

## Prevention strategies for asthma — primary prevention

### Recommendations

#### Primary prevention

1. With conflicting data on early life exposure to pets, no general recommendation can be made with regard to avoiding pets for primary prevention of allergy and asthma (level III). However, families with biparental atopy should avoid having cats or dogs in the home (level II).
2. There are conflicting and insufficient data for physicians to recommend for or against breastfeeding specifically for the prevention of asthma (level III). Due to its numerous other benefits, breastfeeding should be recommended.

#### Secondary prevention

3. Health care professionals should continue to recommend the avoidance of tobacco smoke in the environment (level IV).
4. For patients sensitized to house dust mites, physicians should encourage appropriate environmental control (level V).
5. In infants and children who are atopic, but do not have asthma, data are insufficient for physicians to recommend other specific preventive strategies (level II).

#### Tertiary prevention

6. Allergens to which a person is sensitized should be identified (level I), and a systematic program to eliminate, or at least to substantially reduce, allergen exposure in sensitized people should be undertaken (level II).

It has been assumed that breastfeeding is preventative against early childhood wheezing and the subsequent development of asthma and that exposure to pets is a risk factor for the development of asthma. Recent studies have brought these general assumptions into dispute, and we considered the available data addressing these 2 important issues.

### Breastfeeding and the risk of asthma

#### Literature review

Publications on asthma and breastfeeding were sought

from the MEDLINE database for the period 1 Jan. 2000 to 31 Jan. 2003 by searching for publications that contained both of these terms anywhere in their title, abstract or MESH subject headings. We retrieved 27 citations, of which 10 were primary studies that had collected and analyzed information on the independent association of breastfeeding and asthma. Publications pertinent to this area that appeared through to December 2004 were reviewed, but they contained insufficient data to modify the recommendations.

#### Current evidence

A meta-analysis of prospective studies examining the relation between breastfeeding and asthma<sup>1</sup> reviewed the literature up to 1999. Among the 41 studies reviewed, 12 comprised more than 8000 children whose average age was 4.1 years. Overall, breastfeeding had a protective effect with respect to diagnosed asthma and recurrent wheeze among children with an atopic predisposition (OR 0.52, 95% CI 0.35–0.79). Of interest, the benefit was less pronounced in studies where participants were followed past the age of 2 years. Since the end of 1999, several more studies have examined this association among children <6 years of age at follow-up, using either prospective<sup>2</sup> or cross-sectional<sup>3,4</sup> designs. The results are quite similar to those reported in the meta-analysis; breastfeeding appears to be protective against wheezing syndromes early in life in similar populations.

Two recent prospective cohort studies have evaluated the association of breastfeeding with the presence of asthma after the age of 6 years. Wright and colleagues,<sup>5</sup> reporting on the Tucson Childhood Respiratory Study, found an excess risk of asthma after the age of 6 years with exclusive breastfeeding lasting for 4 months or more. The effect (OR 8.7, 95% CI 3.4–22.2) was confined to those who were atopic (positive skin-prick test) and whose mother had asthma. Of note, breastfeeding was protective against wheezing that occurred before the age of 2 years. Sears and colleagues<sup>6</sup> reported on a birth cohort of over 1000 children assessed repeatedly between the ages of 9 and 26 years. Breastfeeding for 4 weeks or longer was associated with an increased risk of both atopy measured by positive skin-prick test (OR 1.91, 95% CI 1.42–2.58) and asthma (OR 2.33, 95% CI 1.46–3.72) anytime between the ages of 9 and 21 years. These 2 studies employed more stringent criteria for the diagnosis of asthma than the other studies reviewed.

In support of the findings of these 2 prospective studies,

Takemura and colleagues,<sup>7</sup> in a large cross-sectional study of more than 25 000 schoolchildren, ages 6–15 years, found a small excess of asthma among those who were breastfed for 3 months or more (OR 1.2, 95% CI 1.05–1.36). The size of the effect in this study was likely underestimated by including in the comparison group those with some features suggesting asthma and by mis-classifying infant feeding habits. Infante-Rivard<sup>8</sup> first reported a protective effect of breastfeeding against wheezing that required a visit to the emergency department at age 3 or 4 years. On follow-up of these cases up to 6 years later, breastfeeding was not associated with risk of wheezing that persisted beyond the age of 4 years<sup>9</sup> (no breastfeeding OR 1.24, 95% CI 0.93–1.64). Two further cross-sectional studies using the ISAAC protocol found either a trend toward a protective effect of breastfeeding against wheeze among children aged 5–8 years<sup>10</sup> or the risk of wheezing associated with lack of breastfeeding was only apparent among children aged 7–14 who did not report asthma in the family.<sup>11</sup>

