

## Early-Life Environmental Risk Factors for Asthma: Findings from the Children's Health Study

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Early-life experiences and environmental exposures have been associated with childhood asthma. To investigate further whether the timing of such experiences and exposures is associated with the occurrence of asthma by 5 years of age, we conducted a prevalence case-control study nested within the Children's Health Study, a population-based study of > 4,000 school-aged children in 12 southern California communities. Cases were defined as physician-diagnosed asthma by age 5, and controls were asthma-free at study entry, frequency-matched on age, sex, and community of residence and counter-matched on *in utero* exposure to maternal smoking. Telephone interviews were conducted with mothers to collect additional exposure and asthma histories. Conditional logistic regression models were fitted to estimate odds ratios (ORs) and 95% confidence intervals (CIs). Asthma diagnosis before 5 years of age was associated with exposures in the first year of life to wood or oil smoke, soot, or exhaust (OR = 1.74; 95% CI, 1.02–2.96), cockroaches (OR = 2.03; 95% CI, 1.03–4.02), herbicides (OR = 4.58; 95% CI, 1.36–15.43), pesticides (OR = 2.39; 95% CI, 1.17–4.89), and farm crops, farm dust, or farm animals (OR = 1.88; 95% CI, 1.07–3.28). The ORs for herbicide, pesticide, farm animal, and crops were largest among children with early-onset persistent asthma. The risk of asthma decreased with an increasing number of siblings ( $p_{\text{trend}} = 0.01$ ). Day care attendance within the first 4 months of life was positively associated with early-onset transient wheezing (OR = 2.42; 95% CI, 1.28–4.59). In conclusion, environmental exposures during the first year of life are associated with childhood asthma risk. **Key words:** asthma, breast-feeding, cockroach, day care, farm environment, herbicide, pesticide, sibship size, wood smoke. *Environ Health Perspect* 112:760–765 (2004). doi:10.1289/ehp.6662 available via <http://dx.doi.org/> [Online 9 December 2003]

Asthma is the most common chronic disease among U.S. children (Mannino et al. 1998) and is the leading cause of childhood morbidity as measured by hospitalizations and school absences (Weiss and Sullivan 2001). Although a large number of studies of asthma have been conducted, the etiology of childhood asthma remains to be firmly established.

An accumulating body of evidence indicates that both lifestyle factors and environmental exposures during early life may play particularly important roles in asthma occurrence (Johnson et al. 2002). Moreover, timing of such environmental exposures during early development may also be critically important in allergic sensitization and later asthma development. For example, the risks for asthma development associated with exposure to pets, cockroaches, or farming environment appear to vary by age at exposure. Children exposed to cats in the first 2 years of life were sensitized to cat by age 4 and were at increased risk of severe asthma in the presence of secondhand tobacco smoke (Melen et al. 2001). Cockroach sensitization, which often occurs at a very early age in exposed children (Alp et al. 2001), has been associated with increased risk of incident asthma (Litonjua et al. 2001). In a farming environment, children exposed to stables in the first year of life had reduced risk of asthma compared with children who had such exposure after 1 year of age (Riedler et al. 2001). Although early exposure to endotoxin from farm environment is associated with reduced

childhood asthma risk (Braun-Fahrlander 2001), endotoxin exposures later in life may increase asthma occurrence, especially in agricultural settings (Schwartz 2001).

Given the emerging evidence for age-dependent effects of early-life environmental exposures and lifestyle factors in childhood asthma etiology, we hypothesized that environmental exposures in early childhood, especially during the first year of life, are associated with increased occurrence of early transient wheezing and/or early persistent asthma. We further hypothesized that early-life experiences including infant feeding practices, greater sibship size, and day care attendance influence the risk of early childhood asthma. To assess these hypotheses, we conducted a case-control study of risk factors for early-life asthma that was nested in the Children's Health Study (CHS), a population-based study of children's respiratory health in 12 southern California communities.

### Materials and Methods

**Subject selection.** Subjects for this case-control study were selected from the CHS. Details of the CHS have been described previously (Peters et al. 1999a, 1999b). In brief, the CHS is a population-based study in which 6,259 children were recruited from public school classrooms from grades 4, 7, and 10 in 12 communities in southern California. The average classroom participation rate was 82%. The parents or guardians

of each participating student provided written informed consent and completed a self-administered questionnaire.

We used a counter-matched sampling design (Langholz and Goldstein 2001) to select subjects for this nested case-control study. Our study base consisted of 4,244 of the 6,259 children, who were between 8 and 18 years of age at the time of enrollment in the CHS and had completed active follow-up at schools. From these 4,244 children, we selected all children with asthma who had been diagnosed with asthma before 5 years of age ( $n = 338$ ). Matched controls were asthma-free children and were selected randomly from each of the 96 grade-, sex-, and community-specific strata based on the number of cases in each stratum and the cases' *in utero* exposure to maternal smoking status. The number of asthma-free controls ( $n = 570$ ) provided approximately equal numbers of children who were exposed or unexposed to maternal smoking within each sampling stratum. During the study period, mothers of 82.5% cases ( $n = 279$ ) and 72.3% controls ( $n = 412$ ) participated; the remaining mothers could not be located or were unwilling to be interviewed. This resulted in a sample of 691 subjects, with 279 cases and 412 controls. The University of Southern California Institutional Review Board reviewed and approved the study. All subjects gave informed consent.

