Dog Ownership Enhances Symptomatic Responses to Air Pollution in Children with Asthma.

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Evidence shows that ambient air pollution from combustion sources (Peden 2002), indoor allergens such as those from dogs, cats, and cockroaches (Institute of Medicine 2000), and endotoxin (Michel 2003) all exacerbate asthma. In addition, increasing experimental evidence shows that oxidant air pollutants such as diesel exhaust particulate, nitrogen dioxide, and ozone enhance the effect of inhaled allergen on physiologic responses in the lungs of asthmatics and experimental animals (Diaz-Sanchez et al. 1999; Jenkins et al. 1999; Kehrl et al. 1999; Molinoff et al. 1991). In recent studies, diesel exhaust particulate and O₃ have also been shown to promote the symptoms of asthma of co-exposure to ambient air pollution and endotoxin or indoor allergen exposure. We hypothesized that exposure to indoor allergens and/or endotoxin would enhance the symptomatic response to exposure to ambient air pollution among children with asthma. In this study, we tested this hypothesis in the Southern California Children’s Health Study, a prospective study of air pollution and respiratory health. We previously reported that yearly variation in pollutant levels in the 12 Children’s Health Study communities was strongly associated with yearly variation in the prevalence of chronic cough, phlegm, and bronchitis among asthmatic children in this cohort (McConnell et al. 2003). Cough and bronchitis are nonspecific symptoms among asthmatic children that may represent an acute or chronic exacerbation, upper-airway cough syndrome due to rhinosinus conditions, or related conditions such as gastroesophageal reflux disease (Pratter 2006). However, bronchitic symptoms are a sensitive end point for air pollution effects in population-based studies of children (Braun-Fahrlander et al. 1997). We showed that bronchitic symptoms were associated with air pollution only among children with asthma in this cohort (McConnell et al. 1999, 2003), results that are consistent with those of an earlier study (Dockery et al. 1989). We have now examined whether the effect of ambient air pollution on symptoms was larger among asthmatic participants who owned a dog or cat. Ownership of a dog or cat was used as a marker of indoor exposure to allergens and/or endotoxin, because pet ownership has been shown to be a strong predictor of the concentration of the respective allergen, commonly measured in house dust (Arbes et al. 2004). Although both cat and dog ownership have been associated with indoor endotoxin concentration in house dust, the association has generally been stronger and more consistent for dogs (Gehring et al. 2004; Heinrich et al. 2001; Thorne et al. 2002).

Methods

The design of this longitudinal cohort study and the participants contributing to the current analysis have been described previously (McConnell et al. 2003). Briefly, participants in the Children’s Health Study, a population-based evaluation of air pollution and respiratory health, were recruited from schools in 12 communities in Southern California. A lifetime history of physician-diagnosed asthma was determined based on a questionnaire completed by a parent at study entry. A health questionnaire was administered yearly to children in classrooms. Our present study population included all 475 children with asthma among 3,227 participants in the cohort who completed two or more questionnaires between 1996 and 1999. The primary outcome of interest was the period prevalence of bronchitic symptoms, defined as having any
one of the following: a) a cough first thing in the morning or b) at other times of day that lasted for as much as 3 months in a row during the previous 12 months; c) other than with colds, a child who usually seems congested in the chest or brings up phlegm; or d) a report of bronchitis during the previous 12 months.

Also reported yearly was information on the presence of secondhand tobacco smoke in the home (SHS) and personal smoking by the child. Additional information reported by parents on the questionnaire completed at study entry included ownership of a dog or cat, date of birth, sex, and race/ethnicity. We evaluated other characteristics that potentially could confound the interaction of pets and air pollution, including history of asthma in either parent, family socioeconomic status (SES), housing conditions, and outdoor activity. Families were considered to be of low SES if family income was < $15,000 (or, if income was not reported, if the responding parent had less than a 12th grade education). High SES was defined by family income of ≥ $100,000 (or, if income was not reported, by postgraduate training). Remaining families were classified as middle SES. Housing conditions included a history of mildew or mold or of water damage or flooding in the home while the child lived there, or of cockroaches in the home in the previous 12 months. Time reported spent outdoors was dichotomized for each cohort (1993 and 1996) into those children playing more than the median time outdoors and those playing less. (Time spent outdoors might increase the exposure to ambient air pollution and result in asthma exacerbation in more polluted environments.)

