

Does an allergy skin test on school-children predict respiratory symptoms in adulthood?

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Summary

Background It is interesting from the correct point of preventive health care whether allergy skin tests at entry have the positive relationship with common respiratory symptoms such as persistent cough, persistent phlegm and wheeze with colds at end point in longitudinal studies.

Objective The purpose of this study is to investigate this relationship in subjects followed from when they were school-children until they were young adults.

Methods Young adults aged 18–31 years who had participated in an allergy skin test and a health survey for common respiratory symptoms during primary and junior high school were asked about their respiratory symptoms at the end-point in the follow-up study. Three cohort groups were employed in the follow-up study.

Results According to a multiple logistic analysis with adjustments made for sex, symptoms at entry in childhood, and age and smoking habits at the end-point, young adults with a positive skin test to an extract of house dust as school-children showed a higher prevalence of wheeze with colds compared with those with a negative skin test. However, this relationship was not found for persistent cough or persistent phlegm, indeed, the latter symptom was significantly associated with negative skin tests in one cohort group.

Conclusion The respective symptoms at entry in childhood were also predictors of their occurrence in young adults. The results show that the common respiratory symptoms such as persistent phlegm and wheeze with colds in childhood are related to those in young adults rather than is an allergy skin test to an extract of house dust in childhood.

Keywords: allergy skin tests, childhood, extract of house dust, follow-up studies, persistent cough, persistent phlegm, wheeze with colds, young adults

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Introduction

Current data suggest that the prevalence of wheeze in children is increasing [1,2]. Apart from wheeze, cough and phlegm are also common as asthma-related respiratory symptoms in childhood. Studies have shown that

these childhood symptoms can be the initial and sometimes the only manifestation of asthma [3–5]. Furthermore, longitudinal studies of asthma-related symptoms reveal that children with these symptoms are more likely not to be free of these during adolescence [6–8]. As adolescents with these symptoms tend to show impaired lung function, certain indicators to predict this risk during childhood are desirable from the standing point of preventive health care. For this purpose an allergy skin test has been widely used for screening atopic

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characteristics that predispose to asthma-related respiratory symptoms [5,9,10]. In addition, it has been demonstrated that skin reactivity to an extract of house dust of common aeroallergens is also associated with air way hyperresponsiveness [11]. The present authors have reported that an allergy skin test to an extract of house dusts is a suitable procedure for monitoring school-children with asthma-related respiratory symptoms in Japanese rural districts [10,12–14]. This time in a follow-up study on these school-children as young adults the predictability of a skin test for common respiratory symptoms such as wheeze and persistent cough and phlegm was investigated.

Materials and methods

The study was carried out in Awara-machi (population 15 000), a rural district of Japan. The geographical details of this town and its surroundings have been given in a previous report [12,14]. Most of the area is composed of flat paddy fields, and there are no major sources of air pollution except for two heavy-oil-fired steam power stations located in the next town. The first one (350 MW) was commissioned in 1973 and the second (250 MW) in 1978. These induced a small increase in concentrations of air pollutants. However, due to the promotion of anti-air pollution measures such as usage of crude oil of lower sulphur concentration and reduction of factory wastes through chimneys in the power stations since 1974, the concentrations of sulphur dioxide (SO₂) and nitrogen dioxide (NO₂) but not suspended particulates (SP) were decreased. Based on air pollution parameters the area of the present study is still the least polluted in Japan.

A health survey of pupils attending primary and junior high school in Awara-machi had been conducted every summer since 1972 until 1990. The survey consisted of an inquiry on respiratory symptoms standardized by the BMRC (British Medical Research Council's Committee on Research into Chronic Bronchitis) [15], a skin-prick test [16] using an extract of house dust (Torii) in which sensitizing properties have been already demonstrated to be attributed to the presence of mite [17]. The questionnaires for the inquiry were distributed in advance and filled out by parents of the school-children. On the day of the survey each child was interviewed to confirm the accuracy of the contents and received the allergy skin test, in which a weal greater than 5 mm was considered to be positive following the criteria of the Research Committee for Prick Test in Japan. School-children were asked about their respiratory symptoms during the last year. In cases when the answer 'yes' was given to question 1a (usually cough in the morning in winter) and/or