**Data collection.** The biologic mother of each case and control provided detailed information on demographics, family history of asthma, feeding practices in infancy, day care attendance, household environment (pets, cockroaches, and wood smoke, oil, or exhaust), and farm related exposures (crops or dusts, farm animals, herbicide, and pesticides) by a structured telephone interview. In the absence of biologic mother (i.e., 4.7% of the cases and 9.7% of the

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controls), the biologic father, stepmother, or guardian was interviewed.

**Exposure assessment.** For the environmental exposures, including exposures to cockroach, pets, farm animals, herbicide, and pesticide, we recorded whether the child was ever exposed or never exposed. To have a surrogate measure of particulate air pollutant exposures at home, we asked about child's exposure to wood/oil smoke, soot, or exhaust. Similarly, for exposure to farming lands, we asked about the exposure to farm crops or dust. If the child had had such exposures, we sought information about the ages when those exposures occurred. On the basis of the patterns of exposure in participating children, we were able to define exposure in three periods: *a*) never exposed, *b*) exposed since first year of life that continued after 1 year of age, and *c*) exposed only after first year of life.

We defined exclusive breast-feeding as breast-feeding for at least 4 months after birth without any supplement use. We recorded the total number of siblings (sibs; including half-sibs), number of older siblings at birth, and birth order of the child under study. We categorized the number of siblings at birth into five categories: none, one, two, three, and more than three. We also collected information about any day care center attendance before age 5 and the age when the child first attended such a center.

**Outcome assessment.** We defined asthma status using responses to the question "Has a doctor ever diagnosed this child as having asthma?" We classified the age of onset into early (by 3 years of age) and late (after 3 years of age) onset. An asthma case was assigned as having persistent asthma if the child had *a*) one or more episodes of asthma in the 12 months before study entry, *b*) any wheezing in the 12 months before study entry or after starting first grade, or *c*) medication use for asthma in the 12 months before study entry or after starting first grade. Of the 279 cases, 47 (16.8%) had early transient wheezing, 166 (59.5%) had early persistent asthma, and 66 (23.7%) had late-onset asthma.

**Assessment of confounders and effect modifiers.** Maternal smoking during pregnancy was assessed as ever/never as well as pack-years of smoking. Secondhand tobacco smoke exposure was defined using the number of household smokers (none, 1, > 1) during infancy. Family history of asthma or allergy was defined as any first-degree relative with a diagnosis of asthma or allergy. Yearly family income at the study entry was grouped into six categories: < \$7,500, \$7,500–14,999, \$15,000–29,999, \$30,000–49,999, \$50,000–99,999, and ≥ \$100,000. Maternal education at study entry was categorized into 5 groups: < 12th grade education, completed 12th grade, some college, completed college, and some graduate

education. Race/ethnicity was grouped into four categories: non-Hispanic whites, Hispanics, African Americans, and Asians and others.

**Statistical analysis.** Odds ratios (ORs) of physician-diagnosed asthma were estimated by fitting conditional likelihood logistic regression models accounting for the countermatched sampling using the methods described by Langholz and Goldstein (2001). The number of nonparticipants, including those who declined to participate and those who could not be contacted, was considered in the likelihood. Pairwise conditional logistic regression models were used to assess the role of the exposures in different subgroups of asthma (i.e., early transient wheezing, early persistent, and late-onset asthma) and on age at asthma diagnosis (i.e., asthma diagnosis by age 3 vs. diagnosis after age 3).

We investigated whether education, income, race/ethnicity, secondhand smoke, and maternal or family history of asthma confounded the associations between the exposures of interest and asthma. Potential confounding covariates were included in final models if their inclusion resulted in a 10% change in the parameter estimate. To investigate whether any of these characteristics modified the associations of the exposures of interest with asthma, we compared conditional logistic regression models with and without appropriate interaction terms

using likelihood ratio tests. All tests were two-sided at a 5% significance level. We used the statistical software package (SAS, version 8.2; SAS Institute Inc, Cary, NC) for all analyses.

## Results

Most of the study subjects were white and male and had middle socioeconomic status (SES) with an annual family income of US\$30,000–100,000 (Table 1). Family history of asthma was more common among cases than among controls (41.9 vs. 20.6%;  $p = 0.0002$ ). However, there was no statistical difference in maternal education level, yearly family income, or access to health care measured in terms of health insurance coverage between cases and controls.

Exposure to wood or oil smoke, soot, or exhaust was significantly associated with early-life asthma (Table 2). Children ever exposed to wood or oil smoke, soot, or exhaust were at 1.6-fold higher risk of asthma than those who were never exposed [OR = 1.61; 95% confidence interval (95% CI), 1.03–2.51]. This association appeared stronger when exposure occurred in the first year of life (OR = 1.74; 95% CI, 1.02–2.96). In subgroup analysis, exposure to wood/oil smoke, soot, or exhaust was positively associated with both early- and late-onset asthma. However, the ORs were statistically significant for early transient wheezing, for which exposure since the first year of life was

