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport, Isle of Wight, UK, ²Infection, Inflammation and Immunity Division, University of Southampton School of Medicine, Southampton, UK, ³Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC, USA and ⁴Developmental Origins of Health and Disease Division, University of Southampton School of Medicine, Southampton, UK

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Summary

Background Longitudinal studies of the natural history of childhood and adolescent rhinitis are lacking.

Objectives To investigate the natural history of rhinitis up to 18 years of age, and how that is influenced by gender and atopy.

Methods The Isle of Wight birth cohort was recruited in 1989 ($n = 1456$). Questionnaire data on nasal symptoms (rhinitis) were collected at 1, 2, 4, 10 and 18 years of age. To define atopy, skin prick tests were conducted at 4, 10 and 18 years. The 12-month period prevalence plus positive and negative transitions (defined as change in disease status in two consecutive study assessments) were stratified by gender and atopic status.

Results Overall rhinitis prevalence increased from 5.4% at 4 years to 35.8% at 18 years ($P < 0.001$), without gender difference. Atopic rhinitis prevalence increased steadily from 3.4% at 4 years to 27.3% at 18 years ($P < 0.001$), was commoner in boys at 18 years ($P = 0.02$) and associated with greater positive transition in boys from 10 to 18 years ($P = 0.01$).

Prevalence of non-atopic rhinitis also increased from 4 to 18 years ($P = 0.003$) and was greater in girls at 18 years ($P < 0.001$) reflecting higher female positive transition from 10 to 18 years ($P < 0.001$). Non-atopic rhinitis negative transition (remission) was highest in early life and reduced in later childhood/adolescence.

Conclusion Atopic rhinitis becomes increasingly common as children grow into adolescents, with stronger associations to male gender. Non-atopic rhinitis shows a female predominance at 18 years as girls 'grow into' it more during adolescence. Our findings suggest differential gender effects on the increasing prevalence of both atopic and non-atopic rhinitis in adolescence.

Clinical Relevance A better understanding of how gender and atopic status influence rhinitis during adolescence emerges from this study. Application of such knowledge could help to improve clinical recognition, judge prognosis and ultimately improve management of this common condition.

Keywords asthma, atopy, gender, negative transition, positive transition, prevalence, rhinitis
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Correspondence:

S Hasan Arshad, The David Hide Asthma & Allergy Research Centre, St Mary's Hospital, Newport, Isle of Wight PO30 5TG, UK. Email: sha@soton.ac.uk

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Introduction

Rhinitis is an inflammatory disease of the upper airway characterized by nasal itching, rhinorrhoea, nasal congestion or sneezing. It emerged as a common condition associated with substantial morbidity in childhood during the final decades of the 20th century [1, 2]. This same period witnessed a similar rising prevalence of other

allergic states [3], including asthma and eczema. Co-morbidity of rhinitis with asthma is now well recognized and the concept of 'one airway-one disease' [4, 5] to support this association is widely accepted. It has also been previously suggested that allergic co-morbidity follows an 'allergic march' with characteristic evolution of allergic disease [6, 7] from one state to another through childhood. The accepted view of the 'allergic march'

suggests that rhinitis is usually a late allergic manifestation appearing during adolescence. For asthma, a 'gender switch' from male predominance in childhood to female predominance after puberty has been shown in several populations [8–11]. In parallel with the notion of strong co-morbidity between asthma and rhinitis it has been suggested that rhinitis may also undergo similar gender reversal during adolescence [12]. However, the dynamics of changing rhinitis prevalence from childhood to adulthood and factors influencing those changes have not been convincingly determined. The role of atopy in the natural history of rhinitis also merits further consideration as it is now recognized [13] that evidence of allergic sensitization may not be found in all those classed as having allergic diseases.

Given its significant prevalence, associated morbidity and co-morbidity with other common conditions like asthma, we sought to better characterize the natural history of rhinitis through childhood and adolescence in the Isle of Wight Birth Cohort. We specifically focused on gender-specific differences in atopic and non-atopic rhinitis during this period and hypothesized a gender reversal in the prevalence of rhinitis in association with adolescence.

Methods

Isle of Wight 1989 birth cohort

A whole population birth cohort ($n = 1456$) was established on the Isle of Wight, UK, in 1989 to prospectively study the natural history of allergic disorders. The Island is close to the British mainland, semi-rural, with no heavy industry. The population is 99% Caucasian. The Southampton and SW Hampshire Local Research Ethics Committee approved the study (06/Q1701/34). Of 1536 children born between 1 January 1989 and 28 February 1990, and consented, 1456 were available for follow-up. Children were assessed at 1 ($n = 1375$; 94.4%), 2 ($n = 1214$; 84.5%), 4 ($n = 1218$; 83.6%), 10 ($n = 1373$; 94.3%) and 18 years ($n = 1313$; 90.2%). Detailed questionnaires, including International Study of Asthma and Allergy in Childhood, were completed with the parents (or study subject at age 18) regarding allergy prevalence at each follow-up. When a visit was not possible either a telephone questionnaire or modified postal questionnaire was completed. Rhinitis was defined by a positive response to: 'In the past 12 months have you had a problem with sneezing, or a runny or a blocked nose when you DID NOT have a cold or the flu?'

