



Sensitization and exposure to pet allergens in asthmatics versus non-asthmatics with allergic rhinitis

A. H. HENRIKSEN*, T. L. HOLMEN† AND L. BJERMER*

*Department of Lung Medicine, Norwegian University of Science and Technology, Trondheim, Norway

†National Institute of Public Health, Community Medicine Research Unit, Verdal, Norway

In sensitized subjects with allergic rhinitis (AR) or asthma, allergen exposure provokes symptoms. Among non-asthmatics with AR, an association between allergen sensitization, pollen season and lower airway inflammation has been demonstrated. Our aims were to compare AR and asthma with regard to patterns of allergen sensitization, the degree of airway hyperresponsiveness (AHR) and levels of exhaled nitric oxide (ENO). Finally, we wanted to relate our findings to previous or current exposure to household pets.

Four hundred and thirty-one adolescents with different clinical phenotypes were randomly selected from a large-scale epidemiological survey. They were investigated with allergy screening, measurements of ENO and a methacholine bronchoprovocation test.

Sensitization to pet allergens (cat, dog and horse) was associated with increased AHR and ENO both in asthmatics and non-asthmatics with AR. The risk of being sensitized to cat allergens was significantly reduced in those who had kept cats *vs.* those who had never kept them. Keeping dogs or horses did not influence the risk of being sensitized to the respective allergens. Only in steroid-naïve, non-smoking asthmatics, a trend towards increased ENO in those sensitized and exposed to cat or dog allergens was seen.

Although sensitization towards pet allergens was associated with inflammation in the lower airways irrespective of clinical phenotype, keeping pets did not increase the risk of being sensitized to pet allergens.

Key words: asthma; allergic rhinitis; allergen sensitization; allergen exposure; household pets.

RESPIR. MED. (2001) 95, 122–129

© 2001 HARCOURT PUBLISHERS LTD

Introduction

Allergic rhinitis and allergic asthma are closely related diseases. They frequently co-exist and are thought to share common predisposing genetic factors that interact with environmental influences such as allergen exposure, sibship size, early childhood infections and ambient air pollution. As part of a Norwegian large-scale epidemiological survey, 46 adolescents with allergic rhinitis (AR) and no respiratory symptoms were randomly recruited to a longitudinal study (1). We found that those sensitized towards both seasonal and perennial allergens were significantly more hyper-responsive to methacholine and had significantly higher levels of exhaled nitric oxide (ENO) compared to those with sensitization towards seasonal allergens only. In the group sensitized only towards seasonal allergens, there was a significant increase in ENO during the pollen season.

Furthermore, in a study of adults with mild or severe asthma, Tunnicliffe *et al.* found that subjects with severe asthma were exposed to higher allergen concentrations than those with mild asthma (2). These findings indicate an association between allergen exposure and lower airway inflammation in sensitized subjects. One may question if the type of allergen sensitization and degree of allergen exposure determine whether a person with allergic rhinitis will subsequently develop asthma.

If there is a continuous process in those having predominantly rhinitic symptoms leading to subsequent development of airway hyper-responsiveness and asthma, the pattern of allergen sensitization and the intensity of allergen exposure are likely to play important roles. However, the results from previous studies on the association between allergen exposure, allergen sensitization and asthma are somewhat conflicting. Warner and colleagues studied the degree of exposure to indoor allergens among Swedish asthmatic children (3). They found a significant association between the concentration of mite in house dust and both the prevalence of sensitivity to house dust mite and the levels of IgE antibodies. Surprisingly, no such relationship between pet allergen concentration in the home

Received 15 September and accepted 9 October 2000.

Correspondence should be addressed to: Prof. Leif Bjerner, Department of Lung Medicine, University Hospital of Trondheim, N-7006 Trondheim, Norway. Tel: +47 73 86 85 94; Fax: +47 73 86 74 24; E-mail: leif.bjerner@medisin.ntnu.no

dust and sensitivity to pets were found. Similar results were reported by Sporik *et al.* from their study of Australian asthmatic children (4). In contrast, in the study by Lindfors and colleagues of young Swedish children, a dose-response relationship between cat exposure or cat allergen levels in dust, and sensitization both to cat and dog was found (5).

We hypothesized that subjects with both allergic rhinitis (AR) and asthma were sensitized to more allergens, especially indoor allergens, than subjects with AR and no asthma. Further, as measurements of dust from homes generally have demonstrated higher allergen concentrations in homes with pets (6,7), we assumed that current pet-keepers were exposed to higher allergen concentrations than those who did not keep pets, and therefore were more likely to have lower airway inflammation.

