ORIGINAL ARTICLE

Timing and Duration of Traffic-related Air Pollution Exposure and the Risk for Childhood Wheeze and Asthma

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Abstract

Rationale: The timing and duration of traffic-related air pollution (TRAP) exposure may be important for childhood wheezing and asthma development.

Objectives: We examined the relationship between TRAP exposure and longitudinal wheezing phenotypes and asthma at age 7 years.

Methods: Children completed clinical examinations annually from age 1 year through age 4 years and age 7 years. Parental-reported wheezing was assessed at each age, and longitudinal wheezing phenotypes (early-transient, late-onset, persistent) and asthma were defined at age 7 years. Participants' time-weighted exposure to TRAP, from birth through age 7 years, was estimated using a land-use regression model. The relationship between TRAP exposure and wheezing phenotypes and asthma was examined.

Measurements and Main Results: High TRAP exposure at birth was significantly associated with both transient and persistent wheezing phenotypes (adjusted odds ratio [aOR] = 1.64; 95% confidence interval [CI], 1.04–2.57 and aOR = 2.31; 95% CI, 1.28–4.15, respectively); exposure from birth to age 1 year and age 1 to 2 years was also associated with persistent wheeze. Only children with high average TRAP exposure from birth through age 7 years were at significantly increased risk for asthma (aOR = 1.71; 95% CI, 1.01–2.88).

Conclusions: Early-life exposure to TRAP is associated with increased risk for persistent wheezing, but only long-term exposure to high levels of TRAP throughout childhood was associated with asthma development.

Keywords: air pollution; asthma; persistent wheeze; childhood

Decades of research have demonstrated that outdoor air pollution exacerbates preexisting asthma (1–4). The role of long-term exposure in the development of asthma, however, is not established (5), and results of cohort studies to date are inconsistent (4, 6–9). Results from the Southern California Children's Health Study have shown traffic-related air pollution (TRAP) and nitrogen dioxide (NO_2), a marker of TRAP, to be associated with incident asthma in school-aged children (8, 10). NO_2 exposure was also associated with lifetime asthma and wheeze among children with allergic disease in Toronto (11). Longitudinal analysis of a birth cohort study in the Netherlands has found evidence of an association between

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At a Glance Commentary

Scientific Knowledge on the Subject: Prior studies examining exposure to air pollution and childhood respiratory outcomes, including wheeze and new-onset asthma, have reported inconsistent results. Few studies, however, have examined the relationship between timing and duration of traffic-related air pollution (TRAP) exposure and childhood wheezing and asthma development.

What This Study Adds to the Field: This study provides evidence that early-life exposure to high levels of TRAP is associated with wheeze symptoms during childhood. Exposure to high levels of TRAP over the first 7 years of life is associated with asthma development.

exposure to air pollution at birth record addresses and the incidence and prevalence of childhood asthma (7). Furthermore, a dose–response association was observed between asthma symptoms and self-reported exposure to truck traffic in the phase 3 International Study of Asthma and Allergies in Childhood (ISAAC), representing more than 500,000 children across the globe (12). However, recent results from the multisite European Study of Cohorts for Air Pollution Effects (ESCAPE) project found no significant association between air pollution exposure and the prevalence of asthma in five European birth cohorts (9). These incongruent results may be due, in part, to differences in study populations, exposure assessment, and outcome definitions. Significant research gaps also remain regarding the effect of cumulative TRAP exposure and most relevant time periods of exposure in relationship to longitudinal wheeze patterns throughout childhood and asthma development.

Asthma is a complex phenotype and difficult to define in early childhood, but its earliest symptoms, including wheeze, appear during the preschool ages (13, 14). Longitudinal studies have identified distinct patterns of childhood wheeze by the age of wheezing onset and the persistence or resolution of symptoms during childhood. These wheeze phenotypes are referred to as early-transient, late-onset, and persistent wheeze (15–17). Although viral infections, familial history of asthma and atopy, and maternal smoking have been identified as important factors in these childhood wheezing phenotypes, the role of TRAP on these remains unclear. Within the complex mixture of gaseous and particulate components of TRAP, diesel exhaust particles (DEP) are of particular concern with respect to health effects. DEP are estimated to contribute up to 90% of the particulate matter derived from traffic sources; are primarily ultrafine in size ($<$100 nm); can be deposited in the nasal and peripheral airways; and have been shown to induce oxidative stress and airway hyperresponsiveness, enhance allergic responses and airway inflammation, and result in a switch to Th2/Th17 phenotypes with associated increased asthma severity (18–20).

The Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS) is a prospective birth cohort study of children in the greater Cincinnati, Ohio metropolitan area (21). Previous cross-sectional analyses have found early childhood exposure to TRAP to be associated with wheezing at age 1 and 3 years (22, 23). The current study uses the strengths of the CCAAPS cohort, including the duration and frequency of longitudinal follow up and exposure characterization throughout the first 7 years of life, to examine the association between TRAP exposure and childhood wheezing and asthma.

Methods

Study Population

CCAAPS children born to at least one atopic parent were recruited from 2001 to 2003. Detailed information regarding the study's objectives, recruitment, environmental exposure assessments, and health evaluations has been reported (21, 22, 24, 25). The University of Cincinnati Institutional Review Board (IRB) approved the study protocol before subject recruitment, and written informed consent was obtained from the parents before participation.

Health Outcomes

Children enrolled in CCAAPS completed clinical examinations at ages 1, 2, 3, 4, and 7 years. At each clinical examination, parents were interviewed regarding the respiratory health of their child, environmental exposures including secondhand smoke (SHS) exposure, demographic characteristics, and addresses of all locations where their child spent 8 or more hours in an average week (e.g., home, daycare, relative's home, school). Although children were not seen in the clinic at ages 5 and 6 years, parents were queried at age 7 years regarding their address history since the time of last clinical examination to estimate TRAP exposure for the time period between ages 4 and 7 years.

Wheeze was defined at ages 1, 2, 3, 4, and 7 years by parental report of the child wheezing two or more times in the previous 12 months. At age 7 years, four wheezing phenotypes were defined based on prior longitudinal studies of wheezing in children (15–17): (*1*) never wheeze: no parental report of wheeze in the previous 12 months at ages 1 through 4 years and at age 7 years; (*2*) early-transient wheeze: parental report of wheeze at ages 1 or 2 or 3 or 4 years but not at age 7 years; (*3*) late-onset wheeze: parental report of wheeze at age 7 years but no wheeze at or before age 4 years; and (*4*) persistent wheeze: parental report of wheeze at age 7 years and at least once between ages 1 and 4 years.

At age 7 years, children completed spirometry according to American Thoracic Society criteria (26). Predicted values of FEV_1 were calculated for children 8 years or younger (27). Children with either an FEV_1 less than or equal to 90% predicted, a physician diagnosis of asthma, asthma symptoms in the last 12 months (tight chest or throat, difficulty breathing or wheezing after exercise, wheezing and/or whistling in the chest), or an exhaled nitric oxide (eNO) level greater than or equal to 20 ppb received 2.5 mg levalbuterol through a nebulizer followed 15 minutes later by repeat spirometry (28). Children with less than 12% increase in FEV_1 had a methacholine challenge test. Children were defined as having asthma if they showed evidence of asthma symptoms and bronchial hyperreactivity ($\geq$12% increase in FEV_1 after bronchodilation) or a positive methacholine challenge test ($\geq$20% fall in baseline FEV_1 at an inhaled methacholine concentration of $\leq$4 mg/ml) (24). At the time of each clinical examination, parents also reported whether their child had ever been diagnosed with asthma by a physician not associated with CCAAPS and, if so, at what age.

TRAP Exposure

Exposure to TRAP was estimated by a land-use regression (LUR) model as previously described (25). Briefly, ambient air sampling was conducted intermittently at 27 sampling sites from 2001 to 2006, and the average concentration of elemental carbon attributable to traffic (ECAT), a marker of the diesel exhaust component of the TRAP mixture (29, 30), was derived at each site. An LUR model was developed to relate the geographic characteristics surrounding the sampling site with the average concentration of ECAT at each site. The LUR model was then applied to all reported addresses (e.g., home, daycare, relative's home, school, etc.) for each child to derive a time-weighted average daily exposure to TRAP in the previous 12 months at each age from birth through age 7 years (25). Average daily TRAP exposure from ages 4 to 6 years, birth to age 4 years, and birth to age 7 years was determined by averaging the time-weighted average TRAP exposures estimated for those years.