Skin prick testing (SPT) was performed on most children attending the Research Centre at 4, 10 and 18 years to a battery of common allergens (ALK, Horsholm, Denmark). At age 1-or-2, only symptomatic children were invited to participate in SPT. Inhalant allergens tested

were house dust mite, cat, dog, *Alternaria alternata*, *Cladosporium herbarium*, grass pollen mix and tree pollen mix. Food allergens tested were cows' milk, soya, hens' egg, wheat, peanut and cod. Positive and negative controls were included. Atopy (allergic sensitization) was defined by at least one allergen test response with mean weal diameter 3 mm greater than the negative control at 15 min. At each examination, children with both rhinitis and positive SPT were regarded as having atopic rhinitis.

Statistical analyses

At each assessment, 12-month (24-month for 1-or-2 years as those assessments were close together) rhinitis prevalence was determined by dividing the number of children with current rhinitis symptoms by the total number of children with data on rhinitis status. By definition, analysis of atopic and non-atopic rhinitis was confined to children with rhinitis data who underwent SPT. For example, atopic rhinitis prevalence represented the number of children with both rhinitis and positive SPT, divided by the total number of children with SPT and rhinitis information.

Our study represents a dynamic cohort; some children did not participate in one assessment but re-joined the next. The appropriate measures of changes in a dynamic cohort are positive and negative transitions rather than incidence and remission. A positive transition is defined as a change in the individual status from rhinitis-free to rhinitis, independent of whether this is the first occurrence. Calculations of atopic and non-atopic rhinitis positive and negative transitions were based on rhinitis status during two consecutive investigations and SPT information for the second examination. Thus positive atopic rhinitis transition from age 4 to 10 took into account children who were rhinitis-free at age 4 years (children at risk), developed rhinitis at 10 years, and had a positive SPT result at 10 years. This numerator was divided by all children who had SPT information at 10 years of age and were at risk. Negative transition of rhinitis between follow-ups was defined as the individual change in rhinitis status from 'disease' to 'disease-free'. Calculations of negative transition for atopic and non-atopic rhinitis followed similar rules as for positive transition.

For each observation period (age 1-or-2, 4, 10, 18 years), we estimated the difference in boys and girls using χ^2 -tests. Information on prevalence at 1-or-2 years and transitions between 1-or-2 to 4 years are provided in the tables. However, 'nasal symptoms' at 1-or-2 years may part reflect processes triggered by viral infections and potentially a different entity to rhinitis in later childhood/adolescence. Hence the simple use of 1-or-2-year data/1-or-2- to 4-year period data alone as a reference for subsequent transitional analysis of rhinitis may be

inappropriate. Consequently we also made such assessments against references of 4- and 4–10-year period data and present both sets of analysis in the tables. Applying generalized estimating equation (GEE) analysis [14] that takes the within-child effect into account, we estimated marginal probabilities for time and gender and their interaction using GEE (GENMOD) in the SAS system (SAS, Cary, NC, USA). The analyses provided the statistical significance for the development of rhinitis over time, for gender differences and for the interaction of gender $\times$ time. The combined effect of gender $\times$ time assessed whether boys and girls had different patterns of prevalence or transition during the course of the study.

We also restricted the analysis to a subgroup that participated in all follow-ups (stable cohort) and calculated the cumulative incidence for the investigation periods 1-or-2 to 10 years and 1-or-2 to 18 years as the first occurrence of rhinitis in those never affected before. This stable cohort was also used to calculate net remission for the 1-or-2 to 18-, and 4–18-year period. For instance, net remission from age 1-or-2 to 18 years represented those with disease at baseline who had outgrown it by age 18.

To compare co-morbidities of rhinitis with asthma and eczema, we used prospectively collected asthma and eczema data. Briefly, comparable symptom-based questions were used for an investigator-diagnosed definition of asthma (a doctor diagnosis or ever having asthma plus either wheezing or asthma therapy in the past 12 months). Eczema was defined as 'ever eczema' plus an 'itchy rash during the previous 12 months'.

Results

The original cohort ($n = 1536$) included 786 (51.2%) boys and 750 (48.8%) girls. Information about current nasal symptoms (rhinitis) was available for 1377, 1214, 1362 and 1309 children at age 1-or-2, 4, 10 and 18 years, respectively. SPT were performed on children at age 4 ($n = 980$), 10 ($n = 1036$) and 18 ($n = 853$) years. SPT participation was significantly greater in those reporting rhinitis, those of higher socio-economic class and in girls at 18 years but did not differ significantly by gender at other ages or by family history of atopy (data not shown).