The first aim of the present study was to compare allergic rhinitis and asthma with regards to patterns of allergen sensitization. The second aim was to see how these different clinical phenotypes were related to the degree of airway hyper-responsiveness and to levels of ENO, both indirect markers of inflammation in the lower airways. The third aim was to find whether exposure to household pets was related to specific allergen sensitization or associated with airway inflammation in adolescents with allergic rhinitis and/or asthma.

Materials and methods

SUBJECTS (FIG. 1)

As part of the Norwegian health survey of North-Trøndelag (HUNT), 8571 adolescents aged 13–19 years (85% of that entire population) were investigated with a

self-administered questionnaire, a structured interview based on ISAAC (8), and a clinical investigation with flow volume spirometry (YOUNG-HUNT) (9). From their answers during the interview, we defined four symptom groups for a phase II study.

(A) Non-asthmatics with allergic rhinitis: 929 subjects (10.8%) reporting allergic rhinitis without respiratory symptoms. (B) Suspected allergic asthmatics: 665 subjects (7.8%) reporting asthma symptoms when exposed to pollen, pets or house-dust. (C) Subjects with suspected non-allergic asthma: 1577 subjects (18.4%) reporting asthma symptoms not related to allergen exposure. (D) Non-symptomatic controls: 4802 subjects (56%) denying hay fever or asthma like symptoms. For further investigation 1123 adolescents were randomly invited. A total number of 722 subjects attended, leaving an overall attendance rate of 64%. Parts of the phase II study have previously been described (1,10). In the present study we have included 100, 138 and 193 subjects from group A, B and D respectively. One subject from group B had not answered the questionnaire and 11 subjects had not experienced any episodes of wheeze during the 12 months preceding the phase II study. They were excluded together with 20 of the controls from group D who reported at least one episode of wheeze during the preceding 12 months.

Adolescents with allergic rhinitis were investigated during the winter season of 1996–1997, subjects with suspected allergic asthma during the non-pollen seasons of 1997 and 1998, and the controls in the period from September 1997 to June 1998. Those who were taking anti-asthmatic drugs were asked not to take inhaled or oral β_2 -agonists for 12 h before the investigation, and smokers were asked to refrain from smoking 30 min before their appointments. A nurse and a physician carried out the investigations. Those with symptoms of lower respiratory

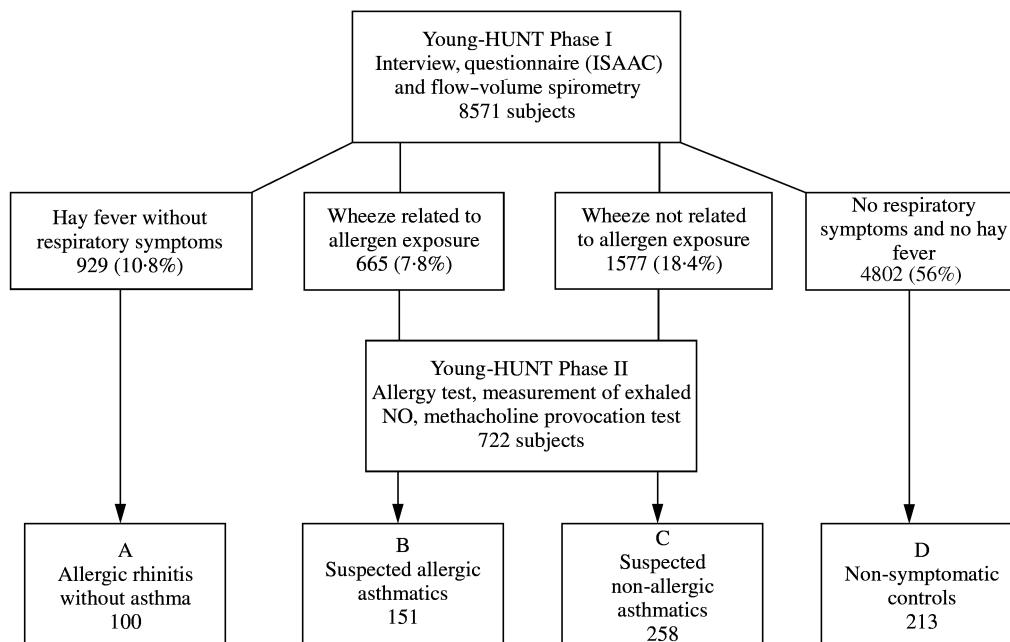


FIG. 1. Flow-chart describing the distribution of subjects through the phase I and the phase II study.

tract infection or sinusitis were not investigated, but tested on a later occasion if possible.

