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# Is allergen exposure the major primary cause of asthma?

Neil Pearce, Jeroen Douwes, Richard Beasley

## Abstract

**In recent decades a number of authors have argued that allergen exposure is the major primary cause of asthma, and that the global increases in asthma prevalence are due to increases in exposure to aeroallergens. We have assessed the epidemiological evidence in support of this hypothesis. No longitudinal studies were identified in which allergen exposure during infancy in a random population sample has been related to asthma risk after the age of six years. Two studies have been conducted in selected populations chosen on the basis of a family history of asthma or allergy; one study found a non-statistically significant association whereas the other study found no association. Many of the identified prevalence studies in children showed negative associations between allergen exposure and current asthma, and the weighted averages of the population attributable risks in children were 4% for *Der p 1*, 11% for *Fel d 1*, -4% for *Bla g 2*, and 6% for *Can f 1*. There was little change in these estimates in studies in which children whose parents had adopted allergen avoidance measures were excluded. Furthermore, evidence from population studies is equivocal and provides little consistent evidence that allergen exposure is associated with the prevalence of asthma at the population level. Population-based cohort studies are clearly required, but currently available evidence does not indicate that allergen exposure is a major risk factor for the primary causation of asthma in children.**

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Keywords: asthma; allergen; childhood exposure; atopy

In recent decades a number of authors have argued that allergen exposure is the major primary cause of asthma,<sup>1-4</sup> and that the global increases in asthma prevalence could be the result of increases in exposure to aeroallergens because of increased indoor exposure levels<sup>1</sup> or because of increasing amounts of time being spent indoors.<sup>3</sup> The hypothesised causal mechanism is that allergen exposure produces sensitisation and continued exposure leads to clinical asthma through the development of airways responsiveness and inflammation.<sup>1</sup>

We have previously examined the evidence for the association of atopic sensitisation with asthma in individuals and in populations<sup>5</sup> and have concluded that the proportion of asthma cases that are attributable to atopy (defined as skin prick test positivity) is usually less than

half.<sup>5</sup> Furthermore, standardised comparisons across populations or time periods show only a weak and inconsistent association between the prevalence of asthma and the prevalence of atopy.<sup>5</sup> Thus, if allergen exposure causes asthma through the development of allergic sensitisation, then the available evidence suggests that at most about one half of asthma cases are caused by allergen exposure,<sup>5</sup> although even this estimate rests on the assumption that the association of allergen sensitisation with asthma is entirely causal.<sup>6</sup>

In this second paper we review the evidence that allergen exposure is the major primary cause of asthma. We commence by discussing the key methodological issues involved, and we then consider the substantive evidence from studies in individuals and in populations.

## Definitions and methodological issues

### ASTHMA AND ATOPY

In order to assess a particular theoretical aetiological mechanism for asthma, it is necessary to define asthma in terms of the physiological (variable airflow obstruction) and clinical (wheeze and other clinical asthma symptoms) phenomena involved without making any aetiological implications.<sup>7</sup> Thus, in reviewing the available evidence we do not consider studies in which asthma has been defined more narrowly in terms of the pathophysiological mechanisms by which variable airflow obstruction is presumed to have occurred (for example, bronchial hyperresponsiveness) since this is in part tautological—that is, it is assuming the hypothesised aetiological mechanism that we are attempting to assess—and leads to the exclusion of a significant proportion of asthma cases.<sup>8</sup> Although our focus is on asthma, the hypothesised mechanism being assessed involves allergen sensitisation (atopy) and we therefore also consider information on skin prick test positivity when this is reported in the asthma studies that are considered, since this is in some instances relative to the interpretation of the findings for asthma itself.

### PRIMARY AND SECONDARY CAUSATION

It is well established that allergen exposure is a secondary cause of asthma in that it can trigger asthma attacks in sensitised asthmatic subjects and prolonged exposure can lead to the persistence of symptoms.<sup>2-9-10</sup> However, as Sporik *et al*<sup>11</sup> note with regard to other risk factors (such as viral infections, cigarette smoke, atmospheric pollution, and stress), the distinction between factors that can precipitate attacks (secondary causation) and those that increase the risk of developing asthma (primary causation) is crucial. In this systematic review

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we focus on evidence of primary causation and we do not consider issues of secondary causation.

