

Childhood allergic rhinitis predicts asthma incidence and persistence to middle age: A longitudinal study

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Background: The association between allergic rhinitis and asthma is well documented, but the temporal sequence of this association has not been closely examined.

Objective: We sought to assess the associations between childhood allergic rhinitis and (1) asthma incidence from preadolescence to middle age and (2) asthma persistence to middle age.

Methods: Data were gathered from the 1968, 1974, and 2004 surveys of the Tasmanian Asthma Study. Cox regression was used to examine the association between childhood allergic rhinitis and asthma incidence in preadolescence, adolescence, and adult life. Binomial regression was used to examine the association between childhood allergic rhinitis and asthma beginning before the age of 7 years and persisting at age 44 years.

Results: Childhood allergic rhinitis was associated with a significant 2- to 7-fold increased risk of incident asthma in preadolescence, adolescence, or adult life. Childhood allergic rhinitis was associated with a 3-fold increased risk of childhood asthma persisting compared with remitting by middle age.

Conclusions: Childhood allergic rhinitis increased the likelihood of new-onset asthma after childhood and the likelihood of having persisting asthma from childhood into middle age.

Clinical implications: Asthma burden in later life might be reduced by more aggressive treatment of allergic rhinitis in early life. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Childhood allergic rhinitis, incident asthma, persisting asthma, effect modification

The prevalence of allergic rhinitis¹ is increasing, and its burden is substantial. It can begin at any age, and there is wide variation in prevalence. In a birth cohort from Arizona, Wright et al² found that 42% had physician-diagnosed allergic rhinitis by 6 years of age. Hurre et al,³ reporting on a Finnish birth cohort, found that the prevalence of allergic rhinitis was 17.5% at age 16 years and 26% at age 32 years. Data from the International Study of Asthma and Allergies in Childhood indicate a prevalence of self-reported allergic rhinitis ranging from 0.8% to 14.9% in 6- to 7-year-olds from different centers.⁴ The prevalence in all age groups in other studies has ranged from 3% to 19%,⁵ perhaps because of differences in definition or aeroallergen prevalence. Allergic rhinitis and asthma commonly occur in the same person.^{6,7} Asthma can be more severe in asthmatic subjects with allergic rhinitis compared with those without allergic rhinitis.⁸

Cross-sectional studies have shown an association between allergic rhinitis and asthma. Guerra et al⁹ and Leynaert et al¹⁰ each showed an association between allergic rhinitis and new asthma in atopic and nonatopic adults, independent of age, sex, smoking, and family history of asthma. Follow-up studies in adults have shown that allergic rhinitis might precede asthma.¹¹ However, there is limited information on childhood-onset allergic rhinitis and asthma developing in preadolescence, adolescence, or adult life or persisting from childhood to adult life. Such information would be valuable in understanding causal mechanisms.

We hypothesized that allergic rhinitis present before age 7 years (childhood allergic rhinitis) was associated

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Abbreviations used

ARR: Adjusted relative risk

TAS: Tasmanian Asthma Study

with incident asthma in later life stages. We analyzed data gathered over a 37-year period from the Tasmanian Asthma Study (TAS). We examined childhood allergic rhinitis and childhood asthma. We then examined childhood allergic rhinitis and incident asthma in preadolescence, adolescence, and adult life. We also examined childhood allergic rhinitis and asthma beginning before the age of 7 years and persisting to age 44 years.

METHODS

Study population and data collection

The TAS began in 1968 when a population birth cohort (n = 8583), then aged 7 years and attending school in Tasmania, was surveyed. The cohort comprised 98.9% of children born in Tasmania in 1961. A questionnaire completed by the parents detailed the child's history of asthma, hay fever, eczema, allergy, and urticaria. At a medical examination in 1968, FEV₁, forced vital capacity, and forced expiratory flow from 25% to 75% of the forced vital capacity were measured with a wedge-bellows spirometer (Vitalograph Limited, Buckinghamshire, United Kingdom). These measurements were recalculated as percent predicted values.¹²

Another survey was done in 1974, when the participants were aged 13 years. The parents of the 7383 children (86% of the original cohort) who could be traced completed another respiratory questionnaire in which data were gathered on the participants' "asthma ever" status, together with age at onset of asthma and history of allergic disorders.

A further survey was conducted in 2004, when 7312 (85.2%) of the participants from 1968 were traced to an address and sent a detailed respiratory questionnaire. Of these, 5729 (78.4%) completed the questionnaire. This questionnaire gathered data on history of "asthma ever," age at asthma onset, history of eczema and hay fever, smoking history, exposure to environmental tobacco smoke, and known allergies to grasses, dust, animals, food, and medicines.

