Which Clinical Subgroups Within the Spectrum of Child Asthma Are Attributable to Atopy?*

Anne-Louise Ponsonby, MBBS, PhD; Paul Gatenby, MBBS, PhD; Nicholas Glasgow, BHB MBChB; Raymond Mullins, MBBS, PhD; Tim McDonald, MBBS; and Mark Hurwitz, MBBCCh, FCCP

Study objectives: The contribution of atopy to childhood asthma has been debated. We aimed to examine the relationship between atopy and asthma, taking into account differences in respiratory symptoms and disease severity.

Design: A cross-sectional asthma survey involving the following: (1) a population sample of 758 (81% of eligible) school children aged 8 to 10 years from randomly selected schools in the Australian Capital Territory in 1999, and (2) a hospital-based sample of 78 (70% of eligible) children attending the hospital for asthma. Skin-prick test results to 10 common aeroallergens were available on 722 children and 77 children, respectively. Baseline spirometry was obtained on a subset of school children (n = 515, 78% of eligible).

Results: The association between atopy and wheeze by wheeze frequency over the past year was as follows: no episodes (odds ratio [OR], 1.00 [reference]), 1 to 3 episodes (OR, 3.27; 95% confidence interval [CI], 2.15 to 4.97), 4 to 12 episodes (OR, 3.44; 95% CI, 1.75 to 6.75), and >12 episodes (OR, 8.70; 95% CI, 3.07 to 24.55), with a higher population attributable fraction (PAF) for >12 episodes (75%) than 1 to 3 episodes (49%). Atopy was moderately related to asthma ever (OR, 2.09; 95% CI, 1.52 to 2.85; PAF, 33%) but strongly related to 1999 hospital attendance for asthma (OR, 16.95; 95% CI, 6.76 to 42.48; PAF, 89%). Adjustment for child age, gas heater use, and maternal smoking near the child did not materially alter these findings.

Conclusions: The clinical features of frequent wheeze or hospital asthma attendance are largely attributable to atopy, but infrequent wheeze or a history of asthma ever are not. Atopic children are overrepresented in the severe range of the asthma spectrum. (CHEST 2002; 121:135–142)

Key words: aeroallergen sensitization; atopy; childhood asthma; disease severity

Abbreviations: ACT = Australian Capital Territory; CI = confidence interval; Der f 1 = Dermatophagoides farinae; Der p 1 = Dermatophagoides pteronyssinus; ISAAC = International Study of Asthma and Allergy in Childhood; OR = odds ratio; PAF = population attributable fraction; SPT = skin prick testing

The heterogeneity of clinical subgroups within asthma patients is likely to partially reflect mixed etiologic components. The relative contribution of allergen-induced, infection-induced, or irritant-induced airway abnormalities to subgroups within the broad spectrum of asthma is not yet well understood. The dominant clinical model for childhood asthma is that of a largely allergic etiology; however, this assumption has been challenged. Pearce et al recently reviewed the epidemiologic evidence implicating aeroallergen exposure in the primary causation of asthma, and concluded that the available data do not indicate that aeroallergen exposure is a major risk factor. Pearce et al also examined population-based studies with at least 600 child subjects. The mean population-attributable risk for childhood asthma due to atopy, as assessed by positive skin-prick testing (SPT) results, was only 38%, suggesting that the proportion of asthma cases due to atopy was less than one half. Furthermore,
ecologic data show only a weak and inconsistent association between atopy and asthma prevalence.3 The authors concluded that the importance of atopy as a cause of asthma in the population may have been overestimated.2,3

Evidence indicating a key role for allergen exposure and allergen sensitization in the pathogenesis of asthma includes birth cohort studies4–6 that have shown a dose–response relationship between allergen exposure and specific sensitization, and prospective studies7–9 linking allergen sensitization with subsequent asthma. However, to date, only one birth cohort study10 has shown infant house dust mite exposure to relate to an increased risk of child asthma as well as house dust mite sensitization. Two birth cohort studies11,12 found no association between infant house dust mite exposure and subsequent asthma. For individuals with allergen sensitization and asthma, there is a large body of work indicating that allergen exposure is clearly associated with increased disease severity.13,14 House dust mite sensitization has been shown15 to be associated with more severe disease. Thus, it may be that the population attributable fraction (PAF) of child asthma due to atopy increases with increasing disease severity.