The study that is in most apparent disagreement with the cohort studies of Wright and colleagues<sup>5</sup> (Arizona) and Sears and colleagues<sup>6</sup> (New Zealand) is that of Oddy and associates from Australia.<sup>12,13</sup> In the first report<sup>12</sup> of their prospective cohort study, which was included in Gdalevich and coworkers' meta-analysis,<sup>1</sup> the introduction of milk, other than breast milk, before the age of 4 months was associated with an increase in the cumulative incidence of wheeze and doctor-diagnosed asthma to the age of 6 years, as well as wheeze in the year before the sixth birthday. The risk of asthma with the introduction of cow's milk earlier than 4 months increased by 25% (OR 1.25, 95% CI 1.02–1.52). Therefore, exclusive breastfeeding was again clearly protective of early wheezing syndromes, but also of wheezing between the ages of 5 and 6. In a follow-up report<sup>13</sup> and in contrast to the findings of Wright and colleagues, the authors showed that the association was not dependent on the presence of asthma in the mother. Further clarification of whether the results of this large ( $n = 2187$ ) Australian study clearly differ will have to wait for a report of a more prolonged follow-up to allow direct comparison with other prospective studies.

In summary, although there is clear evidence that breastfeeding protects against early wheezing syndromes (level III), recent evidence suggests that, rather than being protective, breastfeeding may actually increase the risk of persistent asthma of allergic origin (level III). The reasons for this are speculative but may be related to a lower incidence of infectious diseases among breastfed children (hygiene hypothesis). The benefits of breastfeeding, however, are sufficiently clear that this information should not be used to recommend against breastfeeding.

### **Exposure to pets and the risk of allergy and asthma**

Sensitization to allergens is one of the strongest determinants of subsequent development of asthma. Studies

demonstrate a relation between exposure to house dust mite allergens and sensitization as well as between sensitization and asthma.<sup>14–17</sup> Several recent studies have raised the issue of whether the presence of a cat or dog in the home might *decrease* the risk of developing allergy to those allergens.<sup>18–21</sup> Several theories have been put forward to explain the observed phenomenon and a number of studies have recently been undertaken. Data relating to animal exposure suggest important gene–environment interactions. These are of interest, but remain preliminary and not applicable enough to the clinical situation to allow for specific recommendations.

### **Literature review**

Two systematic reviews on this subject from 1998<sup>22</sup> and 2001<sup>23</sup> were reviewed. A MEDLINE search was then performed using the Boolean search approach for asthma, wheezing, and pets including cats and dogs as described by Apelberg et al.<sup>23</sup> Consideration was given to a recent publication reviewing specific studies published from 1991 through 2002.<sup>24</sup> The authors of this publication note that studies “are heterogeneous both in design and in results; some include exposure to birds and rodents, some are of high-risk children only, some look at early life exposure and many have not measured allergic sensitization, all of which makes it difficult to draw out common themes.”<sup>24</sup> The focus of our review is exposure to cats and dogs in early life for its potential in primary prevention. Wherever possible we attempted to define “early life exposure” as noted in a number of studies.

### **Current evidence**

Apelberg and colleagues<sup>23</sup> undertook a systematic review of the scientific literature to the end of 1999 using the following Boolean command: (asthma [all] OR wheeze\*[all]) AND (domestic animal\*[all] OR pets [all]). They defined pet keeping either as occurring within the first 2 years of life, in the past, or exposure to pets preceding the outcome. Thirty-two of the 217 articles they reviewed fulfilled their eligibility criteria. Their pooled risk estimates for asthma and wheezing showed a small effect limited to studies with a study population older than 6 years. Their overall study demonstrated an OR of 1.11 (95% CI 0.98–1.25) for asthma and 1.19 (95% CI 1.05–1.35) for wheezing with pet exposure. Outcomes for those over 6 years of age reached statistical significance with an OR of 1.19 (95% CI 1.02–1.40). This significant impact disappeared in younger children (OR 0.80, 95% CI 0.59–1.08). They concluded that exposure to pets appeared to increase the risk of asthma and wheezing in older children. They noted that a somewhat, but not statistically significant, lower risk among the young children exposed to pets could relate to a protective effect but could also be explained by selection bias.