#### POPULATIONS

In the context of primary causation, the most relevant evidence comes from longitudinal studies (cohort studies or intervention studies) in which infants are followed from birth and the association of allergen levels early in life with the subsequent development of asthma is considered. However, there are relatively few such studies, and it is therefore also necessary to consider population-based studies of asthma prevalence. The problem with the interpretation of such studies is that asthma prevalence in a population reflects both asthma incidence and the average duration of the condition. Thus, a factor that prolongs or exacerbates asthma symptoms may thereby increase asthma prevalence even if it has no effect at all on the incidence of asthma. When considering prevalence studies we have therefore focused on studies in children where observed differences in prevalence are less likely to be due to duration (rather than incidence) effects. In addition, we have focused on studies of children aged six years or more because “transient early wheezing” in younger age groups is associated with different risk factors and does not usually progress to “classic” asthma in children over the age of five years.<sup>12</sup>

A related issue is that it is important to focus on studies of random population samples rather than selected populations.<sup>5</sup> There are particular problems in studying populations selected on the basis of susceptibility—for example, on the basis of family history of asthma or sensitisation. Not only can such restrictions involve complex biases, but they also make it difficult, if not impossible, to assess the overall importance of allergen exposure as a cause of asthma in the general population, rather than just its importance in the selected subpopulation. Similarly, it is well established that allergen exposure is a primary cause of some cases of occupational asthma in adults,<sup>13</sup> and that in this context the risk is determined in part by the intensity of the exposure.<sup>14</sup> However, studies of specified occupational groups do not provide valid estimates of the importance of allergen exposure as a cause of asthma in the general population. Thus, in the current context we focus on studies of random population samples.

#### ALLERGEN EXPOSURE

Finally, we have focused on studies in which quantitative estimates of allergen exposure were reported. Unfortunately, the reported data do not include information which would permit the assessment of a possible dose-response relationship based on exposure categories. Rather, virtually all studies use a dichotomous “cut off” to define high and low allergen exposure. In the case of house dust mite allergen studies, these have generally used an arbitrary “cut off” of 10 µg/g to define the “exposed” and “non-exposed” groups, because this has been hypothesised to be the “thresh-

old” for sensitisation.<sup>1</sup> However, we have also reported the findings using other “cut off” points when this information was available.

#### IDENTIFICATION OF PUBLICATIONS FOR REVIEW

With the above issues in mind, we conducted a Medline search from 1980 onwards for English language publications. We selected epidemiological studies on asthma (“asthma” combined with “cross-sectional studies”, “case-control studies”, “longitudinal studies” or “prevalence”; or “asthma/epidemiology”). We considered all longitudinal (cohort studies and intervention studies) and cross-sectional studies (including prevalence case-control studies). We then identified studies in which allergen levels and asthma prevalence were reported; we also recorded information on general and specific skin prick test positivity prevalence where this was available. For the reasons noted above, we excluded studies that used bronchial hyperresponsiveness (BHR) in their definition of asthma. For studies with multiple publications we only used one report. We focused on random population samples, but considered studies of selected populations when no information was available from population-based studies.

#### POPULATION ATTRIBUTABLE RISK

As with our previous paper,<sup>5</sup> we not only considered the magnitude of the associations between “exposure” (in this instance allergen exposure) and asthma, but we also considered the proportion of asthma cases that are “attributable” to exposure—that is, the “population attributable risk”.

#### Studies in individuals

##### LONGITUDINAL STUDIES

No studies were identified in which allergen exposure during infancy in a random population sample has been related to asthma risk after the age of six years. However, two studies have been conducted in selected populations chosen on the basis of a family history of asthma or allergy.

The key study linking allergen exposure in infancy to the subsequent development of asthma is that of Sporik *et al*<sup>1</sup> who followed 67 children selected as being at risk because of a family history of atopy. They found a significant dose-response association between *Der p* 1 levels and risk of house dust mite sensitisation, but they did not report the findings for overall sensitisation. None of the measured associations between allergen exposure (more than 10 µg/g in the first year of life) and various definitions of asthma were statistically significant, although some were of borderline significance. In particular, there were non-significant associations with a history of wheezing at the age of 11 years (odds ratio (OR) 2.3, 95% confidence interval (CI) 0.7 to 7.1, *p* = 0.17, population attributable risk (PAR) 44%), “active wheezing and BHR” (OR 7.7, 95% CI 0.6 to 366, *p* = 0.06, PAR 80%), and “receiving medication” (OR >4.5, *p* = 0.07, PAR >78%). These analyses were not adjusted for current exposure, and the authors noted that there was

not a significant association between current exposure and current wheezing, but it is nevertheless possible that the findings could be confounded by current exposure. Although these results suggest that exposure to house dust mite allergen might be an important determinant for the development of asthma, one should bear in mind that they are based on small numbers and the high population attributable risk estimates have confidence intervals which include zero.