We conducted concurrent population and hospital-based childhood asthma studies in the Australian Capital Territory (ACT) in 1999 to 2000. Canberra (35°S), the capital city of Australia, the urban center within this inland region, is surrounded by pastureland and native grasslands. We report here on the association between specific and general aeroallergen sensitization and asthma. We examined the relative contribution of atopy to different indicators of asthma frequency and severity.

**Materials and Methods**

**The Population-Based Sample**

The source population was children born from 1989 to 1990 who attended school in the ACT in 1999. The eligible study sample consisted of children who attended the first 11 randomly selected primary schools from a list of ACT government and nongovernment schools.

A questionnaire was sent home from school to parents. This included questions on asthma, respiratory symptoms, hay fever, and eczema from the International Study of Asthma and Allergy in Childhood (ISAAC).16 Previously, the validity of these questions has been examined. A positive history of wheeze or whistling in the chest over the past 12 months had a sensitivity of 0.85 and specificity of 0.81 for respiratory physician diagnosis of asthma.17 Children with a history of asthma ever have been demonstrated to have significantly greater bronchial hyperresponsiveness to methacholine18 or exercise.19 In addition, data were collected on current home heating, gas cooking, parental smoking, child exposure to active smoking in the same room, child bedroom ventilation, and other factors.

SPT was used to assess the cutaneous reaction to exposure to the house dust mites *Dermatophagoides pteronyssinus* (Der p 1) and *Dermatophagoides farinae* (Der f 1), cat, dog, *Alternaria tenuis*, ryegrass, birch, plantain, *Paspalum notatum* (paspalum grass), and wattle (*Acacia longifolia*, a flowering tree) [Holister-Stier purified allergen extracts; Bayer; Sydney, Australia], and positive (histamine, 6 mg/mL) and negative (glycerine) controls. SPT was conducted on the volar aspect of the forearm using metal lancettes (Bayer) to puncture the skin at an angle of 45° to the skin surface. For aeroallergens, wheal allergen reactions ≥ 3 mm at 15 min after application were classified as positive. Among children with no positive SPT result to aeroallergens, all but one child had a histamine reaction. Among children with at least one positive SPT result, one child also had a positive SPT result to the negative control. Parents and children were instructed that participants should not receive medications with antihistaminic action for the week prior to testing. In addition, baseline lung function measures were obtained for children examined between June 1999 and November 1999 as part of a related study. The children were asked to perform forced expiratory maneuvers without a nose clip while standing following a standard protocol,20 using a Fleisch-type electronic spirometer (Vitalograph Alpha 2, model AL0642; Vitalograph; Buckingham, UK) that was calibrated at the beginning of every session and hourly thereafter. Participants were instructed not to use β-agonist medication within 6 hours of the test.

**The Hospital Sample**

The three participating hospitals were the only hospitals in the ACT with facilities for acute management of pediatric asthma. The ACT hospitals are the major tertiary-care hospitals not only for the ACT but surrounding rural areas. Children born from 1988 to 1991 who attended these hospitals in an acute presentation to the emergency department or in an inpatient for acute asthma during 1999 were eligible to participate in the hospital sample. The children and their parents were invited to attend a hospital clinic after attendance for SPT. A parental questionnaire was completed. The questionnaire and study protocol for SPT were identical for the hospital and population-based groups, and trained research nurses conducted the tests on both samples. The project was approved by the ACT Health and Community Care Ethics Committee.

**Definitions**

Following ISAAC16 terminology, recent refers to "within the past year." Wheeze refers to wheezing or whistling in the chest. A history of eczema is the report of any itchy rash ever that was coming or going for at least 6 months and affected flexural areas. Aeroallergen sensitization or atopy is defined as a positive skin test result (≥ 3 mm) to any of the aeroallergens tested in the population sample. Grass sensitization refers to a positive skin test result to either ryegrass and/or paspalum and/or plantain allergen. Mite sensitization refers to a positive skin test result to either *Der f 1* or *Der p 1*, or both. Asthma status refers to history of asthma ever, history of past hospital attendance ever for asthma, and 1999 ACT hospital attendance for asthma.