**Table 1.** Selected characteristics of the countermatched case-control study participants selected from the CHS.

| Characteristics                       | Case <sup>a</sup><br>[No. (%)] | Control <sup>a</sup><br>[No. (%)] | Control frequency<br>corrected for sampling <sup>b</sup><br>[No. (%)] |
|---------------------------------------|--------------------------------|-----------------------------------|---|
| Sex                                   |                                |                                   |   |
| Male                                  | 177 (63.4)                     | 234 (56.8)                        | 1,382 (52.3)  |
| Female                                | 102 (36.6)                     | 178 (43.2)                        | 1,259 (47.7)  |
| Race/ethnicity                        |                                |                                   |   |
| Non-Hispanic white                    | 164 (58.8)                     | 266 (64.6)                        | 1,524 (57.7)  |
| Hispanic white                        | 66 (23.7)                      | 89 (21.6)                         | 792 (30.0)  |
| African American                      | 13 (4.6)                       | 22 (5.3)                          | 96 (3.6)  |
| Asian and other                       | 36 (12.9)                      | 35 (8.5)                          | 229 (8.7)   |
| Maternal education                    |                                |                                   |   |
| < 12th grade                          | 19 (6.9)                       | 54 (13.4)                         | 313 (12.2)  |
| 12th grade                            | 63 (22.8)                      | 101 (25.0)                        | 686 (26.6)  |
| Some college                          | 137 (49.6)                     | 195 (48.3)                        | 1,127 (43.7)  |
| College                               | 24 (8.7)                       | 22 (5.4)                          | 212 (8.2)   |
| Some graduate                         | 33 (12.0)                      | 32 (7.9)                          | 239 (9.3)   |
| Annual family income (U.S. dollars)   |                                |                                   |   |
| < \$7,500                             | 17 (6.8)                       | 28 (7.7)                          | 100 (4.2)   |
| \$7,500–14,999                        | 20 (8.0)                       | 58 (15.9)                         | 320 (13.4)  |
| \$15,000–29,999                       | 40 (16.0)                      | 59 (16.2)                         | 478 (20.1)  |
| \$30,000–49,999                       | 58 (23.0)                      | 98 (26.8)                         | 654 (27.4)  |
| \$50,000–99,999                       | 99 (39.4)                      | 102 (27.9)                        | 662 (27.8)  |
| ≥ \$100,000                           | 17 (6.8)                       | 20 (5.5)                          | 170 (7.1)   |
| Health insurance coverage             |                                |                                   |   |
| No                                    | 26 (9.4)                       | 62 (15.2)                         | 447 (17.0)  |
| Yes                                   | 250 (90.6)                     | 346 (84.8)                        | 2,180 (83.0)  |
| Family history of asthma              |                                |                                   |   |
| No                                    | 150 (58.1)                     | 296 (79.4)                        | 2,008 (80.4)  |
| Yes                                   | 108 (41.9)                     | 77 (20.6)                         | 489 (19.6)  |
| In utero exposure to maternal smoking |                                |                                   |   |
| No                                    | 211 (75.6)                     | 149 (36.2)                        | 2,154 (81.6)  |
| Yes                                   | 68 (24.4)                      | 263 (63.8)                        | 487 (18.4)  |

<sup>a</sup>Numbers do not necessarily add up to the total number of cases and controls because of missing data. <sup>b</sup>Predicted number of controls in the cohort based on the sampling plan.

associated with more than 5-fold increased risk (OR = 5.65; 95% CI, 1.97–16.20).

Children ever exposed to cockroaches were also at significantly higher risk for childhood asthma (Table 2). Children exposed to cockroaches in their infancy were at 2-fold higher risk of asthma than those not exposed (OR = 2.03; 95% CI, 1.03–4.02). Any cockroach exposure was associated with early transient wheezing (OR = 3.05; 95% CI, 1.01–9.23). This association derived from exposure to cockroaches after the first year, which was associated with increased risk for early transient wheezing. Exposure to pets was not associated with asthma in our data. Furthermore, specific types of pets (e.g., dogs, cats, birds, and other furry animals) were not associated with asthma (results not shown).

Compared with never-exposed children, children exposed to herbicide and pesticide in the first year of life were significantly at higher risk of asthma, with ORs of 4.58 and 2.39, respectively (Table 3). Exposure beginning after the first year was not associated with increased risk of asthma. When pesticide and herbicide exposures were considered together,

children exposed to any pesticide or herbicide in first year of life were at 2.53-fold higher risk of asthma compared with children who were never exposed to either of those (OR = 2.53; 95% CI, 1.25–5.09). The ORs for the association of exposure to herbicide and pesticide and early persistent asthma were largest for exposure beginning in first year of life (OR = 3.78; 95% CI, 1.70–8.41). Adjustments for exposure to the farm environment did not substantially change the estimates for herbicides and pesticides.

Exposure to farm animals, farm crops, or dust was associated with increased risk for asthma (Table 4). Compared with never-exposed children, those who were ever exposed to farm animals, farm crops, or dust had a 60% increased risk of asthma (OR = 1.60; 95% CI, 1.01–2.52). The risk was larger in children who had these exposures in their first year of life than in those who were exposed thereafter (OR = 1.88 vs. 1.32); however, this difference was not statistically significant. In subset analyses, children with exposures to farm animals and farm crops/dust had elevated ORs for both early transient wheezing and early persistent asthma; however, only the ORs for

the latter category reached statistical significance. Early persistent asthma was statistically significantly associated with exposure in first year of life to farm animals (OR = 3.03; 95% CI, 1.00–9.17) and farm crops/dust (OR = 2.06; 95% CI, 1.02–4.15). Inclusion of herbicides and pesticides exposure status in the regression models did not change the effect estimates for the farm environment.

Sibship size at the time of birth was inversely associated with asthma risk ( $p_{\text{trend}} = 0.01$ ; Table 5). Children who had four or more sibs were at 63% reduced risk of asthma (OR = 0.37; 95% CI, 0.18–0.77) compared with children with one sib. Notably, children with no siblings were at lower risk than were children with one sibling. These associations were independent of day care attendance. We observed a weaker association of asthma with maternal parity than sibship size (data not shown). Effect of sibship size did not vary substantially by asthma categories.

