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Diesel Exhaust Exposure, Wheezing and Sneezing

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The rising incidence of allergic disorders in developed countries is unexplained. Exposure to traffic related air pollutants may be an important cause of wheezing and asthma in childhood. Experimental evidence from human studies suggests that diesel exhaust particles, constituents of fine particulate matter less than 2.5 microns ($PM_{2.5}$), may act to enhance IgE mediated aeroallergen sensitization and Th2 directed cytokine responses. To date, epidemiologic investigations indicate that children living in close proximity to heavily travelled roads are more likely to be atopic and wheeze. The Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS) birth cohort study was initiated to test the hypothesis that early high exposure to traffic related air pollutants is associated with early aeroallergen sensitization and allergic respiratory phenotypes. Using an exposure cohort design, more than 700 infants born to atopic parents were recruited at age 1 living either less than 400 meters (high traffic pollutant exposure) or greater than 1,500 meters (low exposure) from a major road. Children were medically evaluated and underwent skin prick testing with aeroallergen at screening, and re-evaluated sequentially at ages 1, 2, 3, 4, and 7. In this study, both proximity and land use regression (LUR) models of traffic air pollutant exposure have been assessed. Proximity to stop and go traffic with large concentrations of bus and truck traffic predicted persistent wheezing during infancy. The LUR model estimated elemental carbon attributable to traffic (ECAT) as a proxy for diesel exhaust particulate exposure. High ECAT was significantly associated with wheezing at age 1 as well as persistent wheezing at age 3. High mold exposure predicted a well defined asthma phenotype at age 7.

Key Words: Air pollution; childhood; asthma; allergy; diesel

INTRODUCTION

In the past 30 years, the prevalence of atopic sensitization, allergic rhinitis and asthma has increased dramatically particularly in younger populations. This trend has been most noticeable in westernized and developing countries. To explain these developments, multiple hypotheses have been proposed linking allergic disease phenotypes with environmental exposures unique to modern urban environments. The most popular explanation for this phenomenon is the notion that changes in host and environmentally encountered microbes can modify regulatory elements of the immune system in such a way that favors persistence of Th2 biased immune responses (i.e., "the hygiene hypothesis") in early childhood. Immune deviation to Th2 could be influenced by reduced numbers of viral and bacterial infections during infancy via routine immunizations or vigorous use of broad spectrum antibiotics, or via early dietary patterns that could alter the intestinal microbiota during the first year of life. For example, atopic disease has been associated with less diverse gut microbiota early in life with higher counts of Bacteroides, Clostridium, Enterobacteriaceae and Staphylococcus.[1]

In addition, a variety of other host and environmental predictors of childhood asthma have been investigated. For example, there is considerable evidence replicated in multiple studies that indices of obesity (e.g., body mass index) is a significant predictor of childhood asthma.[2] Early prenatal and postnatal exposure to environmental tobacco smoke has been associated with decreased lung growth and childhood asthma.[3] Early exposure to ETS during infancy may enhance potential for later sensitization to environmental allergens.[4]

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Other evidence supports a heretofore unproven hypothesis that environmental exposure to traffic pollutants early in life, and particularly diesel exhaust particles (DEPs), may have adjuvant immune effects by enhancing risk of sensitization to common aeroallergens and increase likelihood of development of allergic disorders. Limited epidemiologic evidence suggested that higher exposure to traffic related pollutants may enhance risk for allergy. In one report, children living in close proximity to heavily traveled roads and highways were more likely to be atopic.[5] High exposure to traffic-related particles has been shown to exacerbate preexisting asthma and has been associated with reduced lung function and increased frequency of emergency department visits for asthma.[6,7] Recently, exposure to traffic pollutants has been associated with development of incident asthma in children without preexisting asthma. In a longitudinal study of school-aged children, McConnell reported that modeled exposure to non-freeway traffic related pollutants at home and at school increased risk for development of new onset asthma.[8] Other reports suggest that higher exposure to outdoor pollutants may reduce lung growth in children reflected by diminished lung function.[9]