**Statistical Methods**

Odds ratios (ORs) were calculated using the method of Mantel and Haenszel for univariate analysis and logistic regression for multivariate analysis.21 Respiratory symptoms were examined in the cross-sectional school sample. We used the OR as the estimator of strength of association to allow a direct comparison between our findings and a previous review of studies examining the association between atopy and child asthma. However, it
should be noted that in asthma epidemiologic studies, where the proportion of children with disease is large, ORs will not approximate relative risks well. A case-cohort approach was used for asthma hospital attendance in 1999. That is, the numerator was acute asthma cases attending hospital and the denominator was all children in the population-based sample, including any children who attended the hospital for asthma in 1999. A case-cohort study avoids the need for a rare disease assumption and provides better estimates of incidence-rate ratios than a case-control study in settings where disease is common, as in childhood asthma. Multiple linear regression models were used to examine the associations between respiratory status by questionnaire and continuous outcomes, such as the lung function measures of FEV₁, FVC, and the ratio of FEV₁ to FVC with

**Figure 1.** The proportion of children with atopy, hay fever, or eczema by wheeze episode frequency.
adjustment for relevant covariates. The test for trend in Figure 1 was based on a x² test of linear trend. In the unadjusted analyses, PAF, the proportion of excess risk of disease that is associated with atopy, was calculated as p(OR - 1)/p (OR - 1), where p is the proportion of children with atopy, and OR is the OR for atopy and the specified outcome. In the adjusted analyses, PAF was calculated as pd(AOR-1/AOR), where pd is the proportion of patients with atopy, and AOR is the adjusted OR. We conducted the analyses using statistical software (STATA 6; Stata Corporation; College Station, TX).

RESULTS

General Features

For the population sample, asthma questionnaire data were available on 758 of 935 children (81%) who were enrolled at the school at the time of testing; 722 of these children (95% of questionnaire participants, 77% of total eligible) participated in SPT by research nurses using a standard protocol. Spirometric lung function data were available on 515 of the 657 children initially selected. For the hospital sample, 78 of 111 eligible children participated in the study (mean age, 8.9 years; SD, 1.26 years). Of these 78 children, 31 children were admitted to hospital for ≥ 1 night. SPT data were obtained on 74 children by our study nurses, and SPT data were obtained on 4 children from medical records. One child’s medical record data were incomplete and so excluded. The mean time period between hospital attendance and skin allergy testing was 90.8 days (SD, 81.1 days).

Table 1 shows the prevalences of asthma ever and recent wheeze were 34.3% and 25.2%, respectively. The prevalences of hay fever and eczema were 28.6% and 21.2%, respectively, in the school sample. Of the individual aeroallergens tested, the highest sensitization prevalence was for ryegrass but sensitization to house dust mite allergens was also common. The population means for FEV₁, FVC, and FEV₁/FVC are shown in Table 1. In addition, we examined the distribution of FEV₁ in this population to that expected using a predictive nomogram developed for Australian children. Our population had the following FEV₁ parameters expressed as percentage of predicted: 25th centile, 92.4%; 50th centile, 100.7%; and 75th centile, 108.9%. Here, only 5.7% of children had an FEV₁ < 80% of their predicted value based on age and sex.

We used the baseline ratio of FEV₁ to FVC as a measure of airway obstruction. Children with four or more recent wheeze episodes were more likely (p = 0.002) to have a reduced FEV₁/FVC ratio (adjusted difference, 2.7%; 95% confidence interval [CI], 1.0 to 4.5%) compared with children with three or fewer episodes. Children admitted to hospital ever were more likely to have a significantly reduced FEV₁/FVC ratio (adjusted difference, 2.0%; 95% CI, 0.3 to 3.7%). Children who had a hospital attendance for asthma in 1999 also had a significantly reduced FEV₁/FVC ratio (adjusted difference, 7.1%; 95% CI, 1.9 to 12.4%), but children with a history of asthma ever did not. All differences were adjusted for child height, gender, indoor humidity, indoor temperature, research technician, maternal smoking in same room as child, and home gas heater use. Airway obstruction was thus more evident in children with frequent wheeze or with recent or past hospital attendance for asthma.