The subjects were not paid for attending the study, and all subjects, as well as the parents of subjects <16 years of age, gave written informed consent prior to participation. The study was approved by the regional ethical committee in Trondheim.

Methods

ALLERGY SCREENING

Allergy screening was performed with serological testing. Specific serum immunoglobulin E (IgE) concentrations for house dust mite, mould, mugwort, timothy grass and birch pollen, and dander from cat, dog and horse were determined (Phadiatop CAPTM and RAST Pharmacia Diagnostics, Lund, Sweden). Specific IgE concentrations were recorded on a scale from 0 to 5, and a test result ≥ 2 was regarded as positive RAST. The sum of test results from five indoor (mite, mould, cat, horse and dog) and three seasonal allergens (timothy grass, birch and mugwort) were calculated separately and referred to as total indoor and total seasonal allergy score respectively.

MEASUREMENTS OF EXHALED NITRIC OXIDE

Measurements of exhaled nitric oxide (ENO) were performed in accordance with the European Respiratory Society (ERS) Task Force (11) with an LR 2000 nitric gas analyzer (Loagan Research Ltd., Rochester, U.K.) and defined in parts per billion. The subjects were in a seated position and exhaled from a total lung capacity against a 5-cm H₂O resistance (in order to close the soft palate) to residual volume. The exhalation and sampling flow rates were 250 ml sec⁻¹ and 250 ml min⁻¹ respectively. For each subject the mean of two acceptable curves with a plateau phase of ENO were registered. All tests of NO were taken prior to the bronchial challenge test.

FLOW-VOLUME SPIROMETRY

Flow-volume spirometry was carried out using a Master-Scope spirometer, software version 4.1 (Erich Jaeger GmbH-Höchberg, Germany). Reference values from Zapletal for subjects up to 18 years (12) and The European Community for Coal and Steel (ECCS) for subjects older than 18 years were used (13).

BRONCHIAL PROVOCATION TESTS

Bronchial provocation tests were carried out with a tidal volume triggered equipment, Automatic Provocation System (APS); Erich Jaeger GmbH-Höchberg, Germany, that delivered a cumulative dose of 2000 µg methacholine in five increments. Subjects with a fall in FEV₁ of 20% or more were defined as having confirmed airway hyper-responsiveness (AHR).

Dose response ratio to methacholine (DRR) was calculated as the maximal fall in FEV₁ divided by the total dose of methacholine given during the bronchoprovocation test. If prechallenge FEV₁ was less than 80% of predicted, a reversibility test was performed. The subjects inhaled 0.5 mg terbutalin, and after 10 min a new flow-volume spirometry was carried out. The test was regarded as positive if there was an increase in FEV₁ of at least 15%.

QUESTIONNAIRE

When attending the investigation, the adolescents answered a questionnaire based on ISAAC (9) where questions from the interview in the phase I study were repeated. During January 1999 the 722 adolescents who had been investigated received a questionnaire concerning if and when they had kept pets. Whether or not the subjects were exposed to pets at the time of investigation was calculated. The response rate was 92%.

STATISTICAL ANALYSES

Statistical analyses of the data were performed by the SPSS Windows 10.0 statistical programme. Data from measurements of dose-response ratio (DRR) and ENO were close to log-normal distributed, thus parametric tests were used with log-values, and results presented as a geometric mean. Unpaired data were analysed with independent samples *t*-tests or Mann-Whitney *U*-test when appropriate. One-way ANOVA tests were applied when more than two groups were compared. Categorical data were analysed with χ^2 tests, and the odds ratio was used to measure the relative risk of being sensitized to allergens from animal dander. Associations between continuous variables were calculated with Pearson's correlation coefficient. Logistic and linear regression analyses were made to assess possible influences of smoking on the association between airway hyper-responsiveness (AHR) and various parameters, and the influence of various RAST scores on levels of AHR and ENO respectively.