Air pollution monitoring stations were established in each of the 12 study communities. For each year of follow-up, measurements were made for each pollutant, as previously described (Gauderman et al. 2000; Peters et al. 1999). Each station monitored hourly levels of O₃, particulate matter < 10 μm aerodynamic diameter (PM₁₀), and NO₂. PM < 2.5 μm aerodynamic diameter (PM₂.₅) and acid vapor were measured using 2-week integrated samplers. Elemental and organic carbon (EC and OC) were collected in 2-week integrated samples and subsequently analyzed by the National Institute for Occupational Safety and Health method (NIOSH 1996, 1999; Salmon et al. 2000). Annual averages were computed of the 24-hr PM₁₀ and NO₂, and of the 1000- to 1800-hr averages of O₃. This O₃ metric was selected because O₃ has a marked diurnal pattern, with highest concentrations occurring during mid-day and afternoon periods, when children were more likely to be outside and therefore more exposed. Annual averages also were computed from 2-week averages of PM₂.₅, of coarse PM₁₀–₂.₅ (PM₁₀ minus PM₂.₅), of inorganic hydrochloric plus nitric acid vapor, of organic acetic plus formic acid vapor, and of EC and OC. Four-year mean levels (1996–1999) in each community were computed for each pollutant metric. The yearly deviations from the 4-year mean were computed each year for each community.

The study was approved by the institutional review board at the University of Southern California, and informed consent was obtained from participants.

Data Analysis

We examined the distributions of demographic and other characteristics by cat and dog ownership at study entry using descriptive statistics and tests for overall associations. The distributions of yearly temporal variation within communities in pollutants also were examined.

We used a multilevel modeling strategy that we have described previously (Berhane et al. 2004). We examined the effect of the yearly variability in air pollution levels on bronchitic symptoms, and we examined effect modification by dog and cat ownership and other covariates. To describe briefly a two-level logistic model used in this paper, let i, j denote the community, subject, and year of visit, respectively. In the first level, we examined the association between bronchitic symptoms and the deviation of yearly average air pollution from the 4-year average for each community. Xcj – Xcj represents the 4-year average level of air pollution for each community. This analysis included adjustments for time-dependent covariates zci and estimated pollutant effects specific to pet owners and nonowners. The model has the following form (using dog ownership as an example):

\[
\text{logit} \left[ \Pr(ycij) \right] = \alpha_j + \gamma_1Tzci + \beta_1(Xcj - \bar{X}_j)(\text{dog}) + \beta_0(zci) + \epsilon_j + \epsilon_{cij},
\]

where \( \epsilon_{ci} \) and \( \epsilon_c \) are random effects for subject and community, respectively. This model was adjusted for sex, race/ethnicity, income, maternal education, age at study entry, and other characteristics by cat and dog ownership. These represent the dog stratum-specific effect on bronchitic symptoms of the yearly variation in air pollutants within communities. Children did not contribute to the analysis in years for which they were not available to complete the questionnaire. In all models, missing data were assumed to be missing completely at random (Diggle et al. 1994). We also examined stratum-specific effects of air pollution for homes with a dog only, with a cat only, with both pets, and with neither pet.

Because we were interested in how a pet in the home modified the effect of air pollution, we evaluated whether other exposures that might also interact with air pollution accounted for the effects of a dog or cat in the home. Thus, we assessed confounding of the interaction of dog (or cat) ownership with each pollutant by examining the change in the coefficient of this interaction after adjusting for potential confounding by other interactions (such as sex or parental history of asthma, for example) with air pollution. These interaction confounders were entered into the main model one variable at a time. Changes > 10% in the coefficient of interaction for pet ownership with the pollutant were considered to be evidence that effect modification by pets could be explained partially by another variable modifying the effect of air pollution.