What does the literature since 1999 tell us? There are 2 areas of focus: sensitization and, more pertinent to the issue, the actual outcome of diagnosed asthma. In all the studies, it is important to clarify the timing of the exposure to pets. If we are considering primary prevention of asthma (or allergy), we really must consider early exposure, preferably focused on the first year of life. Apelberg and colleagues considered exposure to pets at any time before the outcome of asthma or asthma-like symptoms. Their assessment of the literature revealed a slight, but significant, increased risk of wheezing in children >6 years of age and a slightly (although not significantly) decreased risk of wheezing in children 6 years and younger with exposure to pets. This may have been more associated with “early life” exposure.

In terms of sensitization, a Nordic interdisciplinary review of the literature published in 1998 (NORDPET)<sup>22</sup> reviewed 1200 articles of which 89 were selected for further study. The authors focused on exposure to pets in infancy and found an increased relative risk (RR 1.0–1.5) of sensitization, but no significant impact on the development of symptoms.

Lau and colleagues<sup>17</sup> have suggested that “the induction of specific IgE responses and the development of childhood asthma are determined by independent factors.” That is, they note a relation between sensitization to indoor allergens with asthma but no relation between indoor allergen exposure and the presence of asthma or airway hyperresponsiveness in children at 7 years of age. They suggest that development of allergy and development of asthma are parallel events. This comment has evoked responses in letters to the editor, one of which states that “the results could be interpreted as evidence that exposure to early life indoor allergens induces sensitization and causes onset of asthma directly in children which contrasts with the conclusion they came to in their report.”<sup>25</sup> A recent publication from the National Health and Nutrition Examination Survey III by Lanphear and colleagues,<sup>26</sup> reporting on 5384 children, 6–16 years of age, found a significantly increased OR for history of allergy to a pet in children with physician-diagnosed asthma (OR 2.4, 95% CI 1.7–3.3). In that study, the current presence of a pet in the household was also associated with an increased risk of asthma (OR 1.5, 95% CI 1.1–2.1).

Melèn and colleagues<sup>27</sup> also demonstrated that the risk of current severe asthma at 4 years of age was associated with a number of factors including exposure to high levels of cat allergen (Fel d 1 > 8 µg/g dust) as well as to parental smoking during the first 2 years of life. In contrast, Platts-Mills and colleagues<sup>28</sup> carefully studied the immune response among 226 children, 47 of whom had asthma and airway hyperresponsiveness. They demonstrated that increasing exposure to house dust mites was associated with an increase in frequency of sensitization to dust mite allergen, but the highest category of exposure to cat allergen was associated with decreased frequency of sensitization

and a higher prevalence of IgG antibody to Fel d 1. However, the occurrence of sensitization to dust mite or cat allergens was the strongest independent risk factor for asthma (mite: OR 4.2, 95% CI 1.6–11.0 and cat: OR 6.1, 95% CI 2.5–15.2).

Thus, while some debate exists about the relation between level of exposure and sensitization, it is quite clear that sensitization, at least to cats and dust mites, is a significant risk factor for asthma. There remain 2 questions to explore:

1. Does the published evidence support an increase or a decrease in the risk of sensitization to pets with exposure?
2. Is there an increased likelihood of developing asthma with increasing exposure to pets, independent of allergy?

*Does early exposure to cat or dog protect against the subsequent development of allergy?* This question was posed in one of the early studies demonstrating a decreased frequency of positive skin tests in children at 12–13 years of age when they had been exposed to cats during the first year of life.<sup>18</sup> The study enrolled 1649 children at 7–9 years of age and reassessed them at 12–13 years of age. The authors found a lower frequency of allergic rhinitis at 7 and 9 years of age and of asthma at 12–13 years of age in exposed children. The history of pet ownership during the first year of life was obtained at the initial visit at 7–9 years of age. The authors concluded that “pet exposure during the first year of life and increasing number of siblings were both associated with lower prevalence of allergic rhinitis and asthma in school children.”<sup>18</sup>

This was followed by 2 studies from the European Community Respiratory Health Survey,<sup>19,20</sup> both of which demonstrated significant decreased sensitization to cats in young adults if there had been “childhood exposure” to pets. This was in spite of the fact that those who owned cats were significantly more likely to be sensitized to cats than those who did not (OR 1.57, 95% CI 1.20–2.06). One of these studies<sup>19</sup> demonstrated a significant negative relation between adult atopy and the presence of a dog in the home in childhood (OR 0.85, 95% CI 0.78–0.92). The effect of a cat in the home in childhood was not statistically significant unless there was parental allergy in which case there was a significant decrease in the likelihood of atopy (OR 0.86, 95% CI 0.76–0.89).