Association Between Allergen Sensitization and Asthma Status

On univariate analysis, sensitization to any allergen was significantly associated with past or 1999 hospital attendance for asthma. The likelihood of being sensitized to one allergen was correlated with sensitization to other allergens. For example, the correlation coefficient between Der p 1 and Der f 1 sensitization was 0.68 (p < 0.0001), between ryegrass and paspalum was 0.73 (p < 0.0001), and between ryegrass and plantain was 0.52 (p < 0.0001). To determine the association between sensitization type and asthma status, taking into account the tendency

<table>
<thead>
<tr>
<th>Variable</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁/FVC ratio</td>
<td>515</td>
</tr>
<tr>
<td>Maximum FEV₁</td>
<td>515</td>
</tr>
<tr>
<td>Maximum FVC</td>
<td>515</td>
</tr>
<tr>
<td>FEV₁/FVC ratio (adjusted)</td>
<td>515</td>
</tr>
</tbody>
</table>

*Data are presented as No (%) or No. (mean; SD).
for children likely to be sensitized to more than one allergen, we constructed several multivariate models and examined the multicollinearity between individual sensitization terms. We chose to group grass allergens together in a composite term not only to account for any cross-reactivity but also because the grass pollens would have a similar seasonal and personal exposure distribution. In addition, the use of mite (Der f 1 and/or Der p 1) and grass (ryegrass and/or paspalum and/or plantain) in a model rather than sensitization to individual grass and house dust mite allergens avoided multicollinearity. After adjustment for these factors, sensitization to Alternaria, cat, dog, wattle, or birch was not significantly associated with asthma ever or past hospital admission for asthma. There were too few children who attended the hospital in 1999 sensitized to an Aeroallergen, but not mite or grass allergens, to examine this issue for this group.

To identify confounders, we then examined factors that were associated with asthma status among nonsensitized children. Male sex, low birth weight, sibling number, and maternal or paternal education or employment were not substantially related to asthma among this group. However, factors associated with poor indoor air quality appeared important. For example, a mother smoking in the same room as the child was associated with an increased risk of hospital attendance ever (OR, 2.92; 95% CI, 1.06 to 8.03), and gas heater use was also associated with higher risk (OR, 2.68; 95% CI, 1.06 to 6.80). Thus, the results were also adjusted for these factors. A parental history of asthma was also significantly associated with asthma status. However, as we did not wish to remove the effect of atopy on disease outcomes that may be due to inherited disposition, adjustment for parental history of asthma was not made. After adjustment for child age, maternal smoking in the same room, home gas heater use, and each other, the risk estimates for mite and grass sensitization for each asthma outcome were as follows: asthma ever, 1.42 (95% CI, 0.97 to 2.09) and 2.24 (95% CI, 1.54 to 3.26); past hospital asthma attendance ever, 2.09 (95% CI, 1.18 to 3.71) and 3.02 (95% CI, 1.68 to 5.41); and 1999 hospital attendance, 2.64 (95% CI, 1.47 to 4.76) and 5.65 (95% CI, 2.91 to 10.97), respectively. This indicates that sensitization to any of the three grasses tested was associated with increased risk of asthma status independently of the contribution of house dust mite sensitization, maternal smoking in the same room, and house gas heater use or child age to each of these indicators of asthma status. Of course, the use of a dichotomous classification may not fully utilize the information provided by the skin allergy assessment. To explore this issue, we also examined SPT reactions as continuous variables. Further examination showed that even among children sensitized to Der p 1, that is, a SPT result > 3 mm, wheal size was associated with 1999 hospital admission (OR, 1.16; 95% CI, 1.04 to 1.30) per 1-mm increase (p = 0.008).

### Relationship Between Atopy and Asthma Using Indicators of Disease Frequency and Severity

Figure 1 shows that the proportion of children with atopy, hay fever, or eczema increased with increasing wheeze frequency. The strength of association between either eczema or hay fever and wheeze increased with increasing wheeze frequency. Table 2 shows that the strength of the association between specific allergen sensitization and wheeze also increased with the number of episodes of wheeze over the past year.