Finally, we previously evaluated the main effects of between-community 4-year average pollutant levels on bronchitic symptoms in these children (McConnell et al. 2003). Here we therefore evaluated whether there was an interaction of pet ownership with average
between-community pollutant levels, and we examined whether adjusting for these between-community effects of air pollution affected the within-community temporal variability, which is the primary focus of this analysis. To do this, we modified the second-level model to include community and pet ownership \((p)\) specific intercepts \((A_p)\) as follows:

\[
A_{ij} = A_p + \gamma_2 x_{ij} + \delta_i(dog)_{ij} + \epsilon_{ij},
\]

We then introduced a third-level model of the form

\[
A_p = \psi_0 + \psi_{(dog)}(\bar{x}_c - \bar{x})_{(dog)} + \psi_{(nodog)}(\bar{x}_c - \bar{x})_{(nodog)} + \epsilon_p,
\]

where \(\psi_{(dog)}\) and \(\psi_{(nodog)}\) denote the between-community effects of ambient air pollution (centered by the overall mean pollution levels) by individual pet (e.g., dog) ownership status.

All analyses were conducted using the SAS software version 8.2 (SAS Institute Inc. 1999). The GLIMMIX macro in SAS was used in fitting the logistic mixed-effects regression models. Statistical significance was assessed using a two-sided test at 5% level of significance.

### Results

Among study participants, 184 (39%) had bronchitic symptoms during the first year they contributed to the analysis. Dogs were present in 292 (62%) of homes and cats in 202 (43%) at study entry. Dogs were more common in the homes of boys and less common in the homes of children of low SES (Table 1). Both pets were more common in homes of non-Hispanic white children and in homes in which the parent reported mildew in the previous year. Few children smoked \((n = 11)\). Children with dogs were similar in age (mean ± SD, 12.6 ± 1.95 years) to children without dogs \((12.5 ± 1.73\) years), as was the distribution of children with \(12.6 ± 1.85\) years and without cats \(12.6 ± 1.89\) years.

Some communities had relatively little yearly variability in pollution (Table 2). In the community with the least yearly change in \(\text{NO}_2\), for example, between the least and most polluted year there was a difference of only 1.1 ppb. However, one community varied by about 13 ppb in annual mean \(\text{NO}_2\) concentration between the least and most polluted year. In general, the most variable communities for each pollutant were also those with higher absolute pollutant levels (data not shown).

The association of yearly variability in each pollutant with bronchitic symptoms was consistently larger in children with dogs than without dogs (Table 3). A community with the median range in yearly variability for each pollutant (from Table 2) was selected to scale the effect estimates shown in Table 3 to represent variability that might be common for that pollutant in communities in Southern California. Among children who owned a dog, an increase in the period prevalence of bronchitis was associated with this variability for all pollutants. The smallest increase was observed for \(\text{PM}_{10–2.5}\) \(30\%\) per \(0.29\ \mu\text{g/m}^3\) and the largest for \(\text{OC}\) \(91\%\) per \(1.2\ \mu\text{g/m}^3\), followed by \(\text{EC}\) \(74\%\) per \(0.29\ \mu\text{g/m}^3\). These associations were significantly larger among children without dogs for \(\text{PM}_{10}\), \(\text{PM}_{10–2.5}\), \(\text{EC}\), and both inorganic and organic acid.

### Discussion

In this study, dog ownership modified the effect of exposure to air pollution in children with asthma. Yearly variation in multiple pollutants within the study communities was associated with the prevalence of bronchitis among children with a dog in the home. Effects of air pollution were greatest among children with both a dog and a cat, and effects were generally not observed among children...
with a cat alone. The effect of air pollution in homes with dogs was not explained by questionnaire-reported mildew, flooding or water damage, markers for damp housing and exposure to mold, and possibly house dust mite allergen (Gereda et al. 2001), or by other likely confounders. Therefore, some exposure associated with dogs may be important in augmenting the effect of air pollution.