Day care attendance itself was positively associated with early childhood asthma (Table 5). Compared with children who never attended day care centers, those who went to

**Table 2.** Associations between early transient wheezing and any, early-onset persistent, and late-onset asthma and exposures to wood/oil smoke, soot, or exhaust; cockroach; and pets.

| Exposure                                  | Controls No. | Any asthma |                          | Early transient wheezing |                          | Early persistent asthma |                          | Late-onset asthma |                          |
|---|--------------|------------|--------------------------|--------------------------|--------------------------|-------------------------|--------------------------|-------------------|--------------------------|
|   |              | No.        | OR <sup>a</sup> (95% CI) | No.                      | OR <sup>a</sup> (95% CI) | No.                     | OR <sup>a</sup> (95% CI) | No.               | OR <sup>a</sup> (95% CI) |
| Wood/oil smoke, soot, or exhaust exposure |              |            |                          |                          |                          |                         |                          |                   |                          |
| Never                                     | 310          | 201        | 1.0                      | 32                       | 1.0                      | 122                     | 1.0                      | 47                | 1.0                      |
| Ever                                      | 102          | 78         | 1.61 (1.03–2.51)         | 15                       | 4.32 (1.80–10.38)        | 44                      | 1.59 (0.94–2.70)         | 19                | 1.12 (0.52–2.43)         |
| In 1st year and later                     | 60           | 46         | 1.74 (1.02–2.96)         | 10                       | 5.65 (1.97–16.20)        | 22                      | 1.62 (0.84–3.10)         | 14                | 1.35 (0.58–3.16)         |
| Not in 1st year                           | 42           | 32         | 1.44 (0.77–2.68)         | 5                        | 2.99 (0.86–10.41)        | 22                      | 1.57 (0.77–3.21)         | 5                 | 0.73 (0.22–2.42)         |
| Cockroach exposure                        |              |            |                          |                          |                          |                         |                          |                   |                          |
| Never                                     | 364          | 240        | 1.0                      | 38                       | 1.0                      | 143                     | 1.0                      | 59                | 1.0                      |
| Ever                                      | 48           | 39         | 1.57 (0.89–2.75)         | 9                        | 3.05 (1.01–9.23)         | 23                      | 1.44 (0.73–2.84)         | 7                 | 1.32 (0.46–3.88)         |
| In 1st year and later                     | 27           | 26         | 2.03 (1.03–4.02)         | 6                        | 2.27 (0.60–8.60)         | 16                      | 2.13 (0.95–4.78)         | 4                 | 1.85 (0.51–6.69)         |
| Not in 1st year                           | 21           | 13         | 0.99 (0.41–2.42)         | 3                        | 5.09 (1.02–25.43)        | 7                       | 0.66 (0.21–2.10)         | 3                 | 0.85 (0.19–3.92)         |
| Exposure to pets                          |              |            |                          |                          |                          |                         |                          |                   |                          |
| Never                                     | 82           | 58         | 1.0                      | 9                        | 1.0                      | 34                      | 1.0                      | 15                | 1.0                      |
| Ever                                      | 330          | 221        | 1.42 (0.88–2.29)         | 38                       | 2.61 (0.89–7.71)         | 132                     | 1.41 (0.80–2.47)         | 51                | 0.73 (0.32–1.64)         |
| In 1st year and later                     | 224          | 146        | 1.48 (0.88–2.47)         | 23                       | 2.34 (0.72–7.55)         | 90                      | 1.47 (0.80–2.68)         | 33                | 0.78 (0.32–1.90)         |
| Not in 1st year                           | 106          | 75         | 1.35 (0.78–2.33)         | 15                       | 2.90 (0.91–9.25)         | 42                      | 1.32 (0.69–2.53)         | 18                | 0.67 (0.27–1.67)         |

<sup>a</sup>ORs are matched on age, sex, and community of residence, countermatched on *in utero* maternal smoking and adjusted for race/ethnicity.

**Table 3.** Associations between early transient wheezing and any, early-onset persistent, and late-onset asthma and exposures to herbicides and pesticides.