The ORs for atopy and various respiratory symptoms are shown in Table 3. Atopy was moderately associated with symptoms such as night cough. Atopy was strongly associated with night wheeze, speech-limiting wheeze, and > 12 episodes of wheeze in the past year with ORs > 4. The proportion of wheeze that was attributable to atopy altered with wheeze frequency. For infrequent wheeze (1 to 3 episodes per year), less than one half was attributable to atopy, but three fourths of frequent wheeze (> 12 episodes) was attributable to atopy. The proportion of respiratory symptoms attributable to atopy increased

### Table 2—Association Between Specific Allergen Sensitization and Wheeze Episode Frequency Over the Past Year in the School Sample*

<table>
<thead>
<tr>
<th>Aerallergens</th>
<th>Episodes of Wheeze in Past Year, No.</th>
<th>1–3</th>
<th>4–12</th>
<th>&gt;12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ryegrass</td>
<td></td>
<td>3.44 (2.28 to 5.19)</td>
<td>2.86 (1.50 to 5.47)</td>
<td>6.21 (2.73 to 14.13)</td>
</tr>
<tr>
<td>Der p 1</td>
<td></td>
<td>2.56 (1.54 to 3.60)</td>
<td>3.06 (1.60 to 5.35)</td>
<td>5.61 (2.50 to 12.38)</td>
</tr>
<tr>
<td>Der f 1</td>
<td></td>
<td>2.67 (1.63 to 4.42)</td>
<td>3.55 (1.81 to 6.90)</td>
<td>3.33 (1.45 to 7.66)</td>
</tr>
<tr>
<td>Cat</td>
<td></td>
<td>3.77 (2.20 to 6.45)</td>
<td>6.91 (3.37 to 14.21)</td>
<td>7.22 (3.06 to 17.14)</td>
</tr>
<tr>
<td>Alternaria</td>
<td></td>
<td>1.38 (0.72 to 2.63)</td>
<td>1.98 (0.81 to 4.87)</td>
<td>10.37 (4.53 to 23.76)</td>
</tr>
</tbody>
</table>

* Data given as OR (95% CI).
with increasing symptom severity and frequency within the population sample (Table 3). A similar pattern was observed for asthma status. Atopy was moderately associated with a history of asthma ever, and only 33% of asthma ever was attributable to atopy. However, atopy was more strongly associated with past hospital attendance ever for asthma, with 54% of this outcome attributable to atopy (Table 3). Atopy was strongly associated with 1999 hospital attendance for asthma (age-adjusted OR, 16.95 [95% CI, 6.76 to 42.48]), and 89% of 1999 asthma attendance at hospital was attributable to atopy in our location. The associations between atopy and respiratory symptoms were not altered substantially by further adjustment for mother smoking in same room and gas heater use and child age. For example, the adjusted associations for atopy and recent wheeze were as follows: 1 to 3 episodes (adjusted OR, 3.42; 95% CI, 2.23 to 5.23; PAF, 47%) and >12 episodes (adjusted OR, 8.70 [95% CI, 3.07–24.55]; 75%). Overall, atopic children appeared overrepresented in the severe or frequent range of the respiratory symptom spectrum in the school sample and also among children who had attended hospital for asthma.

### Discussion

These findings show that the importance of atopy in childhood asthma differs by clinical subgroup. The relative importance of atopy in childhood asthma increases with increasing wheeze frequency and also asthma severity. The major strength of this study is that concurrent population-based and hospital-based child samples were obtained from the same geographic region, allowing a classification of asthma based not only on questions from the ISAAC but also on hospital attendance for acute asthma. The age range of children studied was not large, particularly for the population sample, and adjustment for child age did not alter the study findings. The lung function findings indicated greater airway obstruction among children with frequent wheeze, or children attending hospital in 1999, supporting the assumption that these children had more severe disease.

Similar to other studies, we found the proportion of population-based asthma that was attributable to atopy was low—only one third. However, the proportion of past and 1999 asthma attendance attributable to atopy was higher, with over four fifths of 1999 hospital attendances attributable to atopy. The finding that atopy was more likely to contribute to 1999 hospital attendance than past hospital attendance ever for asthma is consistent with the observation that children with early transient wheeze were more likely to have reduced airway caliber and a mother who smoked, suggesting that other competing causes apart from atopy may be important in the etiology of childhood wheeze that remits by the age of 6 years. An alternative explanation is that the lower response rate for the 1999 hospital sample included a selection bias that favored recruitment of atopic rather than nonatopic hospital attendees. To examine the possible contribution of possible selection bias, we recalculated the PAF due to atopy assuming that the nonresponders from the 1999 hospital sample were no more likely to be atopic than