Approximately 14% of the children had asthma in the period from infancy to 10 years, and 18% at age 18, while 12–14% had eczema during this period. However, at all stages, co-morbidity between rhinitis and asthma was more frequent than that between rhinitis and eczema. For instance, at age 4, 43% also had asthma [95% confidence interval (CI): 31.0–55.1%] and 29.2% had eczema; at age 10, 30.8% had asthma (95%CI: 25.7–36.0%) and 20.8% had eczema; at age 18, 32.7% had asthma (95%CI: 27.5–37.9%) and 17.4% had eczema.

Rhinitis period prevalence

Nasal symptoms occurred in 15.8% of the population at 1-or-2 years, with significant male predominance ($P = 0.006$). Since we had insufficient information for the denominator to calculate the prevalence of atopic and non-atopic rhinitis at 1-or-2 years (SPT was only performed in symptomatic children), only overall prevalence is tabulated for that period (Table 1). However, of the 217 children with rhinitis at 1-or-2 years, 185 (85.3%) participated in SPT and only 31 (16.8%) were atopic. Nasal symptom prevalence (Table 1) fell significantly from 1-or-2 to 4 years ($P < 0.001$). Then, rhinitis prevalence was significantly higher at both 10 and 18 years ($P < 0.001$) than at 4 years. Rhinitis at 18 years (Table 1) was also significantly more prevalent than rhinitis at 1-or-2 years ($P < 0.001$). Overall, linear trend tests showed significant increases ($P < 0.0001$, data not shown). No significant gender differences in overall rhinitis prevalence were detected at 4, 10 or 18 years. There was a significant gender–time interaction for changing rhinitis prevalence from 1-or-2 to 18 years accounted for by a relative change in gender predominance for rhinitis between those time-points. However this was not replicated in the 4–18-year period (Table 1).

The total number of children with allergic sensitization increased from 193 (19.7%) at age 4 to 279 (26.9%) at 10 years and to 352 (41.3%) at 18 years. Atopy was found in 55.0%, 51.3% and 69.8% of rhinitis at 4, 10 and 18 years, respectively. At 4, 10 and 18 years the atopic proportion of prevalent rhinitis was higher for boys (65.7%, 57.0%, 82.4%, respectively) in comparison with girls (40.0%, 45.5%, 58.8%, respectively). One case of atopic rhinitis sensitized to 'food allergen only' was found during the entire course of the study (to wheat at 1 year).

Atopic rhinitis significantly increased in prevalence from 4 to 18 years, with male predominance at both 4 and 18 years (Table 1). Non-atopic rhinitis also significantly increased in prevalence through childhood and was significantly ($P < 0.001$) higher in girls (16.6%) than boys (6.6%) at age 18. Gender–time interaction analysis for non-atopic rhinitis identified a significant difference ($P = 0.016$) likely to be due to this female predominance at 18 years. Comparisons of individual time-points (Table 1) and linear trend analyses indicate statistically significant changes ($P < 0.0001$, data not shown). The different dynamic for boys and girls is illustrated in Fig. 1.

Positive transition and cumulative (first) incidence of rhinitis

Rhinitis positive transition rose significantly between consecutive study periods throughout the study (Table 2). Linear trend tests were significant, overall and for atopic and non-atopic rhinitis ($P < 0.0001$, data not shown).

Table 1. Prevalence of rhinitis (current nasal symptoms) from 1 to 18 years; overall and stratified by sex and atopy

	Age 1-or-2 years % (n/total)	Age 4 years % (n/total)	Age 10 years % (n/total)	Age 18 years % (n/total)	Time and gender interaction P-value [‡]
All					
Time trend [†]					
Total	15.8 (217/1377)	5.4 (65/1214)	22.6 (308/1362)	35.8 (468/1309)	
P-value	Reference	0.0001	0.06	0.0001	0.014
P-value		Reference	0.0001	0.0001	0.19
Sex differences					
Males	18.4 (129/700)	6.3 (39/619)	22.7 (157/692)	34.3 (223/651)	
Females	13.0 (88/677)	4.4 (26/595)	22.5 (151/670)	37.2 (245/658)	
P-value*	0.006	0.14	0.95	0.26	
Atopic rhinitis					
Time trend [†]					
Total	§	3.4 (33/980)	13.3 (138/1036)	27.3 (233/853)	
P-value		Reference	0.0001	0.0001	0.39
Sex differences					
Males		4.7 (23/493)	14.9 (77/516)	31.0 (126/407)	
Females		2.1 (10/487)	11.7 (61/520)	24.0 (107/446)	
P-value*		0.02	0.13	0.02	
Non-atopic rhinitis					
Time trend [†]					
Total		2.8 (27/980)	12.6 (131/1036)	11.8 (101/853)	
P-value		Reference	0.0001	0.003	0.016
Sex differences					
Males		2.4 (12/493)	11.2 (58/516)	6.6 (27/407)	
Females		3.1 (15/487)	14.0 (73/520)	16.6 (75/446)	
P-value*		0.54	0.18	0.0001	

Numbers represent the percentage (number with rhinitis/total number available for analysis at each assessment). The 'All' row shows data for all children. The 'atopic rhinitis' row takes into account children with positive skin prick test (SPT) results; in contrast, 'non-atopic rhinitis' studied only children with negative SPT results.