| Exposure                            | Controls No. | Any asthma |                          | Early transient wheezing |                          | Early persistent asthma |                          | Late-onset asthma |                          |
|-------------------------------------|--------------|------------|--------------------------|--------------------------|--------------------------|-------------------------|--------------------------|-------------------|--------------------------|
|                                     |              | No.        | OR <sup>a</sup> (95% CI) | No.                      | OR <sup>a</sup> (95% CI) | No.                     | OR <sup>a</sup> (95% CI) | No.               | OR <sup>a</sup> (95% CI) |
| Herbicide exposure                  |              |            |                          |                          |                          |                         |                          |                   |                          |
| Never                               | 387          | 257        | 1.0                      | 46                       | 1.0                      | 151                     | 1.0                      | 60                | 1.0                      |
| Ever                                | 25           | 22         | 1.20 (0.58–2.47)         | 1                        | 0.26 (0.02–4.36)         | 15                      | 1.36 (0.61–3.01)         | 6                 | 1.21 (0.40–3.68)         |
| In 1st year and later               | 5            | 11         | 4.58 (1.36–15.43)        | 0                        | —                        | 10                      | 10.08 (2.46–41.33)       | 1                 | 2.26 (0.19–27.43)        |
| Not in 1st year                     | 20           | 11         | 0.58 (0.24–1.39)         | 1                        | 0.26 (0.02–4.36)         | 5                       | 0.36 (0.12–1.11)         | 5                 | 1.09 (0.33–3.58)         |
| Pesticide exposure                  |              |            |                          |                          |                          |                         |                          |                   |                          |
| Never                               | 367          | 239        | 1.0                      | 43                       | 1.0                      | 141                     | 1.0                      | 55                | 1.0                      |
| Ever                                | 45           | 40         | 1.61 (0.93–2.79)         | 4                        | 1.27 (0.31–5.28)         | 25                      | 1.82 (0.96–3.45)         | 11                | 1.54 (0.63–3.80)         |
| In 1st year and later               | 23           | 23         | 2.39 (1.17–4.89)         | 3                        | 2.56 (0.44–14.97)        | 17                      | 3.58 (1.59–8.06)         | 3                 | 0.92 (0.21–4.10)         |
| Not in 1st year                     | 22           | 17         | 1.00 (0.46–2.19)         | 1                        | 0.34 (0.02–5.77)         | 8                       | 0.74 (0.28–1.97)         | 8                 | 2.05 (0.68–6.22)         |
| Herbicide and/or pesticide exposure |              |            |                          |                          |                          |                         |                          |                   |                          |
| Never                               | 360          | 232        | 1.0                      | 43                       | 1.0                      | 138                     | 1.0                      | 51                | 1.0                      |
| Ever                                | 52           | 47         | 1.53 (0.91–2.57)         | 4                        | 1.26 (0.30–5.26)         | 28                      | 1.62 (0.89–2.96)         | 15                | 1.83 (0.81–4.17)         |
| In 1st year and later               | 22           | 25         | 2.53 (1.25–5.09)         | 3                        | 2.56 (0.44–14.94)        | 18                      | 3.78 (1.70–8.41)         | 4                 | 1.33 (0.34–5.20)         |
| Not in 1st year                     | 30           | 22         | 0.93 (0.46–1.86)         | 1                        | 0.31 (0.02–5.72)         | 10                      | 0.64 (0.27–1.55)         | 11                | 2.14 (0.81–5.66)         |

<sup>a</sup>ORs are matched on age, sex, and community of residence, countermatched on *in utero* maternal smoking and adjusted for race/ethnicity.

such a center had a 1.6 times higher risk of developing childhood asthma (OR = 1.60; 95% CI, 1.07–2.39). This increased risk was highest when day care attendance occurred before 4 months of age (OR = 2.42; 95% CI, 1.28–4.59). Although risk was increased in all three disease categories, the ORs were stronger for early transient wheezing. Day care attendance before 4 months of age was associated with more than 5-fold increased risk of early transient wheezing (OR = 5.36; 95% CI, 1.33–21.50). Attending day care centers after 1 year of age also increased the risk of early transient wheezing (OR = 3.27; 95% CI, 1.26–8.48).

We found no associations with exclusive breast-feeding and any asthma outcome. We found no significant differences in the associations of breast-feeding with asthma in children by history of maternal or family history of allergy or asthma.

Family or maternal history of asthma, secondhand tobacco exposure, maternal smoking during pregnancy, gestational age, yearly family

income, health insurance coverage, and maternal education level did not confound the association between any of the early-life exposures and asthma outcomes. Therefore, these variables were not included in the final models. Furthermore, none of the associations between the exposures and early-life asthma varied by family or maternal history of asthma or allergy.

### Discussion

In our population-based study of early-life environmental exposures and asthma, we found that exposures to cockroach; wood/oil smoke, soot, or exhaust; pesticide; herbicide; farm environment; and early day care attendance were associated with increased risk for early-life asthma. The associations were strongest when children were exposed beginning in their first year of life or, in the case of day care attendance, in the first 4 months of life. Thus, the present study, in the context of emerging evidence, suggests that the etiology of childhood asthma is complex and may include early-life environmental exposures

as well as factors related to early allergic sensitization.

The effect of wood or oil smoke and cockroaches on childhood asthma was largely restricted to children with early transient wheezing. Combustion of wood liberates nitrogen dioxide, carbon monoxide, sulfur dioxide, and particulate matter, which have been associated with increased occurrence of respiratory illnesses (Larson and Koenig 1994). Oil smoke exposure has been shown to increase asthma risk significantly (Chen et al. 2002). Particulate matter from wood combustion significantly reduced lung function in elementary school children (Koenig et al. 1993). Similarly, exposure to cockroach allergen was associated with almost a 2-fold increased risk of wheeze in the first year of life (Belanger et al. 2003; Gold et al. 1999). In recent reports, cockroach allergen was found to alter bronchial airway epithelial cell permeability by induction of vascular endothelial growth factor (Antony et al. 2002) and was significantly associated with specific serum immunoglobulin E (IgE) levels (Bener

**Table 4.** Associations between early transient wheezing and any, early-onset persistent, and late-onset asthma and exposures to farm animals and farm crops or dust.