The only other published birth cohort study is that of Burr *et al*<sup>15</sup> which involved 453 infants in South Wales with a family history of allergic diseases. Infants were followed up to the age of seven years and levels of house dust mite allergen in mattress and carpet dust were determined in the first and seventh years of life. The study involved an intervention examining the effect of withholding cows' milk protein during the first three months of life and replacing it with soya milk. Doctor-diagnosed asthma and wheezing at the age of seven years was not associated with mite allergen exposure as determined in the first 12 months, nor with dust mite levels measured at seven years of age (odds ratios were not given). Wheezing was also not associated with cat ownership. No significant differences in mite sensitisation (determined by skin prick test) at the age of seven between children exposed to low, moderate, and high levels of mite allergen were observed (20%, 20% and 22%, respectively when initial exposure was compared, and 19%, 19% and 23% when exposure at the age of seven years was considered). Withholding cows' milk did not have an effect on the incidence of allergy or wheezing, and it thus seems likely that the lack of association observed between exposure to house dust mite allergen and asthma symptoms cannot be explained by confounding effects of the intervention.

The key primary prevention study is the Isle of Wight randomised trial<sup>16</sup> which was conducted in 160 infants with a family history of atopy. However, it involved an intervention "package" including avoidance of house dust mite allergen and allergenic food in a prophylactic group, and it is therefore difficult to isolate the effect of allergen avoidance. At 12 months asthma (defined as three or more separate episodes of cough and wheezing) was more common in the non-intervention group (OR 4.1, 95% CI 1.1 to 15.5). However, at two years the odds ratio fell to 2.2 (95% CI 0.8 to 5.9) and at four years it fell to 1.7 (95% CI 0.8 to 3.8), although the control group continued to show more positive skin prick tests (OR 3.7, 95% CI 1.3 to 10.0),<sup>17</sup> indicating that the intervention had markedly reduced the risk of atopy but had had a less impressive effect on asthma itself.

Finally, because of the paucity of population-based studies which have followed children beyond the age of six years, we also consider studies with shorter follow up periods. Van Strien *et al*<sup>18</sup> studied 104 infants and found an association between exposure to more than 2 µg/g *Der p* 1 and wheeze and prolonged cough (adjusted OR 4.8, 95% CI 1.1 to 21.1,

$p < 0.05$ ) but did not find a significant association when a *Der p* 1 cut off value of more than 5 µg/g was chosen (OR 1.9, 95% CI 0.6 to 6.8). Nafstad *et al*<sup>19</sup> studied 494 infants and found a non-significant association (adjusted OR 2.8, 95% CI 0.7 to 11.7) between exposure to more than 2 µg/g *Der p* 1 and symptoms and signs of bronchial obstruction defined as at least three out of five physician confirmed symptoms or signs of bronchial obstruction (wheezing, chest recession, rhonchi during auscultation, forced expiration, and rapid breathing). However, in this last study positive *Der p* 1 levels were only found in mattresses of 11 (11%) of the asthma cases and three (1%) of the controls. Gold *et al*<sup>20</sup> followed 499 children of asthmatic/allergic parents in metropolitan Boston, measuring home allergen levels within the first three months of life and repeated wheeze in the first year of life. They found no associations with levels of cat or dog allergens, but found a significant association with cockroach allergen levels greater than 0.05 U/g in the family room (RR 1.63, 95% CI 1.05 to 2.55, PAR 9%). Thus, there are several studies showing associations between allergen exposure and respiratory symptoms early in life, although it should be stressed that respiratory symptoms at such a young age may not be considered as valid measures of subsequent childhood asthma,<sup>12</sup> and the findings should therefore be considered with caution.