Results

ALLERGIC RHINITIS WITHOUT ASTHMA SYMPTOMS

Of the 100 (48 females) adolescents with allergic rhinitis (AR) and no asthma symptoms, allergy-screening tests and acceptable curves of ENO were achieved from 98 and 91 subjects, respectively. All adolescents underwent a methacholine bronchoprovocation test, of which 32 subjects tested positive (AHR+) (Fig. 2). In this group the level of ENO and total RAST scores were significantly increased compared to those who were AHR- [geometric mean 9.0 ppb vs. 6.5 ppb, $P=0.03$ and mean (95%CI) 11 (8.5-13) vs. 7.8 (6.3-9.2), $P=0.02$, respectively (Figs 3 and 4)]. The number of smokers was increased, but not significantly,

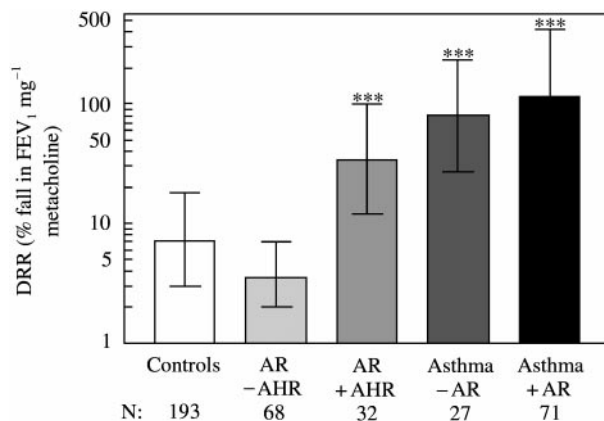


FIG. 2. Dose-response-ratio to methacholine (DRR) and clinical phenotype. AR: allergic rhinitis, AHR: airway hyper-responsiveness. *** $P < 0.001$ when compared to controls. One-way ANOVA: $P < 0.001$ when all five groups are compared.

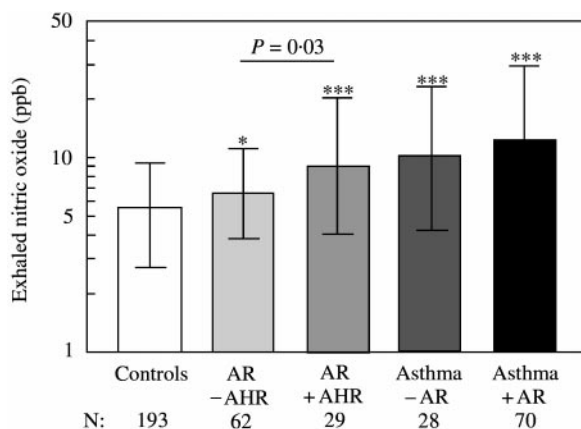


FIG. 3. Levels of exhaled nitric oxide (ENO) and clinical phenotype. AR: allergic rhinitis, AHR: airway hyper-responsiveness. * $P < 0.05$, *** $P < 0.001$ when compared to controls. One-way ANOVA: $P < 0.001$ when all five groups are compared.

among those with AHR+ compared to those with AHR- [25% vs. 12% ($P = 0.09$)].

ASTHMATICS WITH OR WITHOUT ALLERGIC RHINITIS

Of the 138 (67 females) adolescents with asthmatic symptoms on allergen exposure (suspected allergic asthmatics), 102 were AHR+. They were defined as asthmatics and included in the further analyses. An allergy-screening test or acceptable curves of ENO were achieved from 100 and 98 of these adolescents respectively. Of the asthmatics, 74 subjects also reported allergic rhinitis (AR), whereas 28 subjects had no rhinitic symptoms. In asthmatics with AR,

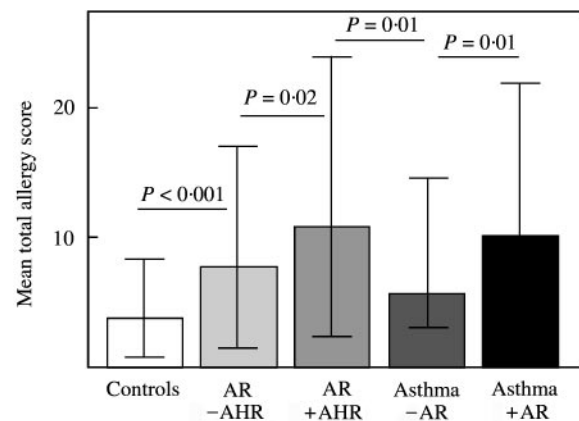


FIG. 4. Mean total RAST scores and clinical phenotype. AR: allergic rhinitis; AHR: airway hyper-responsiveness.

levels of DRR and ENO were increased, but not significantly compared to asthmatics without AR (Figs 2 and 3). However, total RAST scores were significantly increased in the former compared to the latter group, mean (95%CI) 10 (8.3–12) vs. 5.7 (2.7–8.8), $P < 0.01$ (Fig. 4). There was no difference in the number of smokers among asthmatics with or without AR (29% and 24%, respectively).