Definitions

Allergic rhinitis. This was defined in the 1968 questionnaire by an affirmative answer to the following question: "Does he/she get attacks of 'hay fever' (that is, sneezing, running or blocked nose, sometimes with itchy eyes or nose)?" Allergic rhinitis was defined in the 2004 questionnaire by an affirmative answer to the following question: "Have you ever had hay fever (that is, sneezing, running or blocked nose when you do not have a cold or the flu)?" Allergic rhinitis was grouped as a 3-level variable: *childhood*, onset before age 7 years; *later onset*, onset after age 7 years; and *never*.

Asthma ever. Asthma by ages 7 or 13 years was defined by an affirmative answer in the 1968 or 1974 surveys to the following question: "Has your child ever suffered from attacks of asthma or wheezy breathing?" Asthma by age 44 years was defined by an affirmative answer in the 2004 survey to the following question: "Have you ever in your life suffered from attacks of asthma or wheezy breathing?"

Persisting and remitting asthma. Those with asthma ever by age 44 years and an attack within the last 2 years were classed as having

persisting asthma. Those with asthma ever by age 44 years and no attack for more than 2 years were classed as having remitting asthma. These cutoff points were chosen to be as consistent as possible with previously published definitions.¹³

Age at onset of asthma. This was self-reported in the 2004 survey. Participants' responses in the 2004 survey concerning "asthma ever" and age at asthma onset were compared with their parents' prospectively gathered responses to the same questions. Where there was disagreement, the parents' responses were taken to be correct.¹⁴

Serious lung infection. This was defined by an affirmative response in the 1968 survey to the following question: "Have you ever been told by a doctor that he/she had pneumonia or pleurisy?"

Population-attributable fraction. This was defined¹⁵ as "the fraction of all cases (exposed and unexposed) that would not have occurred if exposure had not occurred."

Covariate definitions

Impaired lung function at age 7 years. This was defined as an FEV₁ of less than 80% of predicted value.¹²

Infantile (baby) eczema, physician-diagnosed food or medicine allergy, and urticaria (hives). These were parent defined in 1968 without further prompting as to the meaning of the terms.

Flexural eczema. This was parent defined in 1968 as "eczema in the creases (bends) of the elbows, wrists or knees." Eczema by age 44 years was defined in the 2004 questionnaire by an affirmative response to the following question: "Have you ever had eczema or skin allergy?"

Eczema variable. This was developed from the eczema terms above and consisted of 3 levels: (1) infantile eczema, flexural eczema, or both by the age of 7 years; (2) eczema by age 44 years without a history of infantile or flexural eczema by age 7 years; and (3) never eczema.

Smoking. Smoking at age 44 years was a 5-level variable: (1) daily smoking, (2) at least weekly smoking, (3) less than weekly smoking, (4) former smoking, and (5) never smoking.

Passive smoking. This was defined as exposure to another person's tobacco smoke for at least 1 hour per day.

Socioeconomic status in 1968. This was classified by the occupation of the father of the participant and divided into 5 categories according to the Australian Standard Classification of Occupations.¹⁶

Socioeconomic status in 2004. This was classified by the occupation of the participant and divided into the same 5 categories as in 1968.

Analytic methods

The analysis was carried out using the first 5478 (75% response rate) completed questionnaires received. Categorical data were compared by using the Pearson χ^2 test. Asthma incidence after the age of 7 to 44 years was computed, dependent on childhood allergic rhinitis. The population-attributable fraction was calculated by using the Levin formula.¹⁷

Multivariable logistic regression examined the association between childhood allergic rhinitis and childhood-onset asthma. The model was adjusted for eczema, allergy to food or medicines, urticaria (all by the age of 7 years), impaired lung function at the age of 7 years, and socioeconomic status of the family in 1968.

A Cox regression was used to examine the association between childhood allergic rhinitis and asthma developing between the ages of 8 and 12 years (preadolescence), between 13 and 20 years (adolescence), and after 20 years (adult life). The results are presented as hazard ratios with 95% CIs and were estimated in a series of mutually adjusted models that included eczema, food or medicine allergy, and urticaria (all by age 7 years) and impaired lung function at age 7 years as covariates. The model that examined childhood allergic rhinitis

and adult-onset asthma was also adjusted for active and passive smoking and for socioeconomic status of the participant in 2004. A test of homogeneity across the different life stages was computed by using the Cochran Q statistic. Effect modification by other allergic and nonallergic early-life factors was examined.