### Table 3—Comparison of the ORs and PAFs Due to Atopy for Various Respiratory Symptoms in the School Sample

<table>
<thead>
<tr>
<th>Respiratory Symptoms</th>
<th>With Respiratory Symptoms, No.</th>
<th>With Atopy, %</th>
<th>Without Respiratory Symptoms, No.</th>
<th>With Atopy, %</th>
<th>OR (95% CI) for Respiratory Symptoms</th>
<th>PAF, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma ever</td>
<td>245</td>
<td>58</td>
<td>467</td>
<td>39</td>
<td>2.09 (1.52–2.85)</td>
<td>33</td>
</tr>
<tr>
<td>Past hospital attendance ever for asthma</td>
<td>70</td>
<td>73</td>
<td>643</td>
<td>43</td>
<td>3.59 (2.08–6.19)</td>
<td>54</td>
</tr>
<tr>
<td>Night cough</td>
<td>248</td>
<td>58</td>
<td>467</td>
<td>39</td>
<td>2.21 (1.61–3.02)</td>
<td>35</td>
</tr>
<tr>
<td>Chest tightness</td>
<td>188</td>
<td>61</td>
<td>514</td>
<td>39</td>
<td>2.43 (1.73–3.42)</td>
<td>39</td>
</tr>
<tr>
<td>Night wheeze less than once per week</td>
<td>67</td>
<td>75</td>
<td>611</td>
<td>41</td>
<td>4.22 (2.38–7.48)</td>
<td>59</td>
</tr>
<tr>
<td>Night wheeze more than once per week</td>
<td>22</td>
<td>77</td>
<td>611</td>
<td>41</td>
<td>4.88 (1.84–12.40)</td>
<td>62</td>
</tr>
<tr>
<td>Speech-limiting wheeze</td>
<td>35</td>
<td>77</td>
<td>672</td>
<td>44</td>
<td>4.29 (1.95–9.39)</td>
<td>60</td>
</tr>
<tr>
<td>1–3 episodes of wheeze in past 12 mo compared to no wheeze episodes</td>
<td>119</td>
<td>66</td>
<td>526</td>
<td>38</td>
<td>3.27 (2.15–4.97)</td>
<td>49</td>
</tr>
<tr>
<td>4–12 episodes of wheeze in past 12 mo compared to no wheeze episodes</td>
<td>40</td>
<td>68</td>
<td>526</td>
<td>38</td>
<td>3.44 (1.75–6.75)</td>
<td>49</td>
</tr>
<tr>
<td>&gt;12 episodes of wheeze in past 12 mo compared to no wheeze episodes</td>
<td>25</td>
<td>84</td>
<td>526</td>
<td>38</td>
<td>8.70 (3.07–24.55)</td>
<td>75</td>
</tr>
</tbody>
</table>

1–3 episodes of wheeze in past 12 mo compared to no wheeze episodes

4–12 episodes of wheeze in past 12 mo compared to no wheeze episodes

>12 episodes of wheeze in past 12 mo compared to no wheeze episodes

140 Clinical Investigations
the general school population. Even so, > 60% of 1999 hospital cases remained attributable to atopy. A clinical focus on hospital-based rather than population-based childhood asthma may partially explain the development of the belief that almost all childhood asthma has an atopic basis. Hospital-based clinicians may treat a high proportion of children with asthma due to an allergic etiology, but a community-based family physician may not. Thus, the ratio of atopic to nonatopic asthma will vary across the asthma-care continuum.

Within the population-based sample, the proportion of children with atopy increased with increasing wheeze frequency, and three fourths of frequent wheeze (> 12 episodes in past year) was attributable to atopy. These findings are consistent with the concept that nonatopic causes (eg, viral infection) are more important for infrequent wheeze. The measure of PAF in asthma etiology is a useful concept to clarify the extent of the possible role of atopy in airway disease. It does, however, include the assumption that aeroallergen sensitization plays a causal role in asthma. Past work suggests this assumption is likely to be correct,13,14 but a causal role has not been proven.12 As Pearce et al12 have previously discussed, the choice of any one positive skin prick test in an aeroallergen battery to classify aeroallergen sensitization into a dichotomous yes/no response will tend to increase attributable fraction estimates. However, the use of only a dichotomous classification to record whether a SPT result is positive or negative reduces the informativeness of the wheal-size response to an allergen. Previously, increasing wheal size to Der p 1 allergen has been shown to be associated with increasing asthma symptoms and bronchial hyperresponsiveness.15 Here, we found that even in children sensitized to Der p 1, wheal size was associated with increased risk of hospital admission. Thus, the conventional use of a yes/no response to skin allergen testing in epidemiologic studies is likely to underestimate the relationship between atopy and disease. In addition, practical limitations for the number of allergens that can be tested at one time may underestimate the true proportion of truly atopic children. Furthermore, the lack of data on concurrent allergen exposure also limits our interpretation of the role of aeroallergen sensitization in child airway disease.