NON-SYMPTOMATIC CONTROLS

Of the 193 (104 females) controls, allergy screening test or acceptable curves of ENO were achieved from 187 and from all subjects respectively. Among the subjects with no allergic or asthma-like symptoms, 48 subjects (25%) were AHR+ and 43 subjects (23%) had a positive allergy-screening test.

SUBJECTS WITH ALLERGIC RHINITIS AND NO ASTHMA SYMPTOMS VS. SUBJECTS WITH BOTH ALLERGIC RHINITIS AND ASTHMA

For both DRR and ENO there was a continuous increase from the lowest values in the non-asthmatics with allergic rhinitis (AR) and a negative bronchoprovocation test (AHR-) to the highest values in asthmatics with AR (Figs 2 and 3). Among all subjects with AR independent of presence of asthma, sensitization to timothy grass was the most common allergy of the eight allergens tested for, range 63–68%. In a stepwise linear regression model including all RAST scores, the scores for either cat or dog were independently associated with the level of ENO in asthmatics and non-asthmatics with AR. The highest mean value of ENO was found among asthmatics with AR and a positive RAST for cat (Table 1). When the DRR to methacholine was used in the same model, the strongest association found was for sensitization to horse allergen.

TABLE 1. Mean levels of exhaled nitric oxide (95%CI) in asthmatics and non-asthmatics with allergic rhinitis and a negative (0–1) vs. positive (2–5) RAST for cat or dog

Clinical phenotype (subjects)	Cat		Dog	
	RAST Score 0–1	RAST Score 2–5	RAST Score 0–1	RAST Score 2–5
AR and AHR– (62)	6.2 (5.4–7.0)	8.7 (5.2–15)	6.2 (5.4–7.1)	7.9 (5.1–12)
AR and AHR+ (29)	6.8 (4.6–9.9)	13.0* (8.3–22)	6.9 (5.1–9.3)	12.0 (6.9–21)
Asthma and AR (70)	7.8 (6.0–10)	19.6** (15–26)	8.1 (6.1–11)	17.0** (13–23)

AR: allergic rhinitis; AHR+ : airway hyper-responsiveness.

* $P \leq 0.05$; ** $P \leq 0.001$.

Values of exhaled nitric oxide are expressed in parts per billion (ppb).

TABLE 2. Allergen sensitization vs. pet-keeping and the relative risk of being sensitized to a pet allergen in those who have ever vs. never kept the actual pet

Clinical phenotypes (number of subjects)	Cat			Dog		
	Sensitization to cat (%)	Ever kept cat (%)	Relative risk (95%CI)	Sensitization to dog (%)	Ever kept dog (%)	Relative risk (95%CI)
All (350)	56 (16)	141 (40)	0.5 (0.3–0.9) [†]	63 (18)	136 (38)	1.0 (0.5–1.6)
Asthma and AR (61)	32 (43)	21 (34)	0.4 (0.1–1.2)	37 (50)	22 (36)	0.4 (0.2–1.3)
Asthma only (23)	8 (31)	9 (36)	0.2 (0.0–1.7)	8 (31)	12 (48)	1.7 (0.3–10)
Ar and AHR+ (29)	13 (41)*	16 (55)	0.5 (0.1–2.4)	15 (47)**	11 (38)	1.0 (0.2–4.7)
Ar and AHR– (59)	11 (16)	24 (41)	0.2 (0.0–1.5)	13 (19)	26 (44)	1.0 (0.2–4.2)
Controls (178)	4 (2.1)	71 (39)	1.6 (0.2–12)	4 (2.1)	65 (36)	1.8 (0.2–13)

AR: allergic rhinitis; AHR+ : airway hyper-responsiveness.

* $P \leq 0.05$; ** $P < 0.005$ when subjects with AR and AHR+ vs. AHR– are compared; [†] $P \leq 0.05$ χ^2 -relative risk.

However, the intercorrelation between all pet allergens was strong [Pearson's correlation > 0.76 ($P < 0.001$)].