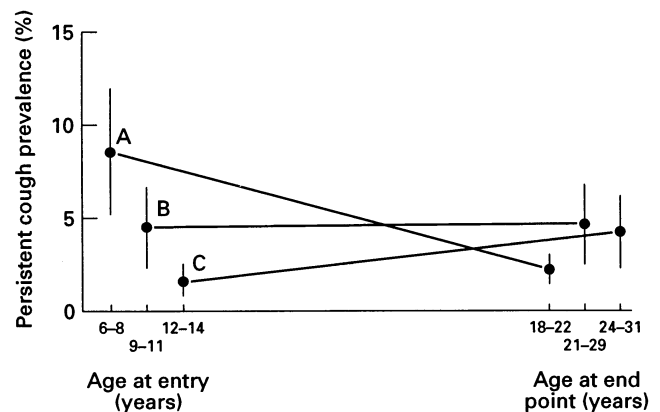


Fig. 1. Prevalence of persistent cough in childhood and adulthood for three cohort groups.

question 3a (usually cough during the day or at night in winter) of the questionnaire, the symptom was designated as persistent cough; when the answer 'yes' was given to question 6a (usually phlegm in the morning in winter) and/or question 8a (usually phlegm during the day or at night in winter), it was designated as persistent phlegm; and when the answer 'yes' was given to question 15a (wheeze triggered by the common cold), it was designated as wheeze with colds.

The survey in young adults was conducted using the BMRC questionnaire with self-administered methods in March 1991. Of the 5334 subjects who had participated in the survey during school, 2155 (40.4%) still lived in the same town and valid replies were obtained from 1763 subjects (a response rate of 81.8%). Although the designation of respiratory symptoms was performed in the same fashion as the survey in school-children inquired about their symptoms for the past 3 years. For the

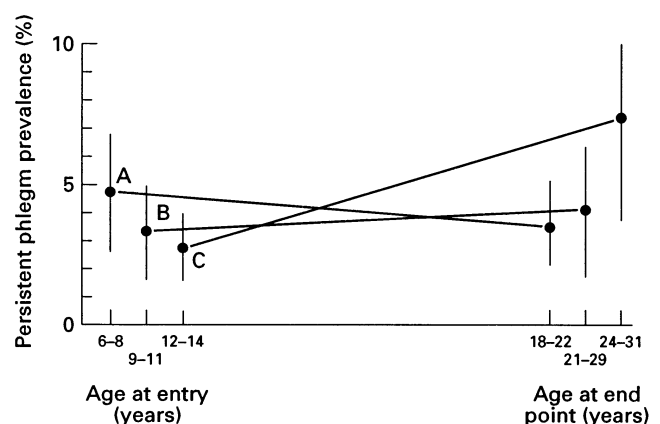


Fig. 2. Prevalence of persistent phlegm in childhood and adulthood for three cohort groups.

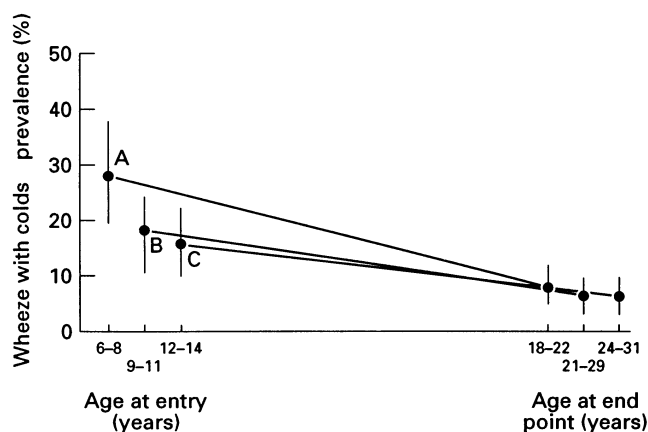


Fig. 3. Prevalence of wheeze with colds in childhood and adulthood for three cohort groups.