#### PREVALENCE STUDIES

Table 1 summarises prevalence studies of house dust mite allergen exposure and asthma in individuals,<sup>21-26</sup> and table 2 summarises the findings for studies of other allergens.<sup>21 22 24 27</sup> It is striking that many of the studies in children show negative associations between allergen exposure and current asthma. For example, Verhoeff *et al*,<sup>23</sup> in a case control study of 516 children aged 6-12, found that 83% of children with chronic respiratory symptoms and 89% of non-symptomatic children were exposed to *Der p* 1 levels of more than 2 µg/g, yielding an odds ratio of 0.6 and a population attributable risk of -55%. Another large case-control study among 474 children aged 7-9 years<sup>26</sup> found only a very modest positive association (not statistically significant) with *Der p* 1 exposure in the living room (OR 1.2, PAR 16%) and bedroom (OR 1.2, PAR 20%), whereas a negative (not statistically significant) association was found with *Der p* 1 levels measured in the bedding (OR 0.5, PAR -90%). Platts-Mills *et al*<sup>24</sup> studied the exposure of approximately 100 children aged 12-14 to various indoor allergens (house dust mite, cockroach, cat and dog) in a case-control study. Using 2 µg/g and 10 µg/g dust as the cut off levels for the various allergen exposures, most of the associations were negative and only a few positive associations were found.

The weighted averages of the population attributable risks in children are 4% for *Der p* 1, 11% for *Fel d* 1, -4% for *Bla g* 2, and 6% for *Can f* 1. These estimates were similar in studies which defined asthma in terms of hospital treatment and those which defined asthma on the basis of symptom questionnaires (tables 1

Table 1 Allergen levels and prevalence of asthma in cross-sectional studies in children: house dust mite allergen (HDM)

Reference	Age	Allergen level	Non-asthmatics		Asthmatics		OR	Population attributable risk	Definition of asthma
			No.	Exposed	No.	Exposed			
Sporik <i>et al</i> <sup>1</sup>	1-15 (asthmatics) 10-12 (non-asthmatics)	> 10 µg/g Der p 1	44	70%	82	76%	1.3*	16%	Asthma patients for hospital treatment
Caill <i>et al</i> <sup>2</sup>	3-15	≥ 10 µg/g HDM grp 1	22	45%	35	26%	0.4*	-39%	Asthma patients for hospital treatment
Verhoeff <i>et al</i> <sup>3</sup>	6-12	> 2 µg/g Der p 1	257	89%	259	83%	0.6*	-55%	Chronic respiratory symptoms
		> 10 µg/g Der p 1	257	57%	259	54%	0.9*	-6%	
Platts Mills <i>et al</i> <sup>4</sup>	12-14	> 2 µg/g HDM grp 1	47	6%	50	4%	1.4*	1%	Chronic respiratory symptoms
		> 10 µg/g HDM grp 1	47	0%	50	0%	-	-	Wheezing
Marks <i>et al</i> <sup>5</sup>	8-10	≥ 10 µg/g Der p 1	35	97%	39	100%	-1.1*	9%	Wheezing or nocturnal cough; Wheezing, whistling or asthma
Wickens <i>et al</i> <sup>6</sup>	7-9	> 10 µg/g Der p 1 (living room)	241	79%	233	82%	1.2	16%	Wheezing or nocturnal cough; Wheezing, whistling or asthma
		> 10 µg/g Der p 1 (bedroom)	241	83%	233	85%	1.2	20%	
		> 10 µg/g Der p 1 (bedding)	241	95%	233	90%	0.5	-90%	

\*Calculated.

Table 2 Allergen levels and prevalence of asthma in cross-sectional studies in children: other allergens