| Exposure                           | Controls No. | Any asthma |                          | Early transient wheezing |                          | Early persistent asthma |                          | Late-onset asthma |                          |  |
|------------------------------------|--------------|------------|--------------------------|--------------------------|--------------------------|-------------------------|--------------------------|-------------------|--------------------------|--|
|                                    |              | No.        | OR <sup>a</sup> (95% CI) | No.                      | OR <sup>a</sup> (95% CI) | No.                     | OR <sup>a</sup> (95% CI) | No.               | OR <sup>a</sup> (95% CI) |  |
| Farm animal exposure               |              |            |                          |                          |                          |                         |                          |                   |                          |  |
| Never                              | 361          | 234        | 1.0                      | 41                       | 1.0                      | 139                     | 1.0                      | 54                | 1.0                      |  |
| Ever                               | 51           | 45         | 1.62 (0.91–2.90)         | 6                        | 1.32 (0.37–4.68)         | 27                      | 1.67 (0.84–3.33)         | 12                | 1.22 (0.47–3.17)         |  |
| In 1st year and later              | 17           | 17         | 2.11 (0.89–5.00)         | 2                        | 3.45 (0.58–30.35)        | 12                      | 3.03 (1.00–9.17)         | 3                 | 0.72 (0.16–3.20)         |  |
| Not in 1st year                    | 34           | 28         | 1.41 (0.72–2.76)         | 4                        | 0.88 (0.21–3.77)         | 15                      | 1.29 (0.58–2.87)         | 9                 | 1.60 (0.54–4.77)         |  |
| Farm crop or dust exposure         |              |            |                          |                          |                          |                         |                          |                   |                          |  |
| Never                              | 349          | 222        | 1.0                      | 40                       | 1.0                      | 135                     | 1.0                      | 135               | 1.0                      |  |
| Ever                               | 63           | 57         | 1.51 (0.91–2.52)         | 7                        | 1.13 (0.36–3.52)         | 31                      | 1.64 (0.89–3.03)         | 31                | 1.99 (0.91–4.33)         |  |
| In 1st year and later              | 39           | 36         | 1.71 (0.94–3.14)         | 5                        | 1.24 (0.31–4.91)         | 22                      | 2.06 (1.02–4.15)         | 22                | 1.75 (0.65–4.71)         |  |
| Not in 1st year                    | 24           | 21         | 1.20 (0.55–2.61)         | 2                        | 0.98 (0.17–5.54)         | 9                       | 0.97 (0.35–2.70)         | 9                 | 2.30 (0.81–4.47)         |  |
| Farm animal, crop or dust exposure |              |            |                          |                          |                          |                         |                          |                   |                          |  |
| Never                              | 317          | 195        | 1.0                      | 35                       | 1.0                      | 117                     | 1.0                      | 43                | 1.0                      |  |
| Ever                               | 95           | 84         | 1.60 (1.01–2.52)         | 12                       | 1.59 (0.58–4.34)         | 49                      | 1.72 (1.00–2.94)         | 23                | 1.48 (0.71–3.09)         |  |
| In 1st year and later              | 49           | 45         | 1.88 (1.07–3.28)         | 7                        | 1.92 (0.60–6.16)         | 28                      | 2.33 (1.19–4.54)         | 10                | 1.32 (0.52–3.37)         |  |
| Not in 1st year                    | 46           | 39         | 1.32 (0.73–2.39)         | 5                        | 1.20 (0.29–4.89)         | 21                      | 1.21 (0.59–2.46)         | 13                | 1.64 (0.66–4.05)         |  |

<sup>a</sup>ORs are matched on age, sex, and community of residence, counter matched on *in utero* maternal smoking and adjusted for race/ethnicity.

**Table 5.** Associations between early transient wheezing and any, early-onset persistent, and late-onset asthma and exposures to breast-feeding, number of siblings, and day care attendance.

| Exposure                  | Controls No. | Any asthma |                          | Early transient wheezing |                          | Early persistent asthma |                          | Late-onset asthma |                          |  |
|---------------------------|--------------|------------|--------------------------|--------------------------|--------------------------|-------------------------|--------------------------|-------------------|--------------------------|--|
|                           |              | No.        | OR <sup>a</sup> (95% CI) | No.                      | OR <sup>a</sup> (95% CI) | No.                     | OR <sup>a</sup> (95% CI) | No.               | OR <sup>a</sup> (95% CI) |  |
| Number of sibs            |              |            |                          |                          |                          |                         |                          |                   |                          |  |
| Continuous (0–8 sibs)     | 412          | 279        | 0.88 (0.77–1.02)         | 47                       | 0.79 (0.57–1.09)         | 166                     | 0.93 (0.79–1.11)         | 66                | 0.91 (0.68–1.22)         |  |
| One                       | 119          | 110        | 1.0                      | 21                       | 1.0                      | 60                      | 1.0                      | 29                | 1.0                      |  |
| Two                       | 132          | 87         | 0.74 (0.45–1.19)         | 15                       | 0.63 (0.23–1.75)         | 54                      | 0.86 (0.47–1.58)         | 18                | 0.99 (0.40–2.43)         |  |
| Three                     | 75           | 39         | 0.76 (0.42–1.37)         | 4                        | 0.68 (0.17–2.83)         | 24                      | 0.77 (0.37–1.61)         | 11                | 1.47 (0.53–4.09)         |  |
| Four or more              | 52           | 21         | 0.37 (0.18–0.77)         | 5                        | 0.40 (0.10–1.60)         | 14                      | 0.49 (0.20–1.20)         | 2                 | 0.17 (0.03–0.93)         |  |
| <i>P</i> <sub>trend</sub> |              |            | 0.01                     |                          | 0.22                     |                         | 0.13                     |                   | 0.24                     |  |
| None                      | 34           | 22         | 0.56 (0.26–1.20)         | 2                        | 0.53 (0.09–3.32)         | 14                      | 0.76 (0.31–1.85)         | 6                 | 0.51 (0.13–2.08)         |  |
| Day care attendance       |              |            |                          |                          |                          |                         |                          |                   |                          |  |
| Never                     | 192          | 103        | 1.0                      | 12                       | 1.0                      | 64                      | 1.0                      | 27                | 1.0                      |  |
| Ever (0–5 years)          | 220          | 176        | 1.60 (1.07–2.39)         | 37                       | 2.93 (1.20–7.15)         | 102                     | 1.55 (0.96–2.48)         | 39                | 1.57 (0.77–3.19)         |  |
| Before 4 months           | 46           | 42         | 2.42 (1.28–4.59)         | 12                       | 5.36 (1.33–21.50)        | 23                      | 2.00 (0.96–4.17)         | 7                 | 1.66 (0.51–5.45)         |  |
| Between 4–12 months       | 30           | 26         | 1.57 (0.76–3.21)         | 3                        | 1.01 (0.19–5.40)         | 22                      | 2.13 (0.95–4.76)         | 1                 | 0.45 (0.05–4.16)         |  |
| After 1st year            | 144          | 108        | 1.42 (0.92–2.21)         | 20                       | 3.27 (1.26–8.48)         | 57                      | 1.29 (0.76–2.19)         | 31                | 1.74 (0.81–3.72)         |  |
| <i>P</i> <sub>trend</sub> |              |            | 0.19                     |                          | 0.05                     |                         | 0.34                     |                   | 0.19                     |  |
| Exclusive breast-feeding  |              |            |                          |                          |                          |                         |                          |                   |                          |  |
| < 4 months                | 280          | 163        | 1.0                      | 32                       | 1.0                      | 100                     | 1.0                      | 31                | 1.0                      |  |
| ≥ 4 months                | 121          | 111        | 1.34 (0.88–2.04)         | 14                       | 1.34 (0.54–3.33)         | 62                      | 1.27 (0.77–2.11)         | 35                | 1.98 (0.96–4.07)         |  |