Data Analysis

For all models and outcomes, exposure to TRAP was modeled as a categorical variable dichotomized at the 75th percentile, based on the distribution at each year (75th percentile ranged from 0.45 $\mu g/m^3$ at birth record address to 0.39 $\mu g/m^3$ at age 7 yr). Exposure was dichotomized to account for extreme values in the exposure estimates and to minimize potential exposure misclassification due to lack of precision with an estimated continuous measure. As a sensitivity analysis to examine the appropriateness of the dichotomization at the 75th percentile, we conducted an unsupervised model-based cluster analysis (*see* online supplement) (31). The log-transformed TRAP concentrations estimated at birth were found to best group into two normal distributions of concentrations—one with a high mean exposure and one with a low mean exposure. Subjects were classified into these "low" or "high" exposure groups during model estimation, which resulted in a cut point of 0.48 $\mu g/m^3$. This was comparable to the 75th percentile cut point at birth (0.45 $\mu g/m^3$) and resulted in less than 5% of the population being differentially categorized.

Polytomous logistic regression was used to estimate the association between TRAP exposure and wheeze phenotypes (early-transient, late-onset, persistent). The relationship between estimated TRAP exposure at specific ages during childhood including at the birth record address, from birth to age 1, age 1 to 2, 2 to 3, 3 to 4, 4 to 6, and 6 to 7 years, and the average estimated TRAP exposure from birth through ages 4 and 7 years, were investigated in separate models. Similarly, logistic regression was used to examine the association between TRAP exposure during childhood and asthma at age 7 years. As a sensitivity analysis, the association between TRAP exposure and the presence of either asthma or persistent wheeze at age 7 years was also examined. In addition, to examine whether TRAP exposure before asthma diagnosis influenced the time to asthma diagnosis, the parental report of age at asthma diagnosis was analyzed using a Cox proportional hazards regression model. As another sensitivity analysis, the same logistic and hazard regression models were also developed with TRAP modeled as a continuous (log-transformed) variable. The results of all sensitivity analyses are included in the online supplement.

Covariates considered for inclusion in all models were selected based on the literature and included familial history of asthma, race, sex, maternal education, breastfeeding ($<$ or $\geq$4 mo), daycare attendance in the first year of life, SHS exposure in the first year of life (average daily number of cigarettes smoked by household member >0), and the presence of a cat and/or dog in the home during the first year of life. Given evidence that child atopy modifies the effects of TRAP on

Table 1. Demographic Characteristics of the Cincinnati Childhood Allergy and Air Pollution Study Cohort at the Clinical Examination at Age 7 Years

Variable	n (%)*
Sex	
Male	338 (54.8)
Female	279 (45.2)
Race	
White	487 (78.9)
Other†	130 (21.1)
Parental history of asthma	
Yes	217 (35.2)
No	400 (64.8)
Breastfeeding	
$\geq$4 mo	307 (49.8)
$<$4 mo	310 (50.2)
SHS exposure	
Yes‡	188 (30.5)
No	429 (69.5)
Maternal education	
Some college ($\leq$3 yr) or less	226 (36.6)
College($\geq$4 yr) or graduate school	391 (63.4)
Annual household income, $	
$\geq$50,000	336 (54.5)
20,000–49,999	156 (25.3)
$<$20,000	93 (15.1)
Cat present§	
Yes	140 (22.7)
No	476 (77.3)
Dog present§	
Yes	219 (35.6)
No	397 (64.5)
Daycare attendance§	
Yes	244 (41.4)
No	345 (58.6)

Definition of abbreviation: SHS = secondhand smoke.
*Numbers may not add up to 617 because of missing data.
†98% African American.
‡Parental report of cigarettes smoked daily by member of household >0.
§Parental report during the child's first year of life.