Binomial regression with the log link function examined childhood allergic rhinitis and persistent asthma while adjusting for eczema, food or medicine allergy, and urticaria (all by age 7 years), impaired lung function at age 7 years, smoking, passive smoking, and socioeconomic status in 2004. The results are presented as adjusted relative risks (ARRs) with 95% CIs. A *P* value of .05 or less was taken to indicate statistical significance for all estimates. The analysis was performed with STATA statistical software, release 9.1 (StataCorp, College Station, Tex).¹⁸

RESULTS

Prevalence of allergic disorders

In the cohort at the age of 7 years (*n* = 8583), the prevalence of “asthma ever” was 16.3% (*n* = 1399). A response to the allergic rhinitis question was obtained for 96.4% (*n* = 8275). Of these, 12.8% (95% CI, 12.1% to 13.5%; *n* = 1061) had allergic rhinitis, which was significantly more common in boys (13.9% vs 11.7%, $\chi^2_1 = 8.7$, *P* = .003). Of this 1061, infantile or flexural eczema was reported by the parents in 27.1% (95% CI, 24.5% to 29.8%; *n* = 228), food or medicine allergy in 15.7% (95% CI, 13.6% to 17.9%; *n* = 167), and urticaria in 29.5% (95% CI, 26.8% to 32.2%; *n* = 313). Of those with allergic rhinitis, 2.5% (*n* = 26) had a history of all childhood allergic disorders.

Of the 5478 respondents in the 2004 survey, 53.9% (95% CI, 52.6% to 55.2%; *n* = 2903) reported allergic rhinitis, which was significantly more common in women (52.3% vs 47.7%, $\chi^2_1 = 39.2$, *P* < .001). Of this 2903, 24.5% (*n* = 711) had allergic rhinitis by the age of 7 years. There was no difference in allergic rhinitis prevalence between respondents and nonrespondents (*n* = 1532) in 2004 (13.0% vs 12.3%, respectively; difference = 0.7%; 95% CI, −1.2% to 2.6%; *P* = .46). The prevalence of allergic rhinitis in 1968 and in 2004 is shown in Fig 1.

Of the 5478 respondents, 28.5% (*n* = 1561) gave a history of “asthma ever.” When these were compared with the parents’ responses in 1968 and 1974, it was found that 10% of the cohort (*n* = 547) disagreed with the parents’ response. The adjusted prevalence of asthma ever by the age of 44 years was 38.5% (*n* = 2108). The distribution of allergic rhinitis phenotypes and asthma at different life stages is shown in Table I.

Childhood allergic rhinitis and childhood asthma

Of the 1061 participants in 1968 with allergic rhinitis, 41.7% (*n* = 442) had asthma by age 7 years. Of the 7214 participants in 1968 without allergic rhinitis, 12.9% (*n* = 932) had asthma by age 7 years. There were 25 participants with childhood asthma for whom no data were available on allergic rhinitis by age 7 years. Childhood allergic rhinitis was significantly associated with asthma by age 7 years (adjusted odds ratio, 4.16; 95% CI,

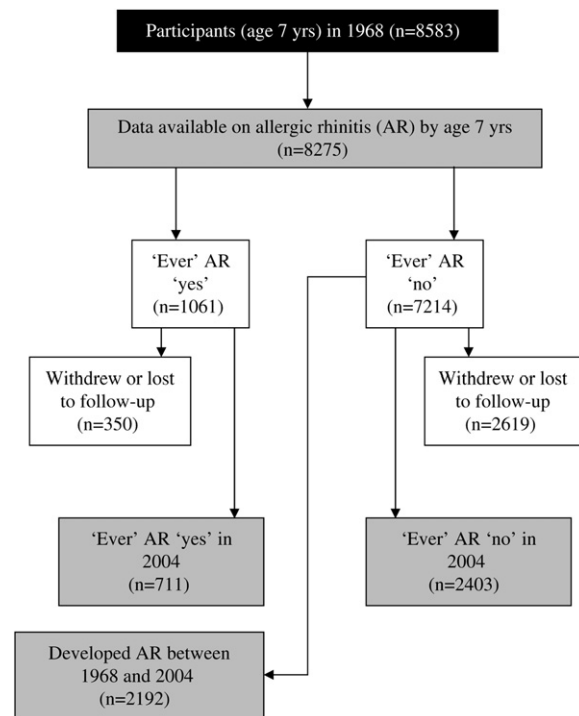


FIG 1. The prevalence of allergic rhinitis in 1968 and 2004.