Reference	Age	Allergen level	Non-asthmatics		Asthmatics		OR	Population attributable risk	Definition of asthma
			No.	Exposed	No.	Exposed			
Sporik <i>et al</i> <sup>1</sup>	1-15 (asthmatics) 10-12 (non-asthmatics)	> 8 µg/g Fe/d 1	44	39%	82	46%	1.4*	13%	Asthma patients for hospital treatment
Call <i>et al</i> <sup>2</sup>	3-15	≥ 10 µg/g Fe/d 1	22	5%	35	3%	0.6*	-2%	Asthma patients for hospital treatment
Platts Mills <i>et al</i> <sup>4</sup> , Ingram <i>et al</i> <sup>27</sup>	12-14	> 2 µg/g Fe/d 1	47	91%	50	86%	0.6*	-57%	Wheezing
		> 10 µg/g Fe/d 1 <sup>a</sup>	47	49% (45%) <sup>a</sup>	50 (51)	58% (57%) <sup>a</sup>	1.4* (1.6*) <sup>a</sup>	17% (21%) <sup>a</sup>	Wheezing
Caill <i>et al</i> <sup>2</sup>	3-15	≥ 2 units/g Bla g 2	22	86%	35	86%	0.9*	-10%	Asthma patients for hospital treatment
Platts Mills <i>et al</i> <sup>3</sup> , Ingram <i>et al</i> <sup>27</sup>	12-14	> 2 units/g Bla g 2	47	2%	50	2%	0.9*	-0.2%	Wheezing
		> 10 units/g Bla g 2	47	0%	50	0%	-	-	
		> 2 µg/g Can f 1	47	94%	50	90%	0.6*	-60%	
		> 10 µg/g Can f 1 <sup>a</sup>	47	68% (62%) <sup>a</sup>	50	70% (52%) <sup>a</sup>	1.1* (0.7*) <sup>a</sup>	6% (-22%) <sup>a</sup>	

\*Calculated.

<sup>a</sup>Same study population and exposure but different results (results from Ingram *et al*<sup>27</sup> in parentheses).

and 2). Thus, overall these studies suggest that allergen exposure is at most a minor risk factor for the development of asthma in children.

A major concern in such cross-sectional studies is that allergen avoidance measures may have been adopted as a consequence of developing asthma. This possibility was examined in only a few studies, and these generally found slightly stronger risks when children whose parents had adopted allergen avoidance measures were excluded from the analysis. For example, in the study by Verhoeff *et al*<sup>23</sup> the odds ratios increased after excluding subjects for whom allergen avoidance measures had taken place in their homes. However, the increase in odds ratios was very small and only noticeable when mite-sensitised cases were compared with non-sensitised controls or non-sensitised cases. Thus, even when allergen avoidance is accounted for, these studies do not suggest that allergen exposure is a major risk factor for childhood asthma.

On the other hand, the only two studies<sup>28 29</sup> identified in adults (not shown in table) both show positive associations of current allergen exposure with current asthma, with estimates ranging from 5% to 37% of cases attributable to exposure. However, as noted above, cross-sectional studies of current exposure and current asthma in adults are difficult to interpret in terms of primary causation.

Tables 1 and 2 are restricted to studies in which quantitative data on allergen levels were collected. However, it is relevant also to consider studies in which the presence or absence of pets was recorded. Several recent studies have investigated the association between exposure to pets early in life and the development of atopy and asthma later. Interestingly, these studies seem to suggest a protective effect of pet keeping early in life. For example, a recent study<sup>30</sup> of 13 932 subjects aged 20–44 years from a large number of countries in Europe showed a protective effect

of the presence of a dog in the home in childhood on atopy, even after adjusting for family history of allergies (OR 0.85, 95% CI 0.77 to 0.94). A protective effect of the presence of a cat in the home in childhood (OR 0.86, 95% CI 0.76 to 0.98) was, however, only seen in subjects with parental allergy, and could possibly be explained by avoidance of pet ownership in atopic families. A recent case-control study in Sweden of 402 children aged 12–13 years showed a strong negative association (OR 0.34, 95% CI 0.07 to 0.77) between pet keeping during the first year of life and asthma.<sup>31</sup> This association remained even after excluding children whose parents had decided against pet keeping during early childhood because of allergy in the family. In addition, the authors showed that children exposed to cats during the first year of life were less likely to have a positive skin prick test to cat allergen at age 12–13 years. These findings appear unlikely to be due to selective pet avoidance. Besides other possible reasons such as a potential increased microbial pressure associated with pet ownership that could favour a non-allergic development of the immune system (see below), it could be speculated that exposure to pet allergens early in life may induce a specific tolerance which reduces the risk of subsequently becoming allergic or asthmatic. Clearly, more studies are needed to elucidate further the role of allergen exposure early in life on the later development of allergies and asthma.