*P-value (two-sided) represents the difference between males and females.

[†]P-value for the time trend for rhinitis compared with reference group by generalized estimation equation.

[‡]P-value for the sex–time interaction which represents the difference between all time-points and the reference group (age 1-or-2 or 4, respectively) in regard to gender and age.

§SPT was performed in symptomatic children only.

Positive transition for rhinitis was significantly greater in boys ($P=0.02$) during the 1-or-2- to 4-year period but significant gender differences in rhinitis positive transition were not observed during the rest of the study (Table 2). Gender–time analysis demonstrated a significant difference between the 1-or-2- and 18-year assessments accounted for by relative shifts in gender predominance between those time-points.

Positive transition for atopic rhinitis rose steadily between study periods (Table 2) and was significantly greater in boys during the 1-or-2- to 4-year ($P=0.009$) and the 10–18-year ($P=0.01$) periods. Non-atopic rhinitis positive transition also rose significantly from the 1-or-2- to 4-year period to the 4–10-year period ($P<0.001$) but then fell significantly during the 10–18-year period ($P=0.038$). Girls showed significantly ($P<0.001$) greater positive transition of non-atopic rhinitis (15.7%) than boys (6.9%) from 10 to 18 years, accounting for the

observed significant gender–time interaction in non-atopic rhinitis positive transition (Table 2).

A first occurrence of rhinitis was detected in 21.5% at 10 years when it was significantly associated with atopic status (48.4% compared with 14.8% without atopy, $P<0.001$) but not gender. At age 18, rhinitis was first detected in 29.5% of the participants, again significantly associated with atopic status (61.8% compared with 15.4% without atopy $P=0.001$). At this age, there were significantly more first occurrence of non-atopic rhinitis in girls (19.3% compared with 9.7% in boys, $P=0.03$).

Negative transition and complete remission of rhinitis

Negative transition of rhinitis was significantly greater in the 1-or-2- to 4-year time period in comparison with subsequent study periods (Table 3). Time trend analysis did not demonstrate significant difference in rhinitis

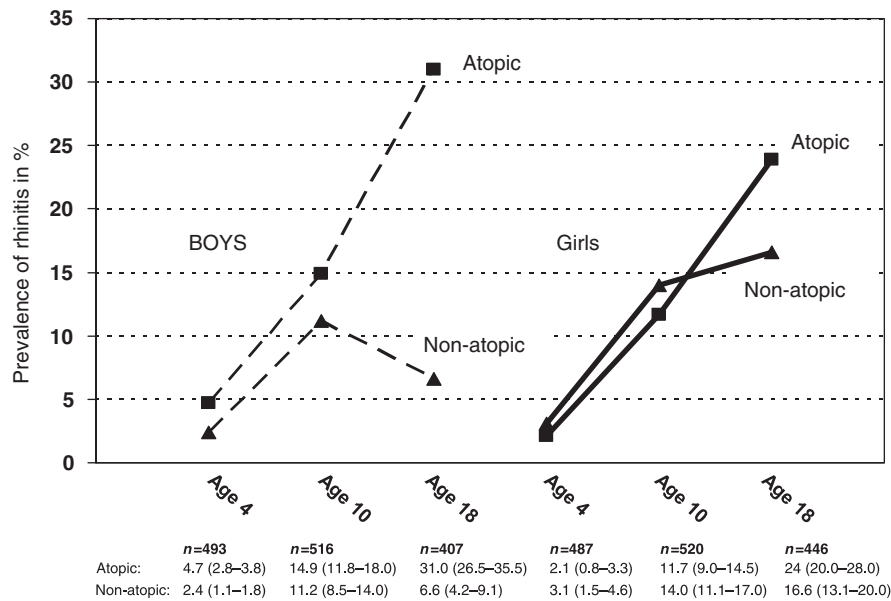


Fig. 1. Changes in atopic and non-atopic rhinitis prevalence for boys and girls over the first 18 years of life. Figures indicate rhinitis prevalence (percentage with 95% confidence intervals) at each assessment for boys and girls, stratified by atopic status.

negative transition between the 4–10- and 10–18-year periods, irrespective of atopic status. Overall and in the non-atopic group, testing for linear trends showed a significant decrease in negative transitions ($P < 0.0001$, data not shown), but not in atopic children. There were no significant gender differences in negative transition of overall rhinitis and non-atopic rhinitis at any stage during the study (Table 3). However, negative transition of atopic rhinitis was significantly ($P = 0.01$) greater in boys (19.8%) than girls (8.2%) in the 10–18-year study period (Table 3).