SENSITIZATION TOWARDS INDOOR ALLERGENS VS. PET-KEEPING (TABLE 2)

There were no significant differences between the various groups and the habit of keeping pets. In total, the percentage of subjects who were currently keeping, or had previously kept, pets were 40%, 2.3% and 38% for cats, horses and dogs, respectively. The risk of being sensitized to cat allergen was significantly lower in subjects who had ever kept cats vs. those who had never kept cats, OR (95%CI) 0.5 (0.3–0.9), $P = 0.03$. With respect to dogs or horses, there was no association between ever having kept a pet and the presence of sensitization to the respective pet allergen. Of those who had ever kept cats or dogs, 26% vs. 25% had kept the pet during the first 2 years of life. Among these there was a trend towards an increased percentage of subjects sensitized towards cat or dog allergens compared to all subjects who had ever kept cats or dogs (17% vs. 11%, and 21% vs. 17% respectively). Among the controls,

all subjects who had ever kept cats still kept cats, but among those with allergic rhinitis and/or asthma 33–38% of ever cat-keepers had got rid of their cat. However, the risk of being sensitized to cat allergens was not increased in this group compared to those who were currently keeping or had never kept cats, RR (95%CI) 0.6 (0.2–1.7). The correlation coefficients between sensitization scores for house dust mite and cat or dog were 0.37 ($P < 0.001$) and 0.38 ($P < 0.001$) respectively, and in a linear regression model this association was not influenced by pet-keeping.

SUBJECTS WITH ASTHMA AND/OR ALLERGIC RHINITIS WHO KEPT PETS DURING THE TIME OF THE INVESTIGATION

There were no significant differences in the FEV₁%, DRR, or ENO between those who kept a pet towards which they were sensitized and those who did not keep pets. Among the asthmatics, the percentage who were on inhaled steroids were equal in those who kept pets vs. those who did not (37%), and usage of inhaled β_2 -agonists was the same in

each group. However, in asthmatics who did not smoke or take inhaled steroids there was a trend towards higher levels of ENO, but not DRR, in those who were both sensitized and exposed to cat or dog (five subjects) compared to those who were sensitized, but not exposed (11 subjects) [geometric mean (95%CI) 36 ppb (17–74) and 20 ppb (12–33) respectively, $P=0.15$].

Discussion

In this study we have analysed the influence of pet keeping and sensitization to various allergens on lower airway inflammation in asthma and AR. We found that asthma-like symptoms (wheeze) combined with AHR were associated primarily with sensitization towards indoor allergens. This is partly in line with our previous reported observations where subjects with AR and sensitization towards perennial allergens were believed to be at higher risk of developing asthma, i.e. latent asthmatics, compared to those with sensitization towards seasonal allergens only (1). Very high levels of DRR were found in asthmatics with AR and positive RAST scores (increased levels of specific IgE) for horse or cat. Moreover, among non-asthmatics with AR, sensitization towards cat and dog allergens were associated with AHR. Thus, sensitization to pet allergens is associated with AHR in subjects with asthma or allergic rhinitis. However, levels of ENO were strongly associated to RAST scores for all indoor allergens in all groups, even when AHR or wheeze was absent. These findings are in keeping with the results from the study by Alvarez *et al.*, of inflammation in asthma and perennial allergic rhinitis (14). They found a higher number of eosinophils in induced sputum in non-asthmatics with AR compared to healthy controls. These are interesting findings indicating that allergen sensitization is associated with inflammation in the lower airways even when bronchial hyper-reactivity is absent.

The relationship between allergen exposure and allergen sensitization is frequently discussed. We found a reduced risk of being sensitized to cat allergens in subjects who had ever versus those who had never kept cats. Keeping horses or dogs had no influence on the risk of being sensitized to those pet allergens. While sensitization to cat or dog allergens were significantly more common in the groups with asthma or AR and confirmed AHR, the number of subjects who had ever kept cats or dogs were not increased in these groups. This is in line with the results from the study by Rönmark *et al.* of children from Northern Sweden (15). They found higher prevalence of positive skin prick tests to cat or dog in children who never had a cat or dog at home, and lower prevalence of asthma among children who had ever kept animals at home. However, Roost *et al.* analysed the association of current and childhood exposure to cat with atopic sensitization to cat in the framework of the European Community Respiratory Health Survey (16). They found that while childhood exposure to pets, including cats, was associated with lower sensitization to cats in adulthood, there were positive correlations between the community prevalence of cat and the prevalence of

sensitization to cat, respiratory symptoms, physician diagnosed asthma and current asthma medication.