### Studies in populations

Table 3 summarises the available evidence on the association between allergen exposure and the subsequent risk of asthma at the population level.<sup>2 32–41</sup> For example, Charpin *et al*<sup>22</sup> found a marked difference in exposure to house dust mite allergen between Matigues and Briancon (15.8 µg/g and 0.36 µg/g, respectively) and found a corresponding difference in specific

Table 3 Allergen levels and prevalence of atopy and asthma in population-based studies comparing different populations, or the same population over time

Reference	Population	No.	Age	Allergen	Units	Levels	Specific atopy (%)	Total atopy (%)	% with doctor diagnosed asthma or "asthma"
<i>Comparisons of populations</i>									
Charpin <i>et al</i> <sup>22</sup>	Matigues (coast)	693	9–11	HDM group 1	µg/g	15.8	17	25	6
	Briancon (Alps)	150	9–11			0.36	4	26	4
	Briancon (non-native)	90	9–11			0.36	10	–	7
Woolcock <i>et al</i> <sup>33 34</sup>	Asaro Valley	743	>20	HD mites	No/g	283	–	24	0.3
Turner <i>et al</i> <sup>35</sup>	South Fore area	736	>20			1371	–	Similar	7
	Peat <i>et al</i> <sup>2</sup>	Broken Hill	794	8–11	Der p 1	µg/g	0.7	13	37
Peat <i>et al</i> <sup>2</sup>	Wagga Wagga	850	8–11			1.4	21	40	29
	Moree/Narrabi	770	8–11			6.5	26	40	31
	Sydney	1339	8–11			22.5	34	42	24
	Belmont	926	8–11			35.7	30	39	38
	Lismore	805	8–11			47.8	29	35	31
Von Mutius <i>et al</i> <sup>36</sup>	Munich (W Germany)	7445	9–11	Der p 1 + Der f 1*	µg/g	2	10	19	6
	Leipzig (E Germany)	1429	9–11			Similar	4	7	4
Nowak <i>et al</i> <sup>37</sup>	Hamburg (W Germany)	3156	20–44	Der p 1 + Der f 1*	µg/g	2	14	36	14
	Erfurt (E Germany)	3272	20–44			Similar	10	30	6
Leung <i>et al</i> <sup>38</sup>	Hong Kong	1062	12–18	Der p 1	≥10 µg/g	69%	55	58	7
	Kota Kinabalu (Mal)	409	12–18			60	64	3	
	San Bu (S China)	737	12–18			50%	43	49	2
Wieringa <i>et al</i> <sup>39</sup>	Urban Antwerp	319	20–44	Der p 1	>2 µg/g	27%	26	–	22
	Suburban Antwerp	337	20–44			42%	17	–	9
<i>Comparisons of time periods</i>									
Peat <i>et al</i> <sup>40</sup>	Belmont (1982)	718	8–10	HD mites	No/g	225	21	28	9
	Belmont (1992)	873	8–10			1240	Similar	29	38
	Wagga Wagga (1982)	769	8–10			67	16	30	13
	Wagga Wagga (1992)	795	8–10			301	Similar	35	30

\*Based on Hirsch *et al*.<sup>41</sup>

sensitisation to house dust mite (17% and 4%) but little difference in overall sensitisation (25% and 26%) or asthma (6% and 4%) (table 3).

Similarly, Leung *et al*<sup>38</sup> found that the prevalence of asthma was high in Hong Kong (6.6% for asthma ever) and low in San Bu, China (1.6%), but exposures to house dust mite allergen were similar in the two locations.

Peat *et al*<sup>2</sup> have previously reported that exposure to house dust mite allergen was associated with the prevalence of specific sensitisation to dust mites in six Australian centres (table 3). However, the overall prevalences of sensitisation and asthma were both unrelated to the levels of house dust mite allergen exposure in the six centres (table 3 and fig 1). In another paper Peat *et al*<sup>12</sup> found similar levels of overall allergic sensitisation and asthma prevalence in seven regions of New South Wales despite differences in climatic conditions and allergen exposures. The dominant allergen varied between regions, with sensitisation to house dust mites increasing towards more humid coastal regions, sensitisation to *Alternaria* increasing towards drier inland regions, and sensitisation to ryegrass increasing towards more temperate southern inland regions, but there was little overall difference in the prevalence of sensitisation or of asthma.