asthma (11), a first-order interaction between TRAP and early-life sensitization (one or more positive skin prick test in at least 2 years between the ages of 1 and 4 years) was explored, as were TRAP, sex, and race interactions. All possible covariates were initially screened for their association with asthma and wheeze phenotypes in a model including TRAP. Covariates retained in the final linear models had a *P* value of less than 0.20 and changed the TRAP coefficient by 10% or more. Statistical analyses were performed using SAS 9.2 and R (version 3.1.0)

Results

A total of 762 children were enrolled in the CCAAPS cohort and completed at least one clinical examination before age 4 years; of these, 617 (81%) were evaluated at age 7 years, and 589 (77%) successfully completed all portions of the study visit, including pulmonary function testing (Table 1). Those participating at age 7 years were similar to those who did not with respect to sex, race, breastfeeding duration, daycare attendance, and pet ownership but differed on parental history of asthma, SHS exposure, and indicators of socioeconomic status (maternal education, household income) (Table 1). Of the 617 children participating at age 7 years, 350 (56.7%) reported never having wheezed, whereas the prevalence of early-transient, late-onset, and persistent wheezing was 28.7, 3.4, and 11.2%, respectively. Of the 589 children completing all procedures required to define asthma, 16.1% (n = 95) were defined as having asthma. There were 18 children with persistent wheeze at age 7 years who did not meet the clinical criteria to be defined as having asthma. The estimated average (SD) daily exposure to TRAP for the cohort decreased, but was significantly correlated, from birth through age 7 years (0.40 [0.14], 0.39 [0.13], 0.38 [0.13], 0.38 [0.12], 0.38 [0.12], and 0.36 [0.10] $\mu g/m^3$, at birth, birth to age 1, age 1 to 2, age 2 to 3, age 3 to 4, and age 6 to 7 yr, respectively).

The association between estimated exposure to TRAP at birth and for the 12 months before ages 1, 2, 3, 4, and 7 years, and the average exposure to TRAP from ages 4 to 6 years, and birth through ages 4 and 7 years and wheeze phenotypes are presented in Table 2. High TRAP exposure at birth was significantly associated with both transient and persistent wheezing phenotypes (adjusted odds ratio [aOR] = 1.64; 95% confidence interval [CI], 1.04–2.57 and 2.31; 95% CI, 1.28–4.15), respectively. In addition, high TRAP exposure in the 12 months before age 1 year (aOR = 2.26; 95% CI, 1.27–4.01), age 2 years (aOR = 1.89; 95% CI, 1.05–3.40), and from birth to age 4 years (aOR = 1.98; 95% CI, 1.09–3.57) were significantly associated with persistent wheezing. TRAP exposure did not predict late-onset wheeze at any time point. There were no significant interactions between TRAP and early-life sensitization, race, or sex in the models predicting wheeze phenotypes. Covariates remaining in wheeze phenotype models included maternal education, daycare attendance, and SHS exposure.

As shown in Figure 1, only children whose average TRAP exposure from birth through age 7 years was greater than the 75th percentile were at significantly increased risk for asthma at age 7 years (aOR = 1.71; 95% CI, 1.01–2.88); although not significant, consistent trends were observed across most time points with the exception of TRAP exposure at age 7 years and between ages 4 and 6 years. We conducted a secondary analysis, which combined subjects with asthma and subjects with persistent wheeze, and similar trends were observed with high average TRAP exposure from birth to age 4 years (aOR = 1.63; 95% CI, 1.01–2.63) and birth to age 7 years (aOR = 1.69; 95% CI, 1.04–2.76) significantly associated with asthma/persistent wheeze. High average TRAP exposure before asthma diagnosis was associated with time to asthma diagnosis in the unadjusted Cox proportional hazards regression model (hazard ratio, 1.47; 95% CI, 1.00–2.16). After adjustment for covariates, however, this finding was no longer statistically significant (hazard ratio, 1.38; 95% CI, 0.92–2.06) (*see* online supplement). There were no significant interactions between TRAP and early-life sensitization, race, or sex in the models predicting asthma. Covariates remaining in the asthma models included maternal education, breastfeeding, daycare attendance, and SHS exposure.