present study young adults who had received a 3 year survey during 6–8 years of age (cohort A: aged 18–22 years at end-point) and 9–11 years of age (cohort B: aged 21–29 at end-point) in primary school, and 12–14 years of age (cohort C: aged 24–31 years at end-point) in

junior high school were selected, respectively. School-children who had the respiratory symptoms in the present study at least once during the respective 3 years mentioned above were incorporated into the 'yes' group and others into the 'no' group. This classification was also taken for the allergy skin test: that is when having a positive reaction at least once during the respective 3 years, school-children were incorporated into the positive skin-test group and others into the negative skin-test group. The follow-up study analysis was performed for each of the three cohort groups between entry of school-children and the end-point as young adults.

For the adjusted relative risk ratio by multiple logistic analysis SAS; the analysis of maximum-likelihood estimates method was used.

Results

Prevalence of common respiratory symptoms in school-children and young adults

The prevalences of persistent cough, persistent phlegm and wheeze with colds in schoolchildren and young

Table 1. Risk of persistent cough at end-point for respective cohorts

Categories	No of total	Prevalence (%)	Crude relative risk	95% Confidence interval	Statistical significance
<i>Sex (Male/Female)</i>					
Cohort A	241/257	2.9/1.9	1.5	0.5–4.8	NS
Cohort B	395/324	7.1/1.9	3.7	1.6–8.9	$P < 0.001$
Cohort C	367/212	6.8/0.5	13.6	1.9–95.0	$P < 0.001$
<i>Persistent cough at entry (Yes/No)</i>					
Cohort A	43/455	2.3/2.4	1.0	0.1–7.5	NS
Cohort B	32/687	9.4/4.5	2.1	0.6–6.8	NS
Cohort C	8/571	12.5/4.5	2.8	0.4–21.0	NS
<i>Allergy skin test at entry (Positive/Negative)</i>					
Cohort A	144/354	2.1/2.5	0.8	0.2–3.1	NS
Cohort B	211/508	2.8/5.5	0.5	0.2–1.2	NS
Cohort C	176/405	3.4/5.0	0.7	0.3–1.7	NS
<i>Years of age at end-point</i>					
Cohort A (≥ 20 / <20)	186/312	1.6/2.9	0.6	0.1–2.0	NS
Cohort B (≥ 25 / <25)	364/355	6.0/3.4	1.8	0.9–3.6	$P < 0.10$
Cohort C (≥ 28 / <28)	268/311	3.4/5.5	0.6	0.3–1.4	NS
<i>Smoking habits and end-point (Smoker/Non-smoker)</i>					
Cohort A	155/343	3.9/1.7	2.3	0.6–6.6	NS
Cohort B	310/409	8.1/2.2	3.7	2.1–11.0	$P < 0.001$
Cohort C	290/289	6.9/2.1	3.3	1.3–8.1	$P < 0.01$

Table 2. Risk of persistent phlegm at end-point for respective cohorts

Categories	No of total	Prevalence (%)	Crude relative risk	95% Confidence interval	Statistical significance
<i>Sex (Male/Female)</i>					
Cohort A	241/257	5.8/1.6	3.6	1.2–10.9	$P < 0.05$
Cohort B	395/324	6.8/1.2	5.7	2.0–16.4	$P < 0.001$
Cohort C	367/212	10.1/2.4	4.2	1.7–10.6	$P < 0.01$
<i>Persistent phlegm at entry (Yes/No)</i>					
Cohort A	24/474	25.0/2.5	10.0	3.7–26.7	$P < 0.0001$
Cohort B	24/695	12.5/4.0	3.1	0.9–10.1	$P < 0.1$
Cohort C	28/551	28.6/6.2	4.6	2.1–10.0	$P < 0.0001$
<i>Allergy skin test at entry (Positive/Negative)</i>					
Cohort A	144/354	3.4/4.2	0.8	0.3–2.2	NS
Cohort B	211/508	3.3/4.7	0.7	0.3–1.6	NS
Cohort C	176/405	4.0/8.9	0.5	0.2–1.0	NS
<i>Years of age at end-point</i>					
Cohort A (≥ 20 / <20)	186/312	2.3/4.5	0.5	0.2–1.5	NS
Cohort B (≥ 25 / <25)	364/355	5.2/3.4	1.6	0.7–3.1	NS
Cohort C (≥ 28 / <28)	268/311	9.7/5.1	1.9	1.0–3.6	$P < 0.05$
<i>Smoking habits and end-point (Smoker/Non-smoker)</i>					
Cohort A	155/343	7.1/2.0	3.6	1.4–9.2	$P < 0.01$
Cohort B	310/409	7.1/2.2	3.2	1.5–7.0	$P < 0.01$
Cohort C	290/289	10.7/3.8	2.8	1.4–5.6	$P < 0.001$