Complete remission could not be calculated after 10 years as only 7 children with rhinitis at age 1-or-2 or 4 years were rhinitis free at 10 and 18 years. Complete remission after 4 years following symptoms at age 1-or-2 years was noted in 124/181 children. It was not associated with the atopic status of the child, but was significantly less common in non-atopic girls than boys (59.7% compared with 76.9% in boys, $P = 0.03$).

Discussion

This study provides longitudinal assessment of the natural history of current nasal symptoms or rhinitis in the first 18 years of life. To the best of our knowledge this is the first paper to present such findings from an unselected whole population birth cohort. High rates of cohort follow-up were achieved throughout, minimizing selection biases and enhancing the reliability of our findings. We have shown that rhinitis (particularly atopic rhinitis) is increasingly common throughout childhood and adolescence. Potentially important differential gender effects upon development of atopic and non-atopic rhinitis during adolescence were found. At age 1-or-2 years, nasal

symptoms were largely non-atopic, more frequent in boys and may not have represented typical allergic rhinitis. By 4 years of age prevalence of nasal symptoms had fallen but appeared to represent a condition more consistent with allergic rhinitis, showing greater association with atopy. From 4 years onwards, new cases of rhinitis increased through childhood and adolescence leading to a steady rise in overall rhinitis prevalence without significant gender differences or significant gender switch in prevalence with puberty. We identified increasing atopic rhinitis development from 4 years onwards, which was significantly greater in boys from 10 to 18 years. After falling from age 1-or-2 to 4 years non-atopic rhinitis prevalence significantly increased thereafter. Non-atopic rhinitis prevalence was significantly higher in girls at 18 years with significantly greater positive transition in girls during adolescence. Although the number of remission cases is small and limits our conclusion, there seem to be a consistent pattern that negative transition of rhinitis was highest in early childhood reflecting loss of early life non-atopic rhinitis. We also observed that with time, negative transition of childhood/adolescent rhinitis reduced significantly and was always lower for atopic than non-atopic disease. Indeed, complete remission of rhinitis from 4 years onwards was scarce indicating a generally persistent condition.

Assessment of rhinitis at all follow-ups used an identical questionnaire-based approach. One potential limitation of that approach is that it can be difficult to differentiate between infectious and other forms of rhinitis in infancy when viral infections are acknowledged as a significant cause of recurrent nasal symptoms [15]. We demonstrated prevalence for current nasal symptoms of

Table 2. Positive transition from 1 to 18 years for rhinitis (current nasal symptoms)

	Age 1 and 2–4 years % (<i>n</i> /total)	Age 4–10 years % (<i>n</i> /total)	Age 10–18 years % (<i>n</i> /total)	Time and gender interaction Age 4–18 <i>P</i> -value [‡]
All				
Time trend [†]				
Total	5.0 (48/955)	22.3 (243/1092)	28.4 (270/951)	
<i>P</i> -value	Reference	0.0001	0.0001	0.047
<i>P</i> -value		Reference	0.046	0.84
Sex differences				
Males	6.8 (32/474)	22.1 (122/552)	27.8 (131/472)	
Females	3.3 (16/481)	22.4 (121/540)	29.0 (139/479)	0.84
<i>P</i> -value*	0.02	0.90	0.67	
Atopic rhinitis				
Time trend [†]				
Total	3.7 (29/777)	12.1 (106/879)	20.2 (124/615)	
<i>P</i> -value	Reference	0.0005	0.0001	0.125
<i>P</i> -value		Reference	0.0001	0.32
Sex differences				
Males	5.6 (21/377)	13.0 (57/437)	24.5 (71/290)	
Females	2.0 (8/400)	11.1 (49/442)	16.3 (53/325)	
<i>P</i> -value*	0.009	0.37	0.01	
Non-atopic rhinitis				
Time trend [†]				
Total	1.9 (15/777)	13.0 (114/879)	11.5 (71/615)	
<i>P</i> -value	Reference	0.0001	0.001	0.076
<i>P</i> -value		Reference	0.038	0.036
Sex differences				
Males	1.9 (7/377)	11.7 (51/437)	6.9 (20/290)	
Females	2.0 (8/400)	14.3 (63/442)	15.7 (51/325)	
<i>P</i> -value*	0.88	0.25	0.0007	

A positive transition represents the change in the individual status from rhinitis-free to rhinitis. Numbers represent the percentage (number with rhinitis/total number available for analysis at each assessment). The 'All' row shows data for all children. The 'atopic rhinitis' row takes into account children with positive skin prick test (SPT) results; in contrast, 'non-atopic rhinitis' studied only children with negative SPT results.