Von Mutius<sup>36</sup> found that asthma was significantly higher in Munich, West Germany (5.9%) than in Leipzig, East Germany (3.9%), and this paralleled the pattern of skin prick test positivity (19.2% and 7.3%). The authors noted that exposure to cats and dogs was more common in the West, but comparative data on house dust mite exposure were not collected. However, another study showed that the levels of house dust mite allergen in dust in East and West German homes were very similar.<sup>41</sup> The patterns of specific sensitisation did not match the patterns of exposure. It is therefore unlikely that allergen exposure explains the differences in the prevalence of skin test reactivity and asthma.

Overall, the only population comparisons in table 3 which show a marked association between allergen exposure levels and asthma prevalence are those in New Guinea<sup>33-35</sup> where

a much higher prevalence of asthma (but not of atopy) was found in the South Fore area than in the Asaro Valley. This has been attributed to the higher prevalence of house dust mite exposure from, for example, the use of blankets in the South Fore area, but it is unclear whether this association is causal or whether increased house dust mite exposure is merely a marker of other aspects of westernisation. On the other hand, Peat *et al*<sup>10</sup> reported increases in house dust mite levels over time, with little change in the prevalence of atopy but a marked increase in the prevalence of asthma (table 3). However, the increase in the prevalence of asthma was also seen in the arid inland region of Wagga Wagga where house dust mite levels were very low.

Table 3 is restricted to studies in which quantitative measures of allergen levels were collected. However, the findings are consistent with evidence from the International Study of Asthma and Allergies in Childhood<sup>43-44</sup> and the European Community Respiratory Health Survey,<sup>45</sup> and other studies which have compared the prevalence of asthma in various populations. In particular, these studies have consistently found uniformly high levels of asthma in English speaking countries even though there is a wide variation in house dust mite levels across these countries.<sup>46</sup> For example, in geographical areas in which house dust mite exposure is very low or absent, including desert regions<sup>42-47</sup> and mountainous regions,<sup>48</sup> the prevalence of asthma is as high or even higher than that in areas where house dust mite exposure is high.<sup>46</sup> The study of Sporik *et al*<sup>48</sup> is particularly interesting in this regard since, in a mite-free environment, asthma prevalence was still high and 64% of non-asthmatic subjects and 73% of asthmatic subjects were skin prick test positive (mainly to cat).

## Discussion

It is striking that, to date, there have been no published studies in which allergen exposure in infancy has been related to the risk of asthma after the age of six years in a random general population sample. The key evidence from longitudinal studies involves selected populations and/or respiratory symptoms measured very early in life when the presence of asthma cannot be established.

The key study linking allergen exposure in infancy to the subsequent development of asthma is that of Sporik *et al*<sup>1</sup> who found a significant association between house dust mite exposure and specific sensitisation in a selected population. However, they did not report the findings for overall sensitisation, and none of the associations for asthma itself were statistically significant. The strongest association was in fact for "active asthma" defined as active wheezing plus BHR which may therefore reflect an association with BHR rather than with asthma itself. More generally, it is possible that we would have obtained stronger associations and higher attributable risks if we had included studies which used BHR in the definition of asthma but, as outlined above, we did not do this because BHR is part of the

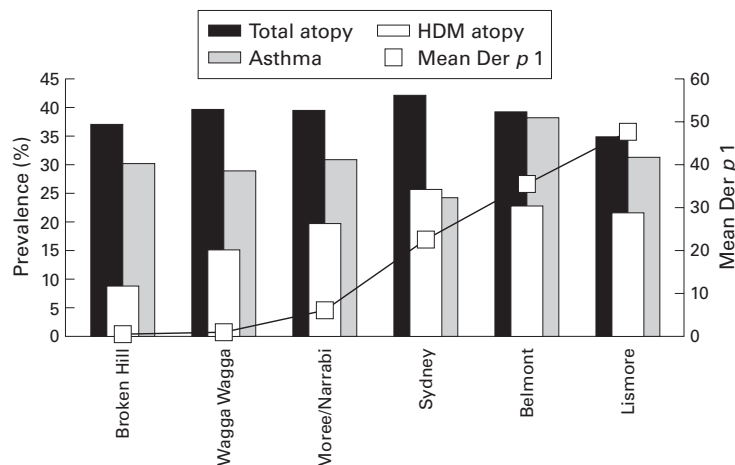


Figure 1 Mean Der p 1 levels and prevalence (%) of house dust mite atopy, total atopy, and asthma in six areas of Australia.