adults are illustrated in Figs 1, 2 and 3, respectively. For school-children all three symptoms show a decline in prevalence with advancing age. The prevalence is higher for wheeze with colds compared with persistent cough and lowest for persistent phlegm in each cohort.

For young adults persistent phlegm shows an increase in prevalence with advancing age. The prevalence of wheeze with colds is still higher compared with the other two symptoms. For the changes in prevalence between school-children and young adults the prevalence of wheeze with colds shows a substantial decrease in the three cohort groups. As for persistent phlegm, a substantial increase in the oldest cohort group (cohort C) was shown.

Prevalence risk of common respiratory symptoms by various categories in young adults

Unadjusted relative risk ratios of various categories for persistent cough, persistent phlegm and wheeze with colds in young adults are shown in Tables 1, 2 and 3, respectively. With regard to persistent cough at end-point, the significant relative risk ratio of sex was

observed for cohort A and cohort B. In addition, the significant relative risk ratio of smoking habits at end point was evident for cohort B and cohort C and years of age at end point for cohort B (Table 1). With regard to persistent phlegm at end-point, the significant relative risk ratios of sex, persistent phlegm at entry and smoking habit at end-point were observed for the all three cohort groups. In addition, the significant relative risk ratio of age at end point was evident for cohort C (Table 2). With regard to wheeze with colds at end point, the significant relative risks ratio of wheeze with colds at entry was observed for the three cohort groups. In addition, the significant relative risk ratio of positive allergy skin test at entry was evident for cohort A and cohort B, and smoking habits at end-point for cohort A (Table 3). In the present case, the positive predictive value, proportion of young adults with wheeze with colds to those who had the same symptom in school-children, was 11.1% (16/144) for cohort A, 11.4% (24/211) for cohort B and 8.5% (15/176) for cohort C. For the negative predictive value, the proportion of young adults without wheeze with colds to those who didn't have the same symptom in school-children was 93.8% (332/354) for cohort A,

Table 3. Risk of wheeze with colds at end-point for respective cohorts

Categories	No of total	Prevalence (%)	Crude relative risk	95% Confidence interval	Statistical significance
<i>Sex (Male/Female)</i>					
Cohort A	241/257	8.3/7.0	1.2	0.6–2.2	NS
Cohort B	395/324	6.6/6.8	1.0	0.6–1.7	NS
Cohort C	367/212	6.8/6.6	1.0	0.5–2.0	NS
<i>Wheeze with cold at entry (Yes/No)</i>					
Cohort A	143/355	11.9/5.9	2.0	1.1–3.8	$P < 0.05$
Cohort B	134/585	15.7/4.6	3.4	1.9–6.0	$P < 0.0001$
Cohort C	96/483	14.4/5.2	2.8	1.5–5.4	$P < 0.0001$
<i>Allergy skin test at entry (Positive/Negative)</i>					
Cohort A	144/354	11.1/6.2	1.8	0.9–3.4	$P < 0.10$
Cohort B	211/508	11.4/4.7	2.4	1.2–4.6	$P < 0.01$
Cohort C	176/405	8.5/6.0	1.4	0.7–2.7	NS
<i>Years of age at end-point</i>					
Cohort A (≥ 20 / <20)	186/312	8.1/7.4	1.1	0.6–2.1	NS
Cohort B (≥ 25 / <25)	364/355	6.0/7.3	0.8	0.5–1.5	NS
Cohort C (≥ 28 / <28)	268/311	7.5/6.1	1.2	0.7–2.3	NS
<i>Smoking habits at end-point (Smoker/Non-smoker)</i>					
Cohort A	155/343	11.0/6.1	1.8	1.0–3.2	$P < 0.10$
Cohort B	310/409	8.1/5.6	1.4	0.8–2.5	NS
Cohort C	290/289	7.2/6.2	1.2	0.6–2.2	NS