**P*-value (two-sided) represents the difference between males and females.

[†]*P*-value for the time trend for rhinitis compared with reference group (age 1-or-2 or 4, respectively) by generalized estimation equation. The time trend is controlled for the trend of gender interaction.

[‡]*P*-value for the gender–time interaction which represents the difference between all time-points and the reference group (age 1-or-2 or 4, respectively) in regard to sex and age.

15.8% at age 1-or-2 years with significant male predominance. This figure may well have included a proportion of 'viral induced infectious rhinitis' thus overestimating rhinitis prevalence. Only 16.8% of rhinitis at 1-or-2 years was associated with atopic sensitization. For these reasons we did not use current nasal symptoms (rhinitis) at 1-or-2 years as the sole reference for comparison in subsequent analysis but also presented those analyses using 4-year data as a reference.

Another potential limitation of our study is that SPT was not available for every subject. However, we did not identify selection biases for SPT participation that were likely to have affected our prevalence figures for atopic/non-atopic rhinitis. Slightly more girls than boys had SPT at 18 years but that would not have influenced the increased prevalence of non-atopic rhinitis in 18-year-

old girls. Children with rhinitis were always more likely to have SPT but we could find no indication that this would have altered the relationships of atopic status and rhinitis we found. More children of lower social class consistently failed to have SPT but again this should not have influenced the nature of our results.

Rhinitis is traditionally regarded as an atopic disorder [16]. We confirmed high manifestation of atopy in those with rhinitis during the first 18 years of life. Our data also demonstrated that positive transition of atopic rhinitis rose steadily between assessments and that incident rhinitis at both 10 and 18 years was significantly more often found to be atopic. Additionally, negative transition of atopic rhinitis became less frequent with time. However, we also identified more surprising findings in relation to atopic rhinitis. We detected atopic rhinitis as early as age

Table 3. Negative transition from 1 to 18 years of life for rhinitis (current nasal symptoms)

	Age 1 and 2–4 years % (n/total)	Age 4–10 years % (n/total)	Age 10–18 years % (n/total)	Time and gender interaction Age 4–18 P-value [‡]
All				
Time trend [†]				
Total	93.1 (175/188)	54.1 (33/61)	39.2 (110/281)	
P-value	Reference	0.0007	0.0001	0.57
P-value		Reference	0.40	NC
Sex differences				
Males	94.3 (100/106)	50.0 (18/36)	41.3 (59/143)	
Females	91.5 (75/82)	60.0 (15/25)	37.0 (51/138)	
P-value*	0.44	0.44	0.46	
Atopic rhinitis				
Time trend [†]				
Total	11.2 (19/169)	21.8 (12/55)	13.7 (29/211)	
P-value	Reference	0.31	0.18	0.24
P-value		Reference	0.87	0.77
Sex differences				
Males	12.6 (12/95)	20.0 (6/30)	19.8 (20/101)	
Females	9.5 (7/74)	24.0 (6/25)	8.2 (9/110)	
P-value*	0.52	0.72	0.01	
Non-atopic rhinitis				
Time trend [†]				
Total	81.1 (137/169)	30.9 (17/55)	25.6 (54/211)	
P-value	Reference	0.0004	0.0001	0.77
P-value		Reference	0.69	0.98
Sex differences				
Males	81.1 (77/95)	26.7 (8/30)	23.8 (24/101)	
Females	81.1 (60/74)	36.0 (9/25)	27.3 (30/110)	
P-value*	0.99	0.46	0.56	

*P-value (two-sided) represents the difference between males and females.

[†]P-value for the time trend for rhinitis compared with reference group (age 1-or-2 or 4 years, respectively) by generalized estimation equation. The time trend is controlled for the trend of gender interaction.

[‡]P-value for the sex–time interaction which represents the difference between all time-points and the reference group (age 1-or-2 or 4 years, respectively) in regard to sex and age.

NC, not calculable.

1-or-2 years. This counters expectations set by the notion of an allergic march [17] predicting an atopic burden of eczema and food allergy in earlier childhood without allergic rhinitis until adolescence. Support emerges for our findings from studies in other populations. Results from the BAMSE birth cohort [18] highlighted substantial aeroallergen sensitization by age 4 years with further incident cases between 4 and 8 years. If such findings are replicated in other data sets, revision of the previously accepted nature of an allergic march may be warranted. Increasing aeroallergen sensitization in the first decade of life could perpetuate a state of tissue inflammation responsible for propagating the development of atopic rhinitis detected in our cohort from 4 to 10 years. The fact that we detected substantial early (at age 4 years) co-morbidity of rhinitis and asthma and that this was greater than the co-morbidity of eczema and rhinitis suggests parallel rather than consequential development of child-

hood allergic manifestations. This high co-morbidity of rhinitis with asthma in all assessment periods (30.8–47.5%) lends further support to the 'one airway-one disease' concept of airways disease [5].