3.57-4.86). This estimate is from a logistic model adjusted for eczema, urticaria, allergy to food or medicine, impaired lung function at 7 years of age, and socioeconomic status of the family in 1968. There was no effect modification by the other childhood allergic disorders or by maternal or paternal asthma; maternal or paternal smoking; serious lung infection before the age of 7 years; exclusive breast-feeding for the first 3 months of life; immunization with diphtheria, pertussis, and tetanus vaccines; or having at least 1 older sibling (data not shown).

Childhood allergic rhinitis and asthma incidence

Asthma incidence after age 7 years to the age of 44 years, dependent on allergic rhinitis by 7 years of age, is shown in Table II. Asthma incidence after age 7 years was more than 3 times higher in those with childhood allergic rhinitis compared with those never having allergic rhinitis, with no significant difference by sex. The rate ratio for female compared with male subjects was 1.25 (95% CI, 0.84-1.88). Consequently, no adjustment was made for sex in the analyses.

The risk of asthma developing at different stages of life in terms of childhood allergic rhinitis is shown in Table III. The estimates presented are from mutually adjusted Cox models, which included eczema, allergy to food or medicine, urticaria, and impaired lung function at the age of 7 years. Incident asthma in adult life was additionally adjusted for active and passive smoking and for socioeconomic status at age 44 years. Childhood allergic rhinitis was associated with a significantly increased risk of asthma in preadolescence, adolescence, and adult life.

TABLE I. Allergic rhinitis phenotypes and the corresponding number with asthma in the different age at onset groups

Cohort in 2004 (n = 5478)	Age at onset of asthma "ever"					
	Childhood (n = 1194)	Preadolescence (n = 156)	Adolescence (n = 124)	Adult life (n = 607)	Never (n = 3370)	Missing (n = 27)
Allergic rhinitis in 2004						
Childhood onset (n = 711)	351	28	16	55	259	2
Later onset (n = 2192)	462	99	84	381	1154	12
Never (n = 2403)	330	21	20	159	1864	9
Missing (n = 172)	51	8	4	12	93	4

TABLE II. Childhood allergic rhinitis and asthma incidence from age 8 to age 44 years

	Person-years at risk	Asthma onset after age 7 y (% (n))	Incidence per 1000 person-years at risk (95% CI)	Rate ratio (95% CI)	Population-attributable fraction
Allergic rhinitis					
Childhood allergic rhinitis (n = 711)	13,755	33.1 (99)	7.20 (5.91-8.76)	3.16 (2.46-4.05)	0.226
Never allergic rhinitis (n = 2403)	87,917	66.9 (200)	2.27 (1.98-2.61)	1.00	
Total*	101,672	100.0 (299)	2.94 (2.61-3.27)		

*In the cohort (n = 5478) there were 2192 subjects with allergic rhinitis that began after age 7 years and 172 with no data on allergic rhinitis. Of those with asthma onset after age 7 years, there were 564 with allergic rhinitis that began after age 7 years.

The increased risk became smaller as the age at asthma onset increased. Because the test for homogeneity was significant, a pooled estimate of risk across the lifespan was not presented.

Effect modification of these associations by the other allergic and nonallergic early-life factors was examined. In adult life incident asthma risk associated with childhood allergic rhinitis was increased by 90% relative to that conferred by childhood allergic rhinitis alone if the participant had been exclusively breast-fed for the first 3 months of life (Table IV). However, exclusive breast-feeding did not modify this association in preadolescence or adolescence. Exclusive breast-feeding was adjusted for socioeconomic status in 2004 in these models. The analysis was repeated while omitting the small number of participants with childhood allergic rhinitis who were exclusively breast-fed and whose mothers had asthma, and the result did not change appreciably (data not shown).

The effect of childhood allergic rhinitis on incident asthma risk in any later-life stage was not modified by any other childhood allergic disorder. In addition, the effect was not modified by maternal or paternal asthma; maternal or paternal smoking; serious lung infection before age 7 years; immunization with diphtheria, pertussis, and tetanus vaccines; or having at least 1 older sibling (data not shown).