95.2% (484/508) for cohort B and 94.0% (379/403) for cohort C. As both positive and negative predictive values were almost equal in the three cohort groups, the repeatability was thought to be acceptable.

Adjusted relative risk ratios of the allergy skin test at entry for respiratory symptoms at end-point in young adults

For each of the three symptoms, adjusted relative risk ratios of the allergy skin test at entry in taking into

Table 4. Adjusted relative risk ratio of allergy skin test in taking into account other categories*

Category	Cohort	Adjusted relative risk ratio for each respiratory symptom at end-point	95% Confidence interval	Statistical significance
Allergy skin test at entry (Positive/negative)	Cohort A	Persistent cough	0.8 0.2–3.3	NS
		Persistent phlegm	0.9 0.3–3.1	NS
		Wheeze with colds	1.7 0.9–3.4	NS
	Cohort B	Persistent cough	0.5 0.2–1.3	NS
		Persistent phlegm	0.7 0.3–1.7	NS
		Wheeze with colds	2.2 1.2–4.1	$P < 0.05$
	Cohort C	Persistent cough	0.5 0.2–1.4	NS
		Persistent phlegm	0.4 0.2–0.9	$P < 0.05$
		Wheeze with colds	1.4 0.7–2.7	NS

* Adjusted for sex (male/female), same respiratory symptom at entry (yes/no), age at end-point (n+1/n) and smoking habits at end-point (smoker/non-smoker).

Table 5. Adjusted relative risk ratio of persistent phlegm at entry to survey taking into account other categories*

Category	Cohort	Adjusted relative risk ratio for persistent phlegm at end-point	95% Confidence interval	Statistical significance
Persistent phlegm at entry (Yes/no)	Cohort A	15.1	4.9–49.4	$P < 0.001$
	Cohort B	3.4	0.9–12.8	$P < 0.01$
	Cohort C	7.3	2.7–19.6	$P < 0.001$

* Adjusted for sex (male/female), allergy skin test at entry (positive/negative), age at end-point ($n + 1/n$) and smoking habits at end-point (smoker/non-smoker).

account sex, respiratory symptoms at entry, and age and smoking habit at end-point are shown in Table 4 for the respective cohort groups. For all three cohort groups, adjusted relative risk ratios were more than 1.0 for wheeze with colds though statistical significance was found in only cohort B. On the other hand the relative risk ratios were less than 1.0 for persistent cough and persistent phlegm for all three cohort groups. Those were not statistically significant except for that of persistent phlegm for cohort C.

Adjusted relative risk ratios of respiratory symptoms at entry for the same symptoms in young adults

In common with the allergy skin test, adjusted relative risk ratios of respiratory symptoms at entry were obtained taking into account sex, allergy skin test at entry, and age and smoking habits at end-point. In Table 5, relative risk ratios of persistent phlegm at entry were all demonstrated to be statistically significant for all the three cohort groups. This was also the same for wheeze with colds at entry as shown in Table 6. On the other hand persistent cough at entry didn't show any significant adjusted relative risk ratio for the respective cohort groups (results not shown).