As a sensitivity analysis, logistic regression was also performed treating TRAP as a continuous independent variable. Although similar trends were observed with respect to wheeze and asthma outcomes, these results did not reach significance at the 0.05 level (*see* Table E1 in the online supplement).

Table 2. Adjusted Association between Wheeze Phenotypes Defined at Age 7 Years and Estimated Traffic-related Air Pollution Exposure through Childhood

	Wheeze Phenotype		
Timing of TRAP Exposure	**Early-Transient**	**Late Onset**	**Persistent**
Birth	**1.64 (1.04–2.57)**	0.71 (0.20–2.53)	**2.31 (1.28–4.15)**
Birth to age 1 yr	1.30 (0.83–2.04)	0.39 (0.09–1.72)	**2.26 (1.27–4.01)**
Age 1–2 yr	1.33 (0.85–2.09)	0.58 (0.16–2.07)	**1.89 (1.05–3.40)**
Age 2–3 yr	1.34 (0.85–2.09)	0.63 (0.18–2.24)	1.45 (0.79–2.66)
Age 3–4 yr	1.04 (0.66–1.62)	0.56 (0.16–1.99)	1.38 (0.76–2.50)
Age 6–7 yr	—	0.64 (0.20–2.04)	0.81 (0.43–1.52)
Average, birth to age 4 yr	1.35 (0.85–2.12)	0.67 (0.19–2.34)	**1.98 (1.09–3.57)**
Average, ages 4–6 yr	—	0.54 (0.15–1.98)	0.93 (0.48–1.78)
Average, birth to age 7 yr	1.03 (0.64–1.67)	0.62 (0.17–2.20)	1.47 (0.80–2.71)

Definition of abbreviations: SHS = secondhand smoke; TRAP = traffic-related air pollution.
Data are presented as odds ratio (95% confidence interval); boldface type indicates significance at the 0.05 level. Models are adjusted for maternal education, daycare attendance, and SHS exposure. Analyses are limited to associations where TRAP exposure precedes outcome. Those not analyzed are denoted by "—" (e.g., early-transient wheeze and TRAP exposure at age 7 yr).

Discussion

In this study we found that early TRAP exposure is associated with transient and persistent wheeze, whereas early and sustained exposure to TRAP was associated with asthma development. Asthma, a complex heterogeneous disease, is characterized by varying wheezing phenotypes, which frequently express during early childhood (16, 17). Each distinct phenotype may associate differently with TRAP exposures, and these differences