Experimental studies conducted in human volunteers have also lent support to the idea that diesel traffic pollutant exhaust constituents may have potential to act as immune adjuvants that may promote IgE mediated allergic sensitization. Diaz-Sanchez et al.[10] reported that nasal exposure to DEPs greatly enhanced ability to induce IgE mediated sensitization to a neoantigen, key limpet hemocyanin (KLH). The same group also demonstrated that nasal exposure to DEP could enhance nasal production of TH2 cytokines as well as IgE after nasal allergen challenge among subjects already sensitized to short ragweed allergen.[11] Exposure to DEP was shown to enhance histamine (and presumably mast cell activation) measured in nasal lavage following nasal house dust mite allergen challenge.[12] Furthermore, following acute inhalation of diesel exhaust particles, proinflammatory effects in the airways have been demonstrated including increased numbers of bronchial neutrophils, mast cells, CD4+/CD8+ T-lymphocytes with upregulation of adhesion molecules, ICAM-1 and VCAM-1.[13] One postulated regulatory mechanism based on an experimental murine study is that DEPs can inhibit IFN gamma production, thereby enhancing Th2 cytokine mediated inflammation.[14]

Genetic susceptibility to the effects of DEP have also been studied in human subjects with allergic rhinitis. Because, glutathione-S-transferases (GSTs) can metabolize reactive oxygen species generated by DEPs, it has been postulated that genetic functional variants could increase risk for DEP associated health effects. In one study, ragweed allergic subjects possessing GSTM1 null or the GSTP1 105 wildtype genotypes exhibited enhanced nasal specific IgE and histamine responses after allergen challenge in the presence of diesel exhaust particles.[15]

THE CINCINNATI BIRTH COHORT STUDY OF ALLERGY AND AIR POLLUTION

These aforementioned earlier studies created a great deal of interest leading to consideration of long term epidemiologic studies to identify possible links between early exposure to traffic pollutants and development of allergic disease in childhood. Because no long-term epidemiologic prospective or longitudinal studies had been published, a team of investigator at the University of Cincinnati, Department of Environmental Health proposed a birth cohort study in 2001 to address these questions. The hypothesis stated that infants with high exposure to traffic pollutants would have a different pattern of aeroallergen sensitization and greater risk for development of atopic disorders in early childhood when compared to infants living distant from traffic.

In 2001, a birth cohort observational study of infants born in the Greater Cincinnati region was initiated. The study recruited "high risk" infants born to at least one atopic parent. All subjects' parents received and signed informed consent statements approved by the University of Cincinnati Institutional Review Board and the consent process was repeated at each visit. For inclusion, at least one parent was required to exhibit a positive allergic history combined with a positive skin prick test to at least one common aeroallergen. This study was a controlled cohort design recruiting either subjects living less than 400 meters or greater than 1,500 meters from a major road. Children were evaluated at screening, and sequentially at ages 1, 2, 3, 4, and 7. Clinical evaluations at each visit included: a medical and environmental history and physical examination; prick skin testing to a panel of regional indoor and outdoor aeroallergens (i.e., pollen, mold spores, house dust mite, cat, dog, and cockroach) and two food antigens (egg white and milk). Shortly after enrollment at age 1, an indoor home assessment visit was conducted collecting information about indoor climactic conditions, visible water damage, visible mold and number of pets. In addition, house dust samples were collected at age one from the floor of the primary living areas in subjects homes. House dust samples were extracted and analyzed for endotoxin, β-glucan and specific indoor allergen levels (Fel d1, Canf1, Bla g1, and Der f1).[16]

Traffic pollutant exposure models were measured in two ways. First, a proximity model of exposure was determined based on the distance of the primary dwellings of subjects from major roads that were classified according to the type of traffic. For the proximity model infants' exposure was classified or defined as: 1) stop and go traffic or less than 100 meters from bus routes and highways with traffic speeds less than 50 miles per hour; 2) moving traffic defined as less than 400 meters from major roads with truck traffic of greater than 1,000 vehicles a day; and 3) unexposed defined as living more than 400 meters from bus routes or major roads.[17]

