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Long-term ozone exposure and lung function in middle childhood

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Abstract

Background: Ozone (O_3) exposure interrupts normal lung development in animal models. Epidemiologic evidence further suggests impairment with higher long-term O_3 exposure across early and middle childhood, although study findings to date are mixed and few have investigated vulnerable subgroups.

Methods: Participants from the CANDLE study, a pregnancy cohort in Shelby County, TN, in the ECHO-PATHWAYS Consortium, were included if children were born at gestational age >32 weeks, completed a spirometry exam at age 8–9, and had a valid residential history from birth to age 8. We estimated lifetime average ambient O_3 exposure based on each child's

residential history from birth to age 8, using a validated fine-resolution spatiotemporal model. Spirometry was performed at the age 8–9 year study visit to assess Forced Expiratory Volume in the first second (FEV_1) and Forced Vital Capacity (FVC) as primary outcomes; z-scores were calculated using sex-and-age-specific reference equations. Linear regression with robust variance estimators was used to examine associations between O_3 exposure and continuous lung function z-scores, adjusted for child, sociodemographic, and home environmental factors. Potential susceptible subgroups were explored using a product term in the regression model to assess effect modification by child sex, history of bronchiolitis in infancy and allergic sensitization.

Results: In our sample (n=648), O_3 exposure averaged from birth to age 8 was modest (mean 26.6 [SD 1.1] ppb). No adverse associations between long-term postnatal O_3 exposure were observed with either FEV_1 (β=0.12, 95% CI: −0.04, 0.29) or FVC (β=0.03, 95% CI: −0.13, 0.19). No effect modification by child sex, history of bronchiolitis in infancy, or allergic sensitization was detected for associations with 8-year average O_3.

Conclusions: In this sample with low O_3 concentrations, we did not observe adverse associations between O_3 exposures averaged from birth to age 8 and lung function in middle childhood.

Keywords

spirometry; ozone; FEV_1; FVC

1. INTRODUCTION

A relatively large literature indicates adverse associations between postnatal air pollutant exposures and child lung function (1). While studies focused on nitrogen dioxide (NO_2) and fine particulate matter ($PM_{2.5}$) have shown associations with reduced lung function, studies of long-term ozone (O_3) exposure are fewer in number and have had more mixed results (2). Studies with longer postnatal O_3 exposure windows have demonstrated an association with reduced lung function, suggesting that cumulative exposure across development may be important (3–7). Additionally, associations of air pollutants and lung function among children have been most consistent with reduced forced expiratory volume in one second (FEV_1), compared to reduced forced vital capacity (FVC), suggesting potentially greater effects of air pollution exposures during childhood on airflow obstruction than on overall lung size (1,2).

Toxicologic studies indicate long-term O_3 exposure interrupts the normal development of the lung. Chronic O_3 exposure in animal models impairs alveolar morphogenesis (8,9), a key phase of pulmonary development, and airway remodeling (10). O_3-induced inflammatory response in the airway leads