The prevalence of specific atopic sensitization and asthma in 8- to 11-year-old children in from 1991 to 1993 in seven different climatic areas of New South Wales has previously been studied.28 Although the prevalence of child asthma was similar across the regions, children in coastal regions were more likely to be sensitized to house dust mite than ryegrass and Alternaria, but the likelihood of sensitization to ryegrass was increased in temperate southern regions and Alternaria sensitization increased in inland areas.29 Here, house dust mite sensitization was independently associated with hospital attendance for asthma. Interestingly, even after adjustment for house dust mite sensitization, sensitization to ryegrass, paspalum, and/or plantain was strongly and independently associated with hospital attendance for asthma. In our setting, grass pollen exposure may be over the threshold to induce airway obstruction in sensitized children. In general, however, grass pollen sensitization, although associated with seasonal rhinitis, has not been consistently associated with asthma.14 Pollen allergy has been previously recognized to be clinically important in our inland region,29 and these findings indicate that grass pollens are likely to be important in the pathogenesis of childhood atopic disease in the ACT.

A high proportion of children in the school sample appeared to have a history of hospital attendance ever for asthma. This outcome, however, included any attendance at a hospital clinic or emergency department as well as inpatient admissions. Previously, the Australian arm of the ISAAC also reported relatively high hospital use.30 In that study, for 6 to 7 year olds with wheeze over the past year, 14.4% attended the hospital as outpatients and 7.7% attended as inpatients in the preceding 12 months.30 Disease misclassification has been a large problem for asthma epidemiology, and it is unlikely that major progress will occur with regard to disease etiology until we can understand the clinical heterogeneity within the current label of asthma. Our findings suggest that the use of indicators of asthma severity may help delineate atopic and nonatopic asthma. In large studies focusing on airway disease, our findings indicate an improved signal-to-noise ratio for allergen-induced airway disease will be obtained by focusing on symptoms that indicate severe or persistent disease. For example, if one wishes to examine the relationship between bedding and house dust mite allergen-induced airway disease, the choice of severe symptoms as the outcome measure should reduce the level of disease misclassification by identifying a subgroup that is more likely to reflect allergen-induced airway disease rather than airway disturbance due to viral infection or other nonatopic factors. A previous report12 of no association between allergen exposure and asthma may partially reflect the high level of misclassification of exposure (eg, bedroom floor mite allergen level as a proxy measure of inhalational allergen dose) and outcome (eg, asthma ever rather than severe wheeze as an indicator of allergen-induced airway disease). Strachan and Carey31 examined the relationship between feather pillow use and severe wheeze, reporting an
adjusted OR ratio of 0.36 (95% CI, 0.24 to 0.53). Our results suggest that the correct choice of severe wheeze as an outcome measure rather than “asthma” in that study increased the likelihood of detecting an association.

In conclusion, this epidemiologic assessment indicates that atopy contributes substantially to frequent or severe asthma but contributes less to infrequent or mild asthma in childhood. These findings demonstrate that disease severity should be taken into account when examining the relationship between aeroallergen sensitization and childhood asthma.

ACKNOWLEDGMENT: We thank B. Pradith, B. Dunn, and A. Cutting for fieldwork; E. Sebo and Y. Zhang for database management; and D. Bass for allergen advice. We also thank participating children, families, and schools, and the ACT Department of Education, the ACT Catholic Education Office, Calvary Hospital, the Canberra Hospital, and the National Capital Private Hospital for their collaboration.

REFERENCES

1 Sears MR. Epidemiology of childhood asthma. Lancet 1997; 350:1015–1020
12 Lau S, Illi S, Sommerfeld C, et al. Early exposure to house-dust mite and cat allergens and development of child-
25 Stata Statistical Software: release 6.0. College Station, TX: Stata Corporation, 1999