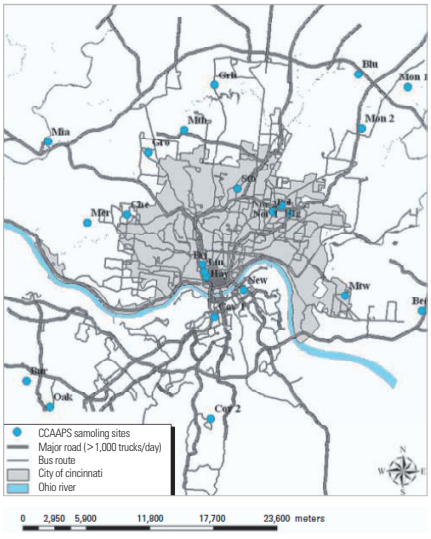
The second model used in the studies employed land use regression (LUR) models for estimating personal exposure to traffic pollutants in primary residences and schools of the children.[18] In the CCAAPS Study, this was achieved by measuring elemental carbon in $PM_{2.5}$ air samples collected in 27 sampling sites in the Greater Cincinnati area during the first year of the study. The advantage of measuring particulate matter constituents is the high spatial variability and sharp drop in the exposure gradient as distance increases from road sources of roads heavily traveled by buses and trucks. In this case, elemental carbon extracted from $PM_{2.5}$ samples, was used as a signature of exposure. In addition to quantifying elemental carbon concentration, the LUR model incorporated key univariate predictors including major roads within 400 meters, bus routes located within 100 meters of dwellings, number of trucks within 400 meters per day and land elevation. The final estimate of personal exposure to traffic related pollutants is referred to as "elemental carbon attributable to traffic" or ECAT. As shown in Figure, average daily ambient ECAT exposure was estimated at each sampling site in the Greater Cincinnati Area.[21]

Year 1 clinical outcomes

As noted, the study was performed in a high risk birth cohort comprised of infants born to known atopic parents. Therefore it was not surprising that in the first year a very high prevalence of skin prick test reactivity was detected to both aeroallergens and selected food antigens. In fact, skin prick test reactivity to at least one of 17 allergens (including 15 aeroallergens, egg white and milk) was confirmed in 29% of 680 infants, with 18% reacting to at least one of 15 aeroallergens.[19] Interestingly, only 68% of the cohort exhibited persistent aeroallergen sensitization when retested at two years of age and 60% of infants were no longer skin test positive to milk and/or eggs at age two. Atopy was found to be a significant risk factor for habitual snoring among infants.[20]

"Wheezing not associated with a cold" during the first year of life was a major outcome captured by questionnaire using a validated question from the international ISAAC study. In year one, the frequency of wheezing without a cold was greater than twice that observed among non-white infants versus white infants.[17] Using the aforementioned proximity model of exposure that utilized a geographic information system (GIS), it was determined that infants living less than 100 meter from stop-and-go bus and truck traffic had a significantly increased likelihood (OR=2.5; 95% CI, 1.15-5.42) of wheezing in year 1 when compared with unexposed infants were those living more than 400 meters from a major road. From this study, it appeared that distance from roads was a better predictor of wheezing than actual estimated traffic volume. Because there was concern that proximity models of exposure could result in exposure misclassification, Ryan et al.[21] developed the aforementioned LUR model in order to estimate personal exposure to elemental carbon attributable to traffic (ECAT) as a surrogate marker of diesel exhaust exposure. As mentioned, variables included in the model were locations of major roads, bus routes, truck traffic count, and elevation. After adjusting for other significant predictors of recurrent wheezing without a cold in year one, ECAT levels ranging from 0.30 to 0.90 μg/m^3 were significantly associated with infant wheezing (Table). In fact, infants exposed to the highest ECAT level (0,90 μg/m^3) were approximately four times more likely to have recurrent wheezing during infancy. Based on comparison with exposure based on the proximity model, ECAT was believed to more accurately estimate individual exposure in subjects' homes, avoiding exposure misclassification.[21]

The relationship of genotypes, environmental factors and clinical outcomes were evaluated year one. Smith et al.[22] examined IL 13 and IL4 receptor single nucleotide polymorphisms