Subsequent to these publications, a number of additional studies of early life exposure to pets with atopy as the outcome have been carried out. The results have been variable: no change in sensitization risk (2 studies),<sup>29,30</sup> decreased risk of atopy with “furred pets in childhood” (1 study),<sup>31</sup> decreased sensitization to pollen with dogs in the first year of life (1 study)<sup>32</sup> and a decrease in atopy at 6–7 years of age with the presence of 2 or more cats and dogs in the first year of life (1 study).<sup>21</sup>

One study demonstrates a greatly increased risk of sensitization to cats with cat ownership (OR 24.6, 95% CI

3.04–199.05)<sup>33</sup>; however, this was in a group of infants with atopy in both parents. In a New Zealand longitudinal study,<sup>34</sup> among children with a family history of asthma or hayfever, the prevalence of a skin-test reaction to cat at age 13 was 14.9% among those who had a cat in the home in early childhood (up to age 9 years) compared with 27.9% among those without a cat in early childhood ( $p = 0.013$ ). Among those without a family history of hayfever, the prevalence of cat allergy was lower and was unaffected by cat ownership (10.5% v. 9.1%).<sup>34</sup> One study suggests that the “inverse association between current pet ownership and sensitization and hayfever symptoms was partly due to removal of pets in families with sensitized and/or symptomatic children.”<sup>32</sup>

### Exposure to pets in early life and asthma

Studies on this issue are more difficult to interpret because of lack of confirmation of the diagnosis of asthma, with wheezing used as a proxy, and confusion of current and early-life exposure to pets. An important confounder is the removal of pets from homes in families with a high risk for developing allergy and asthma. The issue of choice in having pets in the home and the relation to allergy or asthma in the family is complex and has been difficult to define clearly. Most studies fail to show a difference in prevalence of pets in homes of “allergic families” compared with those of families with no history of allergy.

Nafstad and colleagues<sup>35</sup> followed a population-based cohort of 2531 children born in Oslo, Norway, from birth to 4 years of age. Exposure to pets in early life was not significantly associated with less asthma at the age of 4 years (OR 0.7, 95% CI 0.5–1.1). The authors note that “these findings might also be explained by selection for keeping pets.”

Hölscher and colleagues<sup>36</sup> undertook a questionnaire survey among children from the former East Germany (7611 questionnaires from 5360 different children examined between 1992 and 1999). They noted a nonsignificant inverse association between contact with dogs in the first year of life and lifetime prevalence of asthma (OR 0.68, 95% CI 0.43–1.08).

Litonjua and colleagues<sup>37</sup> followed 226 children <5 years of age for 4 years. Exposure to cat allergen and the presence of a dog in the home were both associated with a decreased risk of wheezing. For the presence of a dog in the home, using a multivariate analysis, the OR was 0.34 (95% CI 0.12–0.98). For Fel d 1 concentrations  $\geq 1$   $\mu\text{g/g}$  the OR for wheezing was 0.61 (95% CI 0.37–1.01).<sup>37</sup>

Celedón and colleagues<sup>38</sup> followed 448 children, who had at least 1 parent with a history of atopy, from birth to 5 years of age. Among those whose mother had no history of asthma, exposure to a cat at 2–3 months of age was associated with a significantly reduced risk of wheezing between the ages of 1 and 5 years (RR 0.6; 95% CI 0.4–0.9). However, among children whose mother had a history of

asthma, such exposure was associated with a significantly increased risk of wheezing by 3 years of age, which progressively increased through to 5 years of age (age 3 RR 2.4; 95% CI 1.3–4.5). There was no association between wheezing and exposure to dogs.

The available literature does not provide conclusive guidance related to exposure to pets in early life with 2 possible exceptions — children with 2 atopic parents and those whose mothers have asthma. In these cases exposure to cats is associated with an increased risk of allergic sensitization or wheezing.

### Implications for research

1. Most studies are cohort studies and represent level III evidence. Prospective, randomized controlled studies may be extremely difficult to undertake because of a strong selection bias. Given the issues raised about the impact of breastfeeding and exposure to pets in early life, more extensive study is critical to define the risk or benefit of these factors.
2. Intervention studies will be difficult to conduct given compliance and contamination issues in the general population.

### Implementation strategies

Families frequently wish to know “what are the current recommendations for protecting against development of allergy and asthma” in subsequent pregnancies and subsequent children.

1. To date, environmental tobacco smoke is the only factor for which there are substantive data to support an absolute recommendation.
2. Promotion of *exclusive* breastfeeding for at least 4 months seems reasonable.
3. For families with biparental atopy, maternal asthma or both, it appears that there are substantive data to recommend against the presence of a cat or dog in the home.

This information could be rapidly disseminated as recommendations from this consensus to primary care practitioners and a brief monograph written for parents.

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