Pet antigen is commonly found in our society, with significant levels being detected in public places like schools and transport vehicles (6,17,18). Consequently it is virtually impossible to avoid being exposed to pet antigens. In such a situation it is plausible to assume that, in some individuals, keeping pets at home may result in a certain degree of tolerance development. This is partly in agreement with a recent study by Hesselmar *et al.* (19) who found that exposure to cat allergens before the first 3 years of life protected from later development of asthma and atopy. He also demonstrated an increase in both pet-keeping and frequent colds during the first year of life with the number of siblings. Svanes found that atopy was negatively associated with family size (20). Interestingly, Braun-Fahrlander registered that in a rural district in Switzerland, children from farming families were less likely to be sensitized towards specific IgEs to outdoor than indoor allergens (21). He speculates that high exposure to allergens may contribute to the development of tolerance in these children. This may indicate that allergen exposure in early childhood protects from being sensitized or from developing allergic disease later in life. Alternatively, the life-style in pet-keeping families may differ from other families in ways that positively affect the development and priming of the immune system in early childhood. One can assume that living close to a furred animal implicates a source of allergens that enhances Th2 reactivity in predisposed individuals. However, it also represents a source of microbes, which may contribute to a counterbalance of the immune responses. Thus, keeping pets would both stimulate and inhibit allergen sensitization and development of allergic diseases.

In the present study, the possibility of selection bias cannot fully be excluded. Compared to healthy controls, it was a significantly higher percentage of adolescents with allergic rhinitis and/or asthma who had got rid of their cats. This could indicate a selection bias of those with very mild rhinitic or asthmatic symptoms among current cat-keepers. However, the fact that there was no increase in the percentage of subjects sensitized to cat allergen among previous cat-keepers, speaks against such bias. There is a risk that families of adolescents with more severe rhinitic or asthmatic symptoms or with a family history of asthma or allergic rhinitis may have actively decided against keeping pets. However, there were no significant differences in the percentage of current pet-keepers between the various clinical phenotypes, indicating that Norwegian families keep pets regardless of the presence of allergic or asthma like symptoms among family members.

Chakir *et al.* found structural remodelling in bronchial biopsy specimens from the lower airways of non-asthmatic subjects with seasonal allergic rhinitis which were similar to that seen in asthma (22). Thus, we assumed that in subjects sensitized towards indoor allergens to which they were continuously exposed, a long-standing inflammatory process would have led to increased airway hyper-responsiveness and subsequent wheeze. Surprisingly, we found no significant differences in DRR or use of inhaled steroids or

β -agonists between those who kept a pet (cat, dog or horse) to which they were sensitized and those who did not keep a relevant pet. However, when we looked at only steroid-naïve, non-smoking asthmatics, there was a trend towards increased ENO, but not DRR, in adolescents who were both sensitized and exposed to pet allergens. This finding is in keeping with Simpson *et al.* who found significantly elevated levels of ENO in sensitized asthmatics exposed to increased levels of indoor allergens (23). Our study may have been underpowered for such analyses when groups were studied separately. Nevertheless, we believe the observation to be interesting, adding to the understanding of ENO as an indirect parameter of allergen induced inflammation of the lower airways.

In summary, in allergic rhinitis sensitization towards indoor allergens and specially pet allergens were associated with increased DRR and ENO, indicating an ongoing inflammation in the lower airways also in absence of asthma like symptoms. In asthmatics, concomitance of allergic rhinitis was associated with higher total allergy scores and increased DRR and ENO, indicating more severe disease. Keeping pets was not associated with an increased risk of becoming sensitized towards indoor allergens. On the contrary, keeping cats led to a reduced risk of becoming sensitized to cat allergens. Finally, current exposure to pet allergens did not lead to increase in DRR or elevated levels of ENO in general. However, in non-smoking, steroid-naïve asthmatics a tendency towards increased levels of ENO among those both sensitized and exposed to the actual pet was seen.

Acknowledgements

The skilful technical assistance of T. Skaland is greatly appreciated. AHH is funded with a research grant from The Norwegian Research Council. The study is sponsored by The Norwegian Asthma and Allergy Association and by Glaxo Wellcome.