Site	Average daily ECAT (μg/m^3)[a]
Bee (Beechmont)	0.34
Blu (Blue Ash)	0.45
Bri (Brighton)	0.96
Bur (Burlington)	0.39
Che (Cheviot)	0.40
Cov (Covington) 1	0.69
Cov (Covington) 2	0.29
Grh (Greenhills)	0.35
Gro (Groesbeck)	0.28
Hay (Hays)	0.98
Hig (Highland)	0.35
Lin (Linn)	0.85
Mer (Mernic)	0.20
Mia (Miamitown)	0.49
Mon (Montgomery) 1	0.28
Mon (Montgomery) 2	0.38
Mth (Mt. Healthy)	0.35
Mtw (Mt. Washington)	0.36
New (Newport)	0.58
Nor (Norwood) 1	0.32
Nor (Norwood) 2	0.72
Oak (Oak Brook)	0.26
Pol (Police)	0.35
Stb (St. Bernard)	1.02

[a]Samples collected December 2001-December 2004.

Figure. The Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS) ambient $PM_{2.5}$ monitoring network[21]

Table. AORs (95% CIs) for ECAT exposure levels and wheezing without a cold adjusted for sex, race, maternal smoking, child care attendance, breast-feeding, pet ownership, and visible mold in the home[21]

Exposure to ECAT (μg/m^3)	AOR (95% CI)
0.2	1.00 (reference)
0.3	1.23 (1.01-1.50)
0.4	1.51 (1.01-2.26)
0.5	1.86 (1.02-3.39)
0.6	2.29 (1.03-5.09)
0.7	2.82 (1.04-7.65)
0.8	3.46 (1.05-11.49)
0.9	4.26 (1.06-17.2)

AORs, adjusted odds ratios; CIs, confidence intervals; ECAT, elemental carbon attributable to traffic.

among 560 one year old infants whose parents consented to provide DNA. Environmental tobacco smoke exposure interacting with the CT/TT IL-4C-589T SNP showed a significant tenfold increased risk of wheezing in African American but not Caucasian infants. Schroer et al.[23] were able to identify a gene environmental interaction in the CCAAPS study involving a glutathione-S-transferase (GST)-P1 Ile105Val polymorphism. High ECAT exposure was associated with a signficantly increased risk of persistent wheezing at ages 12 and 24 months among children with the (GST)-P1 Val variant allele.

Prior studies have suggested that exposure to indoor endotoxin and pets can modify allergic disease phenotypes in childhood. Campo et al.[16] reported on modifying effects of indoor endotoxin and pets on clinical outcomes during infancy assessed in the CCAAPS cohort. In this study, it was evident that endotoxin levels measured in settled house dust correlated with numbers of dogs in house. A reduced risk of recurrent wheezing without a cold during year one was detected in infants living with two or more dogs in combination with the presence of high house dust endotoxin. In this study, number of siblings in the house, attendance at day care, history of parental asthma, maternal smoking and increased number of upper respiratory infections were additional factors that predicted recurrent wheezing during year one.[16]

The effects of early exposure to mold and fungal components were also studied this birth cohort. Specifically, exposure to high levels of (1-3)-Beta-D-glucan, a fungal cell wall component, was associated with significantly reduced risk of recurrent wheezing during infancy. This outcome was most pronounced in allergen-sensitized subjects.[24] Cho et al.[25] assess the relationship between visible mold exposure, measured house dust mite allergen (Der f1) in settled dust, and recurrent wheezing at age one. In this study, it was surprising that HDM allergen (Der f1) concentration greater than 2 μg/g of house dust was measurable in only 16% of infants homes surveyed. Although there was no relationship between HDM levels and wheezing, visible mold or major water damage in the home was significantly associated with the two fold risk of wheezing in all infants and six fold increase risk among atopic infants. Thus it was concluded that visible mold (but not house dust mite exposure) was a significant risk factor for recurrent wheezing during infancy.[25]

Year 3 and 4 clinical outcomes

As mentioned, subjects participating in this high-risk birth cohort study were evaluated annually between the ages of 1-4. Allergic eczema, allergic rhinitis and wheeze phenotypes were assessed at age 3. Exposure variants were assessed as predictors of persistent wheezing age three.[18] The ECAT land use regression model was used to estimate time-weighted average exposures in the homes, day care centers, and other locations where children resided from birth through age 36 months. ECAT exposure during the first 12 months was significantly associated persistent wheezing at 36 months. Co-exposure to high levels of endotoxin and ECAT during infancy created a synergistic effect by further increasing likelihood of persistent wheezing at age 3. This finding supported experimental studies in mice showing that co-exposure to endotoxin and diesel particles synergistically enhance generation of reactive oxygen species.