We expected to find male predominance for a strongly atopic disorder such as rhinitis during the prepubertal period since previous studies [11] have described male predominance of related conditions like asthma during that time. It is noteworthy that, after age 1-or-2 years (when nasal symptoms probably did not solely reflect allergic rhinitis) we found no significant gender difference for overall rhinitis prevalence from 4 to 18 years. However, atopic rhinitis was higher in males at both 4 and 18 years. We concluded that puberty occurred between 10 and 18 years for the majority of study subjects as evidence of puberty at the 10-year assessment was minimal. Although overall rhinitis prevalence was higher in 18-year-old girls we could not identify significant change in

gender predominance with puberty for overall rhinitis in our cohort; contrary to previous observations for asthma [8–10]. Much interest has surrounded the concept of a switch in prevalence of atopic disorders from male predominance in childhood to female predominance after puberty [11]. Contributory roles of sex hormonal influences [19] and obesity [20–23] have been proposed in this regard for asthma and may have complex interacting influences on changing dynamics of lower airway disease prevalence during adolescence. Given the common comorbidity of asthma and rhinitis it is plausible that similar influences might be relevant to the changing dynamics of upper airway disease (rhinitis) prevalence during adolescence too. Indeed, recent work [24] has identified potential associations between adipokine levels and expression of childhood allergic rhinitis.

We found differential interactions of gender with rhinitis development based upon adolescent atopic status. Thus, boys showed significantly greater development of atopic rhinitis while girls showed significantly greater development of non-atopic rhinitis during adolescence. A similar differential gender relationship has been previously reported for adolescent asthma [8] in the Dunedin cohort. Several studies have also found greater female incidence of lower airway disease during adolescence [8–10] which when characterized was predominantly non-atopic [8, 10]. Our findings suggest similar expression of non-atopic upper airway disease in adolescent girls. Female predisposition to development of both non-atopic upper and lower airways disease could partly reflect the complex effect of sex hormonal- and adipose-related hormonal (such as leptin or adiponectin) changes associated with the changing physiology of pubertal females. Female sex hormone levels have been linked to increased fat mass [25]; a relationship that might be exacerbated by an altered adolescent hormonal environment. While data is lacking for rhinitis at present, studies have identified associations between central obesity and asthma in parallel with an inverse relationship between atopic sensitization and obesity for both childhood and adult asthma [23, 26]. While adolescent girls appear more predisposed to non-atopic rhinitis development, it is worth considering whether male physiological changes during puberty may also serve a protective role against development of non-atopic rhinitis. We observed that boys had a considerable fall in non-atopic rhinitis

prevalence (11.2% at 10 years to 6.6% at 18 years) due to lower positive transition for non-atopic rhinitis during adolescence and lower incidence at 18 years for non-atopic rhinitis. Conversely, adolescent boys appeared to be more predisposed to developing atopic rhinitis. This may again parallel changes previously seen for wheeze/asthma development [8] or persistence [10] during adolescence in boys where atopy emerged as a significant risk factor. Thus, male-related pubertal factors may protect against development of non-atopic rhinitis but predispose to, or perpetuate, a risk of developing atopic rhinitis. It is probable that perceived pubertal influences of gender on allergic diseases are not determined solely by atopic status but arise from an interaction of as yet undetermined factors. Other differential influences that might be mechanistically relevant include potential roles of genetic predisposition, environmental exposure and the role of obesity.

In conclusion, rhinitis prevalence increases steadily during childhood to affect more than a third of the population at 18 years. Atopic rhinitis becomes increasingly common during adolescence, with male predominance and no evidence of a 'gender switch' in prevalence. Non-atopic rhinitis shows a female predominance at 18 years as girls 'grow into' that state more than boys during adolescence. These findings suggest that differential pubertal-related factors may influence the development of both atopic (in boys) and non-atopic (in girls) rhinitis. Further investigation of relevant mechanisms for these findings could considerably enhance our understanding of rhinitis and is required in future studies.

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References

- 1 Ait-Khaled N, Pearce N. The ISAAC Phase Three Study Group *et al*. Global map of the prevalence of symptoms of rhinoconjunctivitis in children: The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. *Allergy* 2009; **64**:123–48.
- 2 Meltzer EO, Blaiss MS, Derebery J *et al*. Burden of allergic rhinitis: results from the Pediatric Allergies in America Survey. *J Allergy Clin Immunol* 2009; **124**:S43–70.
- 3 Asher MI, Montefort S, Bjorksten B *et al*. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases one and three repeat multicountry cross-sectional surveys. *Lancet* 2006; **368**:733–43.