Discussion

This study focused on the prognosis of common respiratory symptoms in school-children. It is well known from follow-up that a representative obstructive respiratory disease such as asthma has many childhood indicators predicting prognosis [1,2]. However, the long-term prognosis of common respiratory symptoms in school-children such as persistent cough, persistent phlegm and wheeze with colds is not fully known. Since these symptoms also consist of those for asthma the prevalences are much higher than that of asthma as actually confirmed in the present study, too. On the other hand, it has been already demonstrated in our previous studies that persistent cough, persistent phlegm and wheeze with colds are related to the results of the allergy skin test: school-children with positive skin tests to an extract of house dust show a higher prevalence of these respiratory symptoms compared with those with a negative skin test [9,12,13]. Furthermore, positive responders to the skin test showed a higher serum immunoglobulin E (IgE) level compared with negative responders. With regard to environmental factors that also influence the prevalence of respiratory symptoms, the subject district belongs to a low-grade air pollution area where the

Table 6. Adjusted relative risk ratio of wheeze with colds at end-point taking into account other categories*

Category	Cohort	Adjusted relative risk ratio for persistent phlegm at end-point	95% Confidence interval	Statistical significance
Wheeze in cold at entry (Yes/no)	Cohort A	2.0	1.0–4.0	$P < 0.05$
	Cohort B	3.2	1.7–6.0	$P < 0.001$
	Cohort C	2.9	1.4–6.0	$P < 0.01$

* Adjusted for sex (male/female), allergy skin test at entry (positive/negative), age at end-point ($n + 1/n$) and smoking habits at end-point (smoker/non-smoker).

concentrations of three main pollutants, that is SO₂, NO₂ and SP, were lower than the respective values recommended by the national environmental guideline. These air pollutant levels measured in the present study, in general, have not been demonstrated to show any relationship with the prevalence of respiratory illness [18–20]. Although school-children with a positive skin test to an extract of house dust showed a tentative increase in the prevalence of the respiratory symptoms, especially wheeze with colds, after the commencement of the oil-fired steam power stations [14] this increase has disappeared since the introduction of anti-air-pollution measures mainly aimed at reducing sulphur dioxide exhaust. In the present study school-children with a positive skin reaction showed a higher prevalence of wheeze with colds as young adults compared with those with a negative skin reaction. It has been already demonstrated that skin reactivity to allergens is associated with the development of asthmatic respiratory symptoms [21–23]. However, this was not the case for persistent cough and phlegm. The common respiratory symptoms adopted at the end-point in the present study are not necessarily thought to be asthmatic symptoms. In actual fact of the three respiratory symptoms, Rijcken *et al.* [24] recommended only wheeze as the one related to asthma for an epidemiological study. In addition, although chronic dry cough was also included in that category, chronic phlegm was not. Tollerud *et al.* [7] have pointed out that the development of wheezing syndromes except for typical asthma is no more frequent among a positive skin test group of entry age 21–80 years than among the negative skin test group. In an 8-year follow-up study they could not find any significant differences in the development of cough and phlegm excluding typical asthma and other wheezing symptoms between positive and negative skin test groups. Although four common aeroallergens including house dust, ragweed, mixed trees and mixed grasses were used for the prick test, the allergic skin reactivity failed to distinguish those respiratory symptoms which developed in middle-aged and older men apart from typical asthma. With regard to cough in children Spelman [25] reported that many children with chronic recurrent cough are responsive to asthma therapy. Although pollen and animal allergens have recently been given attention [26] the extract of house dust was the most common air-borne allergen in the subject districts [9]. The present authors also confirmed that persistent cough and phlegm in school-children are related to allergic skin reactivity in an extract of house dust [12–14]. These results indicate that chronic common respiratory symptoms such as wheeze with colds, persistent cough and persistent phlegm in children are more atopy-related than those in adults. In fact, environmental