Codispoti et al.[26] investigated host and environmental predictors of allergic rhinitis at age 3. Allergic rhinitis at age three was defined as sneezing, runny, or blocked nose in the prior 12 months and a positive skin prick test to at least one aeroallergen. A major finding was that prolonged breastfeeding in African-American infants and multiple children in the home during infancy were significantly protective of allergic rhinitis at age 3. A positive skin test to milk or egg white or tree pollen at age one significantly increased risk for allergic rhinitis at age 3. The house dust endotoxin level at age 1 modified likelihood of allergic rhinitis at age 3. The risk of allergic rhinitis was positively correlated with house dust endotoxin at medium ranges of endotoxin exposure; at the highest and lowest levels of endotoxin exposure, however, the likelihood of allergic rhinitis at age 3 was significantly reduced.

Environmental and host risk factors were also examined for clinical outcomes of eczema at ages two, three and four. In this cohort, 39% of children were diagnosed with eczema by age three.[27] It was discovered that children living in homes with a pet dog are less likely to develop eczema by ages 1-3 when compared to children without a dog. The modifying effect of dog ownership on expression eczema was significantly increased among subjects with if the CD14-159C/T CC combined genotype, whereas risk of eczema at both ages 2 and 3 was increased in subjects with CD14-159C/T and IL-4R-alpha I75V single-nucleotide polymorphisms (SNPs). Risk factors were also examined in 90 children or 14% of the cohort with eczema at age four.[28] Among children with early positive skin prick tests to dog, not having a dog during the first year of life significantly increased the likelihood of eczema and age four. Among dog owners, however, the risk of eczema was not increased among dog-sensitized children. Cat ownership before age one greatly increased risk of eczema at age four and can sensitized children. Does this study demonstrated that where is dog ownership reduced risk for eczema in dog sensitized children, cat ownership had the opposite effect.

Year 7 clinical outcomes

As already mentioned, children were investigated intensively at ages 1-4. Children were invited to return at age seven two. Informed consent was obtained. In addition to studies performed at prior visits, including medical history and physical examination and skin testing, objective evaluations for asthma were performed. To confirm reported lower respiratory symptoms or physicians diagnose suggestive of asthma, spirometry was performed before and after administration of inhaled bronchodi-

lator. In symptomatic children without airway obstruction or reversibility, methacholine challenge testing was performed. A subset of 176 children from the CCAAPS cohort were studied at age 1 and 7 for indoor exposure to 36 mold spore species using PCR based analysis and expressed as the Environmental Relative Moldiness Index (ERMI). Of these, 18% met the case definition for asthma at age seven using the aforementioned objective criteria. After adjusting for relevant variables, children living in a high mold environment at age one were more likely to develop asthma at age seven when compared to infants living in a lower mold exposure environment. Interestingly, living in air-conditioning at age one reduced risk for asthma at age seven. Allergic sensitization to house dust mite and parental asthma are also significant predictors of asthma at age seven.[29]

CONCLUSIONS

The health effects of traffic air pollutants on infants and children have been investigated. Personal exposure defined by ECAT, an exposure model serving as surrogate measure of diesel exhaust exposure, did not predict allergic rhinitis at ages three and four or atopic dermatitis at ages three or four. It remains to be demonstrated in a longitudinal birth cohort study if high traffic pollutant exposure predicts development of aeroallergen sensitization. However, ECAT exposure during infancy was predictive of wheezing without a cold at age 1 and persistent wheeze at age 3. An exposure interaction of endotoxin and ECAT was demonstrated for persistent wheezing at age 3. Early high level exposure to indoor mold spores is a risk factor for development of childhood asthma. The environmental, host and genetic predictors of asthma at age 7 in the entire CCAAPS cohort are being analyzed and results are forthcoming. As already demonstrated thus far in CCAAPS, it is more likely that interactions of multiple environmental variates will determine mature childhood allergic phenotypes including asthma.

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