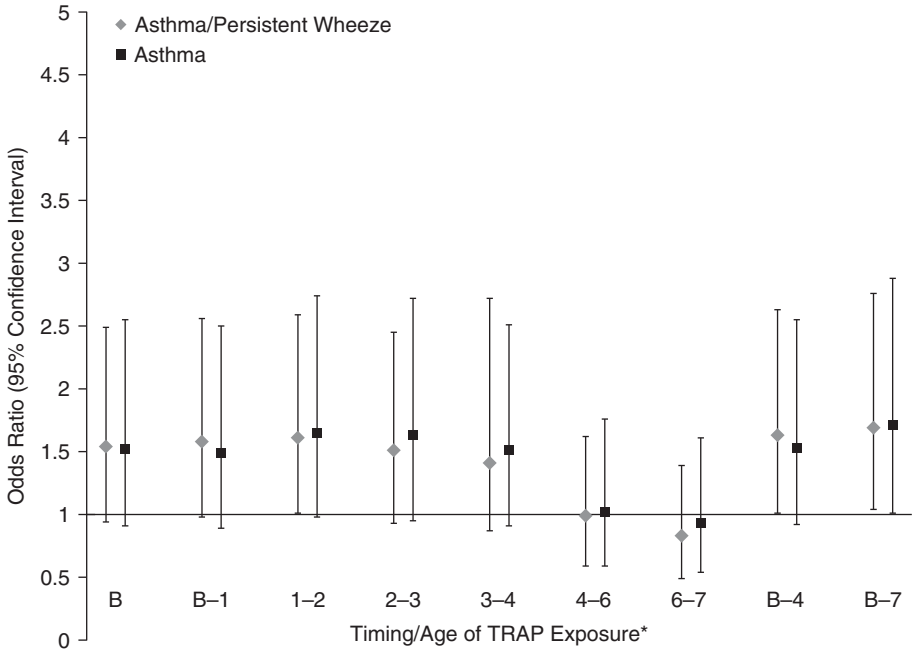

Figure 1. Adjusted associations between high traffic-related air pollution (TRAP) exposure throughout childhood and asthma incidence. Parental history of asthma, maternal education, and daycare attendance were significant covariates at each exposure window (P values < 0.05); cat/dog exposure remained in all models but was not significant ($0.05 \leq P < 0.10$). *Exposure to TRAP in the previous 12 months at each age from birth through age 7 years (e.g., B–1 is the time-weighted average TRAP exposure in the 12 months before age 1 yr); B–4 and B–7 are the average TRAP exposures from birth to age 4 and 7 years, respectively.

can reveal clues to the origins of asthma (13). We examined multiple time points of TRAP exposure with respect to longitudinal wheezing phenotypes, including early-life exposure at birth, and for the 12 months before ages 1, 2, 3, and 4 years, and current exposure (age 7 years), and average exposure between ages 4 and 6 years, birth and 4 years, and birth and 7 years to investigate timing and duration of TRAP exposure. We found that a child's risk for persistent wheeze and asthma development varies depending on the timing and duration of TRAP exposure. Children exposed to high levels of TRAP at time of birth were nearly twice as likely to experience persistent wheezing at age 7 years; however, a longer duration of exposure to high levels of TRAP (beginning early in life and continuing through age 7 years) was the only time period of exposure related to asthma development.

Both human and animal studies have shown that chronic exposure to ambient air pollution is associated with markers of airway remodeling, including timing and pattern of alveolar growth, fibrotic walls, and excess muscle growth on airway walls (32). Thus, it is possible that exposures of longer duration at elevated levels are necessary to generate pathophysiological changes leading to asthma development. The Southern California Children's Health Study has shown impaired lung growth and asthma incidence to be associated with air pollution exposures that occur later in childhood (8, 10); however, validation by other cohorts will help to disentangle the effect of early exposure versus exposures with greater duration and/or latency that may occur later in childhood.

Despite the mounting evidence, including the findings of this study that suggest TRAP is associated with the development of persistent wheeze and asthma during childhood (6–8, 10, 33), a recent multicenter study in the ESCAPE project found no significant associations between air pollution exposure and childhood asthma prevalence across five European birth cohorts (9). One potential explanation for these disparate results is differences in populations, as CCAAPS is a high-risk birth cohort with at least one atopic parent confirmed by skin prick test and the presence of allergy symptoms. It is possible that children in our cohort are more susceptible to the health effects of TRAP. In the present study, the strongest relationship between TRAP and the persistent wheeze phenotype was observed for high exposures to TRAP in the first 2 years of life. This finding is consistent with previous studies and suggests that very early life exposure to traffic pollution may represent a critical window for the effects of exposure on development of chronic childhood respiratory illness (6, 8, 23, 34, 35). Although elevated exposure to TRAP through age 7 years was the only exposure period significantly associated with asthma development, similar trends were observed across most time points. This finding may be a result of our strict asthma definition, which required a positive methacholine challenge test at concentrations that are more conservative than the American Thoracic Society/European Respiratory Society guidelines. Furthermore, it is possible that some children with persistent wheeze at age 7 years may be misclassified and truly have asthma or develop asthma at later ages. Our analysis of combined children with asthma and children with persistent wheeze resulted in similar findings to the analysis of children meeting our strict definition of asthma, further supporting this possibility. We are also unable to rule out the potential for high TRAP exposure beginning early in life to also be sufficient for the development of asthma given an adequate, still-unknown latency period. Interestingly, exposure to TRAP occurring later in childhood (between the ages of 4 and 6 yr) was not significantly associated with the development of asthma, suggesting that a latency period may exist for TRAP to cause disease onset. In addition to latency, our findings regarding persistent wheeze suggest that TRAP exposure at birth and during infancy represent critical periods for respiratory development; perhaps a greater proportion of the risk associated with asthma development is due to exposure during these time periods. Continued follow-up of the CCAAPS cohort will be conducted to further investigate the role of timing, duration, and latency of TRAP exposure most relevant for asthma development.