The effect of dog might be explained by dog allergen or indirectly by an exposure such as endotoxin that is associated with dog ownership. Endotoxin is a component of the cell wall of gram-negative bacteria, and it has been suggested that early-life exposure to endotoxin may protect children from developing asthma and allergy by altering T-cell regulation (Eder and von Mutius 2004). However, inhaled endotoxin produces a marked inflammatory response in the fluid lavaged from the lungs (Jagielo et al. 1996), and in asthmatic subjects endotoxin exposure may cause bronchoconstriction (Michel 2003). In individuals who already have asthma, endotoxin may also contribute to airway remodeling and fixed obstruction in the airways (Reed and Milton 2001). Recently, endotoxin has been shown to enhance the inflammatory effect of inhaled high levels of O3 (Takano et al. 2002), and high levels of PM10–PM2.5 (Elder et al. 2004), diesel exhaust particulate (Platts-Mills et al. 2005). Cats are generally smaller animals, and dogs that walk or roll in endotoxin-laden soil may track more into the home. It has also been suggested that dogs are more likely to disturb house dust, which increases the levels of airborne endotoxin (Platts-Mills et al. 2005). There is limited evidence that higher endotoxin levels occur in homes with both pets than with either alone (Gereda et al. 2001). In our study, although the assessment of effects of air pollution in subgroups with different combinations of cats and dogs was limited by smaller numbers of children in these subgroups, the stronger effects observed in homes with both pets in Table 4 are consistent with an interaction of air pollution with endotoxin.

An alternative explanation for the larger effect of air pollution among children with a dog in the home is that allergen exposure was responsible for modifying the effect of air pollution. Asthmatic subjects allergic to house dust mite who were exposed experimentally to NO2 had larger decrements in forced expiratory volume in 1 sec (FEV1) if they were co-exposed to the allergen (Jenkins et al. 1999). Ragweed and ozone co-exposure among asthmatic subjects allergic to ragweed resulted in larger associated FEV1 decrements than did ragweed alone (Molfino et al. 1991). In another experiment, diesel exhaust particulate enhanced the ragweed-specific immunoglobulin E (IgE) in nasal lavage in response to allergen exposure (Diaz-Sanchez et al. 1997). Therefore, it is plausible that asthmatic subjects allergic to a pet might also have larger air pollution-associated exacerbation of symptoms if there were co-exposure to pet allergen in the home. The generally weaker interactions of cat ownership with air pollution and the absence of an effect of air pollution among children with only a cat in the home suggest that allergen exposure may be less likely to be responsible for the observed effects than endotoxin. Effect modification by allergen might be expected to occur among children allergic to the relevant pet. Allergy to dog dander assessed by IgE seropositivity is uncommon among asthmatic children in Southern California, and allergy to cat dander is common (Ferdman R, unpublished data).

Other interpretations of our results are possible, and additional information about allergy and exposure to pet allergen and endotoxin is needed to evaluate fully our hypothesis that endotoxin is responsible for the observed modification by dogs of the effect of air pollution on bronchitic symptoms. Atopic status to dog and cat allergen was not known for our study population, and only those allergic would be likely to respond to the respective allergen. The relationship between exposure, allergy, and asthma is complex and may vary by age of exposure, especially for ownership of cats, which has been shown to be protective for wheeze and asthma in some studies, perhaps...
observed odds ratio of 1.60 for PM10 among participants with higher concentrations of house dust mite exposure was larger among sensitized asthmatics (Arbes et al. 1999).

The effects of relatively small yearly variations in air pollution were remarkably large. The concentration in pollutants were remarkably large. The consistent independent effects in two-pollutant models (McCann et al. 2003), the absence of a significant interaction of either of these pollutants with dog ownership in this new analysis may indicate that the effect was not attributable to a single pollutant. This is consistent with the known inflammatory effects of these pollutants and the central role of airway inflammation in asthma.

The effects of relatively small yearly variation in pollutants were remarkably large. The observed odds ratio of 1.60 for PM10 among children with dogs (for example), occurred for a modest 0.1 μg/m³ variation between years in average yearly exposure (from Table 3). One possible explanation is that the measured air pollutants were not those responsible for the observed effects in these children, but that they were indicators of other pollutants that varied relatively more between years than the pollutants we measured. Ambient ultracfine particulate matter, for example, has been hypothesized to be responsible for cardiorespiratory effects associated with NO2 (Seaton and Benneman 2003). Ultracfine particle number is known to vary markedly in the Los Angeles Air Basin (Sardar et al. 2004; Zhu et al. 2002).

REFERENCES