theoretical aetiological mechanism that we are attempting to assess, and the findings would then only have applied to the subset of asthmatic subjects with BHR rather than to asthmatic subjects in general.<sup>49</sup>

The Sporik study provides the main direct evidence for a primary causal role of house dust mite exposure in the development of asthma. The only other cohort study to date which has measured allergen exposure early in life and related this to overall asthma risk after the age of five years is that of Burr *et al*<sup>5</sup> and the findings do not support those of Sporik *et al*.<sup>1</sup> Of course, the absence of compelling evidence from longitudinal studies means that firm conclusions cannot be drawn either way. This absence of consistent evidence from longitudinal studies would be of less concern if the findings of Sporik *et al* were supported by prevalence studies in individuals (tables 1 and 2) and/or populations (table 3). However, this does not appear to be the case.

It could be argued that these studies do not show clear associations or dose-response relationships with specific allergen exposure levels because, in Western countries, virtually everyone has exposure levels higher than the "threshold" for sensitisation. However, numerous studies—for example, Sporik *et al*<sup>1</sup>—in these same populations have shown dose-response relationships for specific sensitisation so the hypothesised existence of a "threshold" cannot explain the absence of a dose response for asthma itself. Furthermore, there are a number of populations with house dust mite allergen levels well below the hypothesised sensitisation threshold but with asthma prevalence levels similar to those in high exposure areas.<sup>2 47 48</sup>

Similarly, studies in individuals may be prone to non-differential information bias because of difficulties in accurately measuring individual allergen exposure levels, but this has not prevented the demonstration of clear dose-response relationships of allergen exposure with specific allergen sensitisation.<sup>1</sup> Furthermore, studies in populations (table 3) are less likely to be affected by inaccuracies of measuring individual allergen exposure levels. Although the findings in prevalence studies in individuals are likely to be biased by allergen avoidance, this bias does not appear to be major and, in any case, such biases are of less concern in comparisons of populations (table 3) than of individuals (tables 1 and 2). It is therefore particularly interesting that population comparisons show little or no evidence of associations of asthma or atopy with allergen levels, even when the analysis is confined to English speaking countries in which there are less likely to be problems of comparability of information across populations.

Thus, the evidence linking allergen exposure to asthma is weak and, if the association is causal, the population attributable risk appears to be small. Why is this conclusion so different from that of some previous reviews which have concluded that allergen exposure is the major primary cause of asthma? The key difference is that we have focused on direct evidence of pri-

mary causation, whereas other reviews have mainly considered indirect evidence and have mixed together issues of primary and secondary causation.<sup>4 10</sup> For example, Sporik *et al*<sup>11</sup> concede that there is little direct evidence relating allergen exposure in early life with the subsequent development of asthma, but they argue that there is strong indirect evidence in that specific allergen exposure causes specific allergen sensitisation, and allergen sensitisation (in general) is a major risk factor for asthma. However, as noted above, such indirect evidence is subject to complex biases and is difficult to interpret. The Australian studies of Peat *et al*<sup>2</sup> are particularly interesting in this regard since the prevalence of sensitisation to house dust mites showed a significant correlation with mean *Der p 1* levels in the six areas, but the prevalence of sensitisation in general, and asthma itself, showed no such correlation (fig 1). One interpretation of this evidence that has frequently been offered is that the prevalence of asthma is related more to the total burden of aeroallergens than to exposure to a particular allergen.<sup>50</sup> However, there is currently no evidence for this hypothesis, and it would be surprising if the total burden of aeroallergen was the same across centres in English speaking countries despite major differences in exposure to specific aeroallergens. An alternative explanation is that specific allergen exposure may not be a major primary cause of sensitisation or of asthma itself, but may determine the specificity of the sensitisation in susceptible individuals.

In summary, the case that allergen exposure is a major primary cause of asthma is largely based on indirect evidence which is susceptible to a variety of interpretations. Population-based cohort studies are clearly required, but currently the direct evidence is relatively weak and is far from convincing, with the exception of some studies in specific selected populations such as in occupational asthma. In both research and public health terms, the danger is that overemphasis on a hypothesis for which the evidence is weaker than is commonly assumed may have led to the neglect of research into other possible aetiological mechanisms and risk factors for asthma and other possible causes for the global increases in its prevalence.

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