- 4 Demoly P, Bousquet J. The Relationship between asthma and allergic rhinitis. *Lancet* 2006; **368**:711–3.
- 5 Bousquet J, Khaltaev N, Cruz AA *et al.* Allergic rhinitis and its impact on asthma (ARIA) 2008 update. *Allergy* 2008; **63** (Suppl. 86):8–160.
- 6 Bergmann RL, Edenharter G, Bergmann KE *et al.* Atopic dermatitis in early infancy predicts allergic airways disease at 5 years. *Clin Exp Allergy* 1998; **28**: 965–70.
- 7 Kulig M, Bergmann R, Tacke U, Wahn U, Guggenmoos-Holzmänn I. Long-lasting sensitization to food during the first two years precedes allergic airway disease. *Pediatr Allergy Immunol* 1998; **9**:61–7.
- 8 Mandhane PJ, Greene JM, Cowan JO, Taylor R, Sears MR. Sex differences in factors associated with childhood- and adolescent-onset wheeze. *Am J Respir Crit Care Med* 2005; **172**:45–54.
- 9 Tollefsen E, Langhammer A, Romundstad P, Bjørner L, Johnsen R, Holmen TL. Female gender is associated with higher incidence and more stable respiratory symptoms during adolescence. *Respir Med* 2007; **101**:896–902.
- 10 Nicolai T, Pereszlenyi I, Bliznakova L, Illi S, Reinhardt D, von Mutius E. Longitudinal follow-up of the changing gender ratio in asthma from childhood to adulthood: role of delayed manifestation in girls. *Pediatr Allergy Immunol* 2003; **14**:280–3.
- 11 Almqvist C, Worm M, Leynaert B. Impact of gender on asthma in childhood and adolescence: a GA2LEN review. *Allergy* 2008; **63**:47–57.
- 12 Robertson CF, Dalton MF, Peat JK *et al.* Asthma and other atopic diseases in Australian children. *Med J Aust* 1998; **168**:434–8.
- 13 Kurukulaaratchy RJ, Matthews S, Arshad SH. Defining childhood phenotypes to investigate the association of atopic sensitization with allergic disease. *Allergy* 2005; **60**:1280–6.
- 14 Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986; **42**:121–30.
- 15 van Bentin I, Koopman L, Niesters B *et al.* Predominance of rhinovirus in the nose of symptomatic and asymptomatic infants. *Pediatr Allergy Immunol* 2003; **14**:363–70.
- 16 Zaczaraszewicz A, Douwes J, Pearce N. What proportion of rhinitis symptoms are attributable to atopy? *J Clin Epidemiol* 2003; **56**:385–90.
- 17 Kjellman NI, Nilsson L. From food allergy and atopic dermatitis to respiratory allergy. *Pediatr Allergy Immunol* 1998; **9** (Suppl. 11):13–7.
- 18 Asaranoj A, Ostblom E, Kull I *et al.* Sensitization to inhalant allergens between 4 and 8 years of age is a dynamic process: results from the BAMSE birth cohort. *Clin Exp Allergy* 2008; **38**:1507–13.
- 19 de Marco R, Locatelli F, Sunyer J, Burney P, The European Respiratory Community Health Survey Study Group. Differences in incidence of reported asthma related to age in men and women. A retrospective analysis of the data of the European Respiratory Health Survey. *Am J Respir Crit Care Med* 2000; **162**:68–74.
- 20 Hancox RJ, Milne BJ, Poulton R *et al.* Sex differences in the relation between body mass index and asthma and atopy in a birth cohort. *Am J Respir Crit Care Med* 2005; **171**:440–5.
- 21 Castro-Rodriguez JA, Holberg CJ, Morgan WJ, Wright AL, Martinez FD. Increased incidence of asthmatic symptoms in girls who become overweight or obese during the school years. *Am J Respir Crit Care Med* 2001; **163**:1344–9.
- 22 Guerra S, Wright AL, Morgan WJ, Sherrill DL, Holberg CJ, Martinez FD. Persistence of asthma symptoms during adolescence: role of obesity and age at the onset of puberty. *Am J Respir Crit Care Med* 2004; **170**:78–85.
- 23 Musaad SM, Patterson T, Ericksen M *et al.* Comparison of anthropometric measures of obesity in childhood allergic asthma: central obesity is most relevant. *J Allergy Clin Immunol* 2009; **123**: 1321–7.
- 24 Hsueh K-C, Lin Y-J, Lin HC, Lin C-Y. Serum leptin and adiponectin levels correlate with severity of allergic rhinitis. *Pediatr Allergy Immunol* 2010; **21** (Part 2): e155–9.
- 25 Grodstein F, Clarkson TB, Manson JE. Understanding the divergent data on postmenopausal hormone therapy. *N Engl J Med* 2003; **348**:645–50.
- 26 Appleton SL, Adams RJ, Wilson DH, Taylor AW, Ruffin RE. North West Adelaide Health Study Team. Central obesity is associated with nonatopic but not atopic asthma in a representative population sample. *J Allergy Clin Immunol* 2006; **118**:1284–91.