<sup>a</sup>ORs are matched on age, sex, and community of residence, counter matched on *in utero* maternal smoking and adjusted for race/ethnicity.

et al. 2002). Our results are consistent with observations that early transient wheezing is associated with reduced lung function and/or increased reactivity of the airways in infancy and that exposure to combustion products and/or cockroach allergen may be important in these pathophysiological processes.

The associations between asthma and the environmental exposures examined in this study were not due to confounding by SES. Although lower SES was significantly associated with sensitization to cockroach exposure and asthma prevalence in previous studies (Sarpong et al. 1996; Stevenson et al. 2001), most of our subjects belonged to middle socioeconomic class as evidenced by the relatively higher maternal education level and annual family income > \$30,000, and most had health insurance coverage. In this SES-homogeneous population, we did not observe any significant association between asthma and cockroach exposure with SES or race. In addition, subjects were matched on community of residence, further restricting the variability in SES.

We did not observe an association between pet exposures and childhood asthma, findings that are consistent with several birth cohort studies (Lau et al. 2000; Nafstad et al. 2001; Ronmark et al. 2002). Although some studies have found positive associations (McConnell et al. 2002; Zheng et al. 2002), others have found pets to be protective (Hesselmar et al. 1999; Remes et al. 2001). In a review of 32 articles, presence of pets in the first 2 years of life was associated with a nonsignificant 11% increase in asthma risk (Apelberg et al. 2001). It is difficult to explore the association of pet exposure and childhood asthma even in prospective studies because of concerns over temporality and other lifestyle factors that might be associated with pet keeping. For example, families with asthma or allergic disease might avoid keeping pets. Further prospective studies are needed to examine the associations between childhood asthma and age at pet exposure, duration of pet exposure, and measured levels of allergens and endotoxin.

Although studies have observed positive associations between asthma and pesticide and herbicide use in adults (Bener et al. 1999; Hoppin et al. 2002), data on pesticides and childhood asthma are limited. We found that exposure to either pesticides or herbicides, beginning in the first year of life, was associated with an increased risk for early-onset persistent asthma. The exposures occurred in both farm and nonfarm settings in our study. Our results are consistent with a previous study that reported > 3-fold increased risk of asthma in children between 7 and 10 years of age who had at least 0.3 µg/L of the organochlorine compound dichlorodiphenyldichloroethene in their blood (Karmaus et al. 2001b). It has been suggested that children's hand-to-mouth

behavior, closeness to the playground, low ratio of skin surface to body mass, reduced ability to detoxify toxic substances, and increased sensitivity of cholinergic receptors to pesticides make them more vulnerable to the toxic effects of pesticides, especially during their early lives (Ernst 2002; Faustman et al. 2000; Landrigan et al. 1999). Moreover, immature respiratory systems and immune systems as well as developing nervous systems may be more vulnerable to the deleterious effects of pesticide and herbicide. Given the widespread use of pesticides and herbicides in the home and farm environments and the magnitude of the observed risks, additional studies of the role these exposures in asthma etiology across childhood are needed.