Childhood allergic rhinitis and persisting asthma

Childhood allergic rhinitis was associated with a significantly increased risk (ARR, 3.00; 95% CI, 1.98-4.56) of having childhood asthma persist to age 44 years. There was no association between childhood allergic rhinitis and later-onset asthma persisting to age 44 years (ARR, 1.04;

95% CI, 0.79-1.36). The analysis was repeated with the definition of persisting asthma changed to "asthma ever by age 44 years and an attack within the last 12 months," and the result did not change appreciably (data not shown). For all of these associations, the comparison groups were "never" allergic rhinitis and "remitted asthma by the age of 44 years."

DISCUSSION

Childhood allergic rhinitis and childhood asthma were strongly associated, independent of other childhood allergic disorders, impaired lung function at the age of 7 years, and socioeconomic status. Furthermore, childhood allergic rhinitis was associated with a 7-fold increased risk of incident asthma in preadolescence, a 4-fold increased risk in adolescence, and a 2-fold increased risk in adult life, independent of those same covariates. Incident asthma risk in adult life was also independent of active and passive smoking.

The nature of the relationship between allergic rhinitis and asthma has been controversial. Although coexistence of these diseases is common, either one can occur first.¹⁹ Upper and lower airways form an anatomic continuum with structural and functional differences, but the concept of "one airway, one disease"²⁰ has appeal. An accepted explanation of the relationship is that the 2 diseases are different occurrences on a common atopic pathway. However, there is evidence that the association remains significant, even when the subject is nonatopic.^{9,10} Various alternative mechanisms have been suggested as linking allergic rhinitis and asthma. Aspiration of pharyngeal contents has been shown in deep sleep.²¹

TABLE III. Adjusted hazard ratios and 95% CIs for asthma in different life stages after the age of 7 years, dependent on childhood allergic rhinitis

	Age (y) at asthma onset*			Homogeneity test, <i>P</i> value
	>7-12, preadolescence (n = 156)	>12-20, adolescence (n = 124)	>20-44,† adult life (n = 607)	
	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Childhood allergic rhinitis vs Never allergic rhinitis	7.12 (3.97-12.75), <i>P</i> < .001	4.34 (2.23-8.46), <i>P</i> < .001	2.19 (1.59-3.01), <i>P</i> < .001	<.001

HR, Hazard ratio.

*There were 27 persons of the 2108 with a history of “asthma ever” for whom no age at onset of asthma could be determined and 1194 with asthma onset by age 7 years.

†Additionally adjusted for socioeconomic status, current smoking, and passive smoking at age 44 years.

TABLE IV. Modification of the association between childhood allergic rhinitis and incident asthma risk in adult life by exclusive breast-feeding for the first 3 months of life*

Exposure	Effect modifier	HR (95% CI)	No. with adult incident asthma†	Interaction <i>P</i> value
Allergic rhinitis phenotype	Exclusive breast-feeding			
Childhood	Yes	2.91 (1.92-4.43)	30‡	.01
Childhood	No	1.54 (0.98-2.41)	25	
Never	Yes	0.84 (0.60-1.17)	55	
Never	No	1.00	103	

HR, Hazard ratio.

*The result is taken from the mutually adjusted model described in the text, with additional adjustment for socioeconomic status. Exclusive breast-feeding and its interaction term with childhood allergic rhinitis were added to the model.

†Of the 607 participants with incident adult asthma, 18 had missing data on childhood allergic rhinitis or breast-feeding status.

‡Of these 30, there were 5 who had a mother with asthma.

Leukotrienes and inflammatory cells are active in both upper and lower airways and are present in nasal secretions of subjects with allergic rhinitis.^{22,23} Inhalation of these agents into the lower airway or their systemic absorption might initiate a bronchial inflammatory response that strengthens with continued exposure, leading to clinical asthma. Other suggested links include a nasobronchial reflex and mouth breathing. A nasobronchial reflex was postulated after the observations that the application of cold air to the nasal mucosa of healthy subjects²⁴ and histamine²⁵ or antigenic material²⁶ to the nasal mucosa of subjects with allergic rhinitis and asthma provoked an immediate and substantial increase in airway resistance. A study of subjects with perennial asthma²⁷ demonstrated that mouth breathing during exercise led to a worsening of airway resistance that was abolished by exclusive nose breathing. Mouth breathing in subjects with allergic rhinitis might allow entry of antigenic material to the bronchial tree.²⁸ It is quite likely that more than 1 of these mechanisms might operate in patients with allergic rhinitis/asthma.

Guerra et al⁹ showed an independent association between allergic rhinitis and incident asthma in a nested case-control study and suggested the possibility of a direct causal link. Our results showed that childhood allergic

rhinitis predicted incident asthma in preadolescence, adolescence, and adult life, which is consistent with the events being sequential on a common biologic pathway. However, this temporal association is also consistent with the possibility that childhood allergic rhinitis and later-life incident asthma might be causally linked. Of the 9 criteria discussed by Hill,²⁹ temporality is “a sine qua non for causality.”³⁰ Our data from 1968 did not include a measure of allergic rhinitis severity, and we could not examine any possible dose-response effect. This would have been helpful in assessing a possible causal association. Our results, like those of Guerra et al,⁹ leave unanswered the question of a causal link between allergic rhinitis and asthma. Well-designed intervention studies are needed to examine asthma-free subjects with allergic rhinitis for subsequent asthma risk.

It is widely held that breast-feeding protects against allergic disease.³¹ However, studies examining breast-feeding and asthma have given conflicting results. Some of the conflicting results might be related to breast-feeding behavior being changed by early signs of atopy in the infant.³² A protective effect from breast-feeding (either any or exclusive breast-feeding and breast-feeding of varying duration) on asthma risk was found in a systematic review of 56 studies.³³ A prospective birth cohort study³⁴ found a

protective effect from exclusive breast-feeding for at least 4 months on asthma risk to age 6 years. On the other hand, the Tucson Children's Respiratory Study³⁵ found that exclusive breast-feeding was protective against recurrent wheeze in early life but was associated with an increased risk of asthma and recurrent wheeze from age 6 to 13 years, although only in atopic children of asthmatic mothers. However, the numbers in these subgroups were small. A New Zealand birth cohort study³⁶ found that breast-feeding (not always exclusive) for at least 4 weeks might have increased current asthma and atopy risk from age 9 years to early adulthood.

Our study found that incident asthma risk in adult life from childhood allergic rhinitis was increased if the affected child had been exclusively breast-fed to 3 months of age. If childhood allergic rhinitis in our study indicated atopy, this result would have similarities to the Tucson study.³⁵ However, our study did not include the objective assessment of childhood atopy, and we cannot be confident that the subjects with adult-onset asthma were atopic as children. Another limitation is that infant feeding was recalled when the participant was aged 7 years. Effect modification by exclusive breast-feeding was one of many interactions examined. It is possible that the result was due simply to the play of chance with multiple hypotheses being tested. Nonetheless, the observed interaction adds to the body of knowledge concerning the possible long-term effects of breast-feeding.

Allergic rhinitis is a highly prevalent disorder. By age 7 years, 12.8% of our cohort had allergic rhinitis, with a significant male preponderance. These data are almost identical to those reported in another large Australian study.³⁷ By middle age, nearly 54% of our cohort reported allergic rhinitis, with reversal of the childhood male preponderance, which is comparable with the 45.8% prevalence reported by Settiple et al.¹¹ The population-attributable risk of incident asthma from childhood allergic rhinitis was substantial. If the association was truly causal, this suggests the potential importance of early interventions in lessening the burden of asthma in later life.

The major strengths of our study are the longitudinal nature of the data collected from a large population-based cohort over a 37-year period, modest loss to follow-up, measurement of lung function in childhood, and the availability of parent-reported data on asthma history and age at asthma onset. The prevalence of childhood allergic rhinitis in the responders and nonresponders to the 2004 survey did not differ, indicating that response bias related to this was unlikely.

Our study has limitations. Childhood asthma defined by the parent will include some nonasthma wheeze. Such an error could be important if it was differentially related to childhood allergic rhinitis, and we were unable to assess this. Despite this limitation, we believe that parent-defined childhood asthma is acceptable. Others have found that this definition compares well with one including bronchial hyperresponsiveness,^{38,39} and a looser definition will shift estimates toward the null.⁴⁰ The use of physician-diagnosed asthma can result in underdiagnosis.^{41,42} In any case, the

asthma question in the 1968 TAS questionnaire was a valid measure of asthma in the previous 12 months when compared with a respiratory physician's diagnosis.³⁹

In conclusion, our study is novel in that it provides evidence for an association between childhood allergic rhinitis and incident asthma risk at different life stages from preadolescence to middle age. The finding of a temporal relationship between childhood allergic rhinitis and later-life incident asthma raises the possibility that the association might be causal. Intervention studies in children with only allergic rhinitis are required to further examine this possibility.

The Archives Office of Tasmania provided archived data from the 1968 and 1974 TAS questionnaires.

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