In a secondary analysis (*see* online supplement), asthma was defined by parental report of age at doctor-diagnosed asthma. This analysis showed that time to

asthma diagnosis (by child's physician) was associated with TRAP exposure, although this association was not significant after adjustment. Similar analyses have been used to assess the association between asthma onset in children and TRAP (8, 10). McConnell and colleagues (8) followed kindergarten and first-grade children for 3 years to assess new-onset asthma and found that traffic-related pollution exposure at school and homes was significantly associated with new-onset asthma. Using NO_2 as a marker of TRAP, Jerrett and colleagues (10) found that TRAP exposure at the home was also associated with asthma. Both studies reported similar estimates of effect (i.e., hazard ratios) as those reported in this study. In our study there are potential limitations to this approach, which include the outcome being based on parental report and subject to recall bias. Furthermore, there is potential for misdiagnosis of asthma by pediatricians. Thus, an important strength of our study is our rigorous definition of asthma, which incorporates parental report of symptoms and previous diagnosis and also objective measures of the child's respiratory function.

There are some additional limitations to this study that should be considered. Our estimate of TRAP exposure (ECAT) is likely correlated with exposure to other traffic-related air pollutants, and the causative agent(s) within the complex TRAP mixture is unknown. DEP are one component of the TRAP mixture of interest due to their ability to induce inflammation and Th17 cytokines (20). A significant source of elemental carbon in fine particulate matter is diesel combustion, and we have shown that our marker of diesel exhaust is specific to the diesel fraction of the TRAP mixture (29). It should also be noted that estimates of TRAP exposure were derived from an LUR model developed using ambient air samples collected at 27 sampling sites. Therefore, it is possible that the estimates of TRAP underestimate the true variation in the exposure, leading to results biased toward the null under the assumption of nondifferential error. Furthermore, our results regarding late-onset wheeze should be interpreted with caution, given the low prevalence in our population (3%); our study may not be sufficiently powered to examine the effects of TRAP on this wheeze phenotype. It is also a possibility that the selection of the cut point for the dichotomization of the TRAP variable affected the results. However, it should be noted that the results of the continuous and dichotomized exposure analyses were similar in direction. In addition, the choice of cut point was supported by the unsupervised clustering approach. Last, the CCAAPS cohort is considered high risk for allergic and respiratory disease, as enrolled children have at least one atopic parent. Therefore, the results of this analysis may not be generalizable to children born to nonatopic parents.

An important strength of this study is its longitudinal design with repeated measures of both exposure and health outcomes. With respect to exposure assessment, previous LUR-based studies have typically estimated exposure at a single point in time (e.g., birth record address) without consideration of the subjects' complete address history (7, 36, 37). In contrast, we have considered changes in exposure over the first 7 years of a child's life, which represents a critical period of enhanced susceptibility to environmental exposures as the lung undergoes rapid growth and expansion during this time period. Previously, we have shown differences in estimated TRAP exposures when considering all residential and nonresidential addresses beyond the birth record address (25). Thus, it is important to document the time spent and location outside of the home to accurately characterize traffic-related exposures.

In conclusion, this study demonstrates that children exposed to elevated levels of TRAP during early infancy are at increased risk for persistent wheezing during childhood. Furthermore, exposure to high levels of TRAP throughout childhood is associated with the development of asthma at age 7 years. These findings provide new evidence that early-life exposure to high levels of TRAP sets a trajectory toward persistent wheeze and that chronic early-life exposure to high levels of TRAP may be necessary for sufficient pathophysiological changes to occur in the lungs of children leading to asthma development. A strategy of prevention or intervention during this critical time period may be able to interrupt this chain of events. ■

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