Several European cross-sectional studies have suggested a reduced risk of asthma with early-life exposures to a farming environment (Riedler et al. 2001; Von Ehrenstein et al. 2000). It has been suggested that exposure to a farming environment (e.g., livestock, dust, crop) causes higher levels of bacterial endotoxin exposure, and the latter eventually leads to the production of several cytokines (e.g., interleukin-12, interferon- $\gamma$ ) that tip the balance toward the  $T_H1$ - over  $T_H2$ -mediated immunity, thereby reducing asthma risk (Braun-Fahrlander 2001). However, we did not see such an inverse association with early-life farm exposures in our study. In fact, our results suggest an increased risk for early-onset persistent asthma with farm-related exposure, and we observed a significant increased risk of asthma in children who were exposed to farm animals, crops, or dust in their first year of life. Other studies in the United States and Canada have found that growing up in a farming environment is associated with increased risk of asthma and that endotoxin exposures may increase asthma risk. Explanations for this discrepancy between studies include differences in farming practices, crops, and differences in dietary, lifestyle, and other unrecognized "rural" factors that might influence this risk reduction in Europe but not in California and other regions of the world. Moreover, it has been suggested that proximity of the stables to the home and time spent in such stables might be important determinants for assessing asthma risk in the European studies (Braun-Fahrlander 2001). We were not able to address these issues because we did not have appropriate information on our study subjects.

Our finding of a protective role of sibship size on asthma is consistent with the results of many epidemiologic studies (Infante-Rivard et al. 2001; Wickens et al. 1999). Infections from older siblings during early life have been proposed to prevent asthma by enhancing the  $T_H1$ -mediated immunity (Strachan 2000). However, the contrasting increased risk with early-life day care attendance is not consistent with an explanation for the sibship association. Although

parity was not as strongly associated with asthma as sibship size, part of the protective effect of birth order is likely to be imparted *in utero*, because studies have shown that cord blood IgE, mononuclear cell proliferative responses, and essential fatty acids reduce significantly with increasing parity or birth order (Devereux et al. 2002; Karmaus et al. 2001a). We also observed that children with no siblings were at lower risk for asthma than were children with one or two siblings, a finding that suggests the need for a more complex "hygiene hypothesis."

Our finding of an increased asthma risk for early transient wheezing with day care attendance agrees with the findings of several cross-sectional studies (Nafstad et al. 1999; Wickens et al. 1999). Moreover, we observed that the risk of asthma is highest when children were sent to day care centers before 4 months of age. This finding fits the hypothesis that respiratory infections spread in early childhood from day care centers (Celedon et al. 1999) and thereby increase the risk of early transient wheezing (Castro-Rodriguez et al. 1999). If early-life infections protected children from asthma, then we would have expected to observe a reduced risk of developing asthma in children sent to day care centers in their early lives. Although we observed a significant reduction in asthma risk in children with larger sibship size, day care attendance was not protective for asthma occurrence in any of our asthma categories. Taken together, our data support the hypothesis that early-life infections increase the risk for early transient wheezing, and the protective effect of having many siblings may result from differences in the *in utero* environment with successive pregnancies or other aspects of lifestyle in larger families.

The present study has several strengths as well as some limitations. Our study was nested in a large population-based cohort of children from 12 communities with a wide range of exposures. We used a well-characterized cohort as our population and employed an innovative sampling design to maximize efficiency while minimizing confounding. However, our results are based on cross-sectional data and are subject to the biases of this design. We defined asthma status using parental report of physician-diagnosed asthma. Although medical practice may vary among providers, this case definition has been widely used in epidemiologic studies of asthma. Parental report of physician diagnosis has been found to accurately reflect physician diagnoses (Burr 1992). We did not use parental recall of early-life wheezing episodes because recall of transient wheezing is less complete. Our environmental exposure assessment was broad and based on questionnaire responses. It is likely that inaccurate recall produced some misclassification in exposure status. However, because it is unlikely that a mother of a case or a control

would differentially recall her child's exposures during and after his or her first year of life, this misclassification is likely nondifferential. Furthermore, most of the children's exposures continued beyond age 5 (73.6% for cockroach and > 90% for all the other exposures), suggesting that their home environment did not change appreciably in relation to these exposures over time or after the children were diagnosed with asthma. In this situation, we believe that recall was accurate enough to obtain the information to classify subjects for these chronic exposures. The temporal relationship between exposure and outcome is always a concern when assessing the validity of a study that collected data cross-sectionally. Because many of the exposures of interest in this study are not widely appreciated as asthma risk factors, the retrospective recall in this study would likely have been nondifferential and would bias the ORs toward the null. One exception may be the reports about the presence of pets in the home. Our lack of association may be caused by mothers of children with asthma not reporting pets, because pets are often the focus of clinical interventions. We do not believe that there is likely to be any bias in reporting the number of children at home or child's age at attending day care. The latter might be related to maternal occupation, and it seems unreasonable to assume that mothers would fail to remember when they had sent their children to day care centers on return to work. Furthermore, it is not likely that recall bias accounts for the stronger associations in the first year of life, because recall of early-life exposure status by mothers is unlikely to be more accurate for their child's first year of life than for later years of life. Given that we observed associations using questionnaire-based exposure status, these associations may be stronger if true exposure status was known and misclassification nondifferential. We lacked information on some exposures of interest including presence of fungi, molds, and gas stoves in the house. Levels of dust mites are generally low in the southwestern United States and as such are unlikely to explain our results. We cannot rule out the possibility of chance as an explanation for observing some significant results in subgroup analyses.

In conclusion, our results suggest that environmental exposures and lifestyle factors are important for early-life asthma development and both indoor and outdoor environmental exposures in the first year of life may play crucial roles in the etiology of childhood asthma. Exposures to herbicides, pesticides, and the farm environment in the first year of life may increase the risk for early-onset persistent asthma, a subtype of asthma associated with long-term morbidity. Interventions to reduce the burden of asthma may need to target early life as a critical window for asthma

pathogenesis. Given the enormous burden from childhood asthma, further research is needed to assess the role of these and other environmental exposures during critical windows of development.

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