References

- Henriksen AH, Sue-Chu M, Lingaas Holmen T, Langhammer A, Bjermer L. Exhaled and nasal NO levels in allergic rhinitis: relation to sensitization, pollen season and bronchial hyperresponsiveness. *Eur Respir J* 1999; **13**: 301–306.
- Tunnicliffe WS, Fletcher TJ, Hammond K, *et al.* Sensitivity and exposure to indoor allergens in adults with differing asthma severity. *Eur Respir J* 1999; **13**: 654–659.
- Warner AM, Bjorksten B, Munir AK, Moller C, Schou C, Kjellman NI. Childhood asthma and exposure to indoor allergens: low mite levels are associated with sensitivity. *Pediatr Allergy Immunol* 1996; **7**: 61–67.
- Sporik R, Squillace SP, Ingram JM, Rakes G, Honsinger RW, Platts-Mills TA. Mite, cat, and cockroach exposure, allergen sensitization, and asthma in children: a case-control study of three schools. *Thorax* 1999; **54**: 675–680.
- Lindfors A, van Hage-Hamsten M, Rietz H, Wickman M, Nordvall SL. Influence of interaction of environmental risk factors and sensitization in young asthmatic children. *J Allergy Clin Immunol* 1999; **104**: 755–762.
- Dotterud LK, Van TD, Kvammen B, Dybendal T, Elsayed S, Falk ES. Allergen content in dust from homes and schools in northern Norway in relation to sensitization and allergy symptoms in schoolchildren. *Clin Exp Allergy* 1997; **27**: 252–261.
- Dybendal T, Elsayed S. Dust from carpeted and smooth floors. VI. Allergens in homes compared with those in schools in Norway. *Allergy* 1994; **49**: 210–216.
- Asher MI, Keil U, Anderson HR, *et al.* International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; **3**: 483–491.
- Holmen TL, Barrett-Connor E, Holmen J, Bjermer L. Health problems in teenage daily smokers versus nonsmokers, Norway, 1995–1997: the Nord-Trøndelag Health Study. *Am J Epidemiol* 2000; **151**: 148–155.
- Henriksen AH, Lingaas-Holmen T, Sue-Chu M, Bjermer L. Combined use of exhaled nitric oxide and airway hyperresponsiveness in characterising asthma on a large population survey. *Eur Respir J* 2000; **15**: 849–855.
- Kharitonov S, Alving K, Barnes PJ. Exhaled and nasal nitric oxide measurements: recommendations. The European Respiratory Society Task Force. *Eur Respir J* 1997; **10**: 1683–1693.
- Zapletal A, Paul T, Samanek M. Normal values of static pulmonary volumes and ventilation in children and adolescents. *Cesk Pediatr* 1976; **31**: 532–539.
- Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Coal and Steel. Official Statement of the European Respiratory Society. *Eur Respir J* 1993; Mar (Suppl.): 5–40.
- Alvarez MJ, Olaguibel JM, Garcia BE, Rodriguez A, Tabar AI, Urbiola E. Airway inflammation in asthma and perennial allergic rhinitis. Relationship with nonspecific bronchial responsiveness and maximal airway narrowing. *Allergy* 2000; **55**: 355–362.
- Ronmark E, Jonsson E, Platts-Mills T, Lundback B. Different pattern of risk factors for atopic and nonatopic asthma among children—report from the Obstructive Lung Disease in Northern Sweden Study. *Allergy* 1999; **54**: 926–935.
- Roost HP, Kunzli N, Schindler C, *et al.* Role of current and childhood exposure to cat and atopic sensitization. European Community Respiratory Health Survey. *J Allergy Clin Immunol* 1999; **104**: 941–947.
- Almqvist C, Larsson PH, Egmar AC, Hedren M, Malmberg P, Wickman M. School as a risk environment for children allergic to cats and a site for transfer of cat allergen to homes. *J Allergy Clin Immunol* 1999; **103**: 1012–1017.

18. Partti-Pellinen K, Marttila O, Makinen-Kiljunen S, Haahtela T. Occurrence of dog, cat and mite allergens in public transport vehicles. *Allergy* 2000; **55**: 65–68.
19. Hesselmar B, Aberg N, Aberg B, Eriksson B, Bjorksten B. Does early exposure to cat or dog protect against later allergy development? *Clin Exp Allergy* 1999; **29**: 611–617.
20. Svanes C, Jarvis D, Chinn S, Burney P. Childhood environment and adult atopy: results from the European Community Respiratory Health Survey. *J Allergy Clin Immunol* 1999; **103**: 415–420.
21. Braun-Fahrlander C, Gassner M, Grize L, *et al.* Prevalence of hay fever and allergic sensitization in farmers's children and their peers living in the same rural community. SCARPOL team. Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution. *Clin Exp Allergy* 1999; **29**: 28–34.
22. Chakir J, Laviolette M, Boutet M, Laliberte R, Dube J, Boulet LP. Lower airways remodeling in nonasthmatic subjects with allergic rhinitis. *Lab Invest* 1996; **75**: 735–744.
23. Simpson A, Custovic A, Pipis S, Adisesh A, Faragher B, Woodcock A. Exhaled nitric oxide, sensitization, and exposure to allergens in patients with asthma who are not taking inhaled steroids. *Am J Respir Crit Care Med* 1999; **160**: 45–49.