factors including infectious agents, smoking and so on become more related to respiratory symptoms in adulthood. Therefore, it is reasonable that the skin test finding is a predictor for only wheeze with colds in young adults. With regard to persistent phlegm in young adults school-children with a negative skin test showed a higher prevalence than positive school-children in one follow-up group. The relationship was also observed by multiple factor analysis taking into account both male–female differences in respiratory problems [27] and additive effects of smoking and skin test reactivity [28] demonstrated already. So far the reason why such an opposite relationship was observed is open to question. When comparing common respiratory symptoms to skin test findings with an extract of house dust in school-children as a predictor of those respiratory symptoms in young adult, persistent phlegm and wheeze with colds are better than the skin test. Based on a longitudinal study Kelly *et al.* [6] have reported that a considerable proportion of adolescents who had wheezed in childhood were not free of symptoms. In addition antecedent pneumonia, bronchiolitis, hay fever and sinusitis which are accompanied by persistent phlegm have also been pointed out as childhood predictors of asthma [29]. Actually, school-children with wheeze with colds showed a higher prevalence of the symptom in young adults compared with those without the symptom in childhood. Therefore, from a practical point of view self-administrated questionnaires on respiratory symptoms in childhood are more acceptable and a better cost-performance procedure as adulthood predictors of respiratory symptoms. For predicting the symptoms in adulthood, however, the positive predictive value is still not good enough for usage in screening. Although the allergy skin test has the same limitation for screening school-children with atopy, the test is also important because their development or spirometric lung function may be impaired [10] and the test is a procedure easily available which can predict the prevalence of wheeze, one of the asthmatic symptoms in young adults which seems to indicate the evolution of ventilatory impairment [30] and is a disadvantage for occupational activities [31].

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References

- 1 Robertson CF, Heycock E, Bishop J *et al.* Prevalence of

- asthma in Melbourne schoolchildren: changes over 26 years. *BMJ* 1991; 1116–8.
- 2 Higgins MW, Thom T. Incidence, prevalence, and mortality: Intra- and intercountry differences. In: Hensley MH, Saunders NA. eds. 'Clinical epidemiology of chronic obstructive pulmonary disease' Marcel Dekker, Inc, New York and Basel, 1983:23–43.
 - 3 Cloutier MM, Loughlin GM. Chronic cough in children: a manifestation of airway hyperreactivity. *Paediatrics* 1981; 67:6–11.
 - 4 Spelma R. Chronic or recurrent cough in children: a presentation of asthma: *J R Coll Gen Pract* 1984; 34:221–2.
 - 5 Tollerud DJ, O'Connor GT, Sparrow D, Weiss ST. Asthma, hay fever, and phlegm production associated with distinct patterns of allergy skin test reactivity, eosinophilia, and serum IgE levels. *Am Review Respir Dis* 1991; 144:776–81.
 - 6 Kelly WJW, Hudson I, Phelan P, Pain MCF, Olinsky A. Childhood asthma in adult life: a further study at 28 years of age. *BMJ* 1987; 294:1059–62.
 - 7 Beck GJ, Doyle CA, Schacter EN. A longitudinal study of respiratory health in a rural community. *Am Rev Respir Dis* 1982; 125:375–81.
 - 8 Johnstone DE. A study of the natural history of bronchial asthma in children. *Am J Epidemiol* 1968; 115:213–6.
 - 9 Kagamimori S, Naruse Y, Watanbe M, Nohara S, Okada A. An epidemiological study on total and specific IgE levels in Japanese schoolchildren. *Clin Allergy* 1982; 12:561–8.
 - 10 Sherrill D, Sears MR, Lebowitz MD et al. The effects of airway hyperresponsiveness, wheezing, and atopy on longitudinal pulmonary function in children: A 6-year follow-up study. *Pediatr Pulmonol* 1992; 13:78–85.
 - 11 Sears MR, Herbison GP, Holdaway MD et al. The relative risks of sensitivity to grass pollen, house dust mite and cat dander in the development of childhood asthma. *Clin Exp Allergy* 1989; 19:419–24.
 - 12 Kagamimori S, Okada A, Sato T, Katoh T, Kawano S. A plant indicator of air pollution and human health in Japanese rural communities. *Environ Res* 1978; 17:33–45.
 - 13 Kagamimori S, Katoh T, Naruse Y et al. The changing prevalences of respiratory symptoms in atopic children in response to air pollution. *Clin Allergy* 1986; 16:299–308.
 - 14 Kagamimori S, Katoh T, Naruse Y et al. An ecological study on air pollution: changes in annual ring growth of the Japanese cedar and prevalence of respiratory symptoms in schoolchildren in Japanese rural districts. *Env Res* 1990; 52:47–61.
 - 15 British Medical Research Councils Committee on Research into Chronic Bronchitis. Instruction for the use of the questionnaire of respiratory symptoms. Dover: WJ Holman Ltd, 1966:1–24.
 - 16 Burrows B, Halonen M, Lebowitz MD, Knudson R, Barbee RA. The relationship of serum immunoglobulin E, allergy skin tests, and smoking to respiratory disorders. *J Allergy Clin Immunol* 1982; 70:199–204.
 - 17 Voorhorst R, Spieksma F Th M, Varekamp H, Leupen MJ, Lyklema AW. The house-dust mite (*Dermatophagoides pteronyssinus*) and the allergens it produces identity with house-dust allergen. *J Allergy* 1967; 39:325–39.
 - 18 Melia RJW, Florey C du V, Swan AV. Respiratory illness in British schoolchildren and atmospheric smoke and SO₂, 1973–1977. I. Cross-sectional findings, *J Epidemiol Commun Health* 1981; 35:161–7.
 - 19 Love GJ, Lan SP, Shy CM, Struba RJ. The incidence and severity of acute respiratory illness in families exposed to different levels of air pollution. New York metropolitan area, 1971–1972. *Arch Environ Health* 1981; 36:66–74.
 - 20 Goren AI, Hellmann S. Prevalence of respiratory symptoms and disease in schoolchildren living in a polluted and in a low polluted area in Israel. *Environ Health* 1988; 45:28–37.
 - 21 Hagy GW, Settipane GA. Prognosis of positive allergy skin tests in an asymptomatic population. A three year follow-up of college students. *J Allergy Clin Immunol* 1971; 48:200–11.
 - 22 Anderson HR. The epidemiological and allergic features in the New Guinea Highlands. *Clin Allergy* 1974; 4:171–83.
 - 23 Roorda RJ, Gerritsen J, van Aalderen WM, Knoi K. Skin reactivity and eosinophil count in relation to the outcome of childhood asthma. *Eur Respir J* 1993; 6:509–16.
 - 24 Rijcken B, Schouten JP, Rosner B and Weiss ST. Is it useful to distinguish between asthma and chronic obstructive pulmonary disease in respiratory epidemiology? *Am Rev Respir Dis* 1991; 143:1456–57.
 - 25 Spelman R. Two-year follow up of the management of chronic or recurrent cough in children according to an asthma protocol. *Brit J Gener Prac* 1991; 41:406–9.
 - 26 Burr ML, Limb ES, Andrae S, Barry DM, Nagel F. Childhood asthma in four countries: A comparative survey. *Int J Epidemiol* 1994; 23:241–7.
 - 27 Kakiuchi H, Naruse Y, Sokejima S, Berif, Yamagami T, Kagamimori S. Respiratory symptoms in young adulthood in relation to the results of house dust skin test during childhood: A 20 year follow-up survey. *Jap J Public Health* 1993; 40:291–301 (in Japanese).
 - 28 Burrows B, Lebowitz H, Barbee R. Respiratory disorders and allergy skin test reactions. *Ann Intern Med* 1976; 84:129–33.
 - 29 Sherman CB, Tosteson TD, Tager IB, Speizer FE, Weiss ST. Early childhood predictors of asthma. *Am J Epidemiol* 1990; 132:83–95.
 - 30 Jaakkola MS, Jaakkola JJK, Ernst P, Becklake MR. Respiratory symptoms in young adults should not be overlooked. *Am Rev Respir Dis* 1993; 147:359–66.
 - 31 Dosman JA, McDuffie HH, Pahwa P. Atopic status as a factor in job decision making in grain workers. *J Occup Med* 1991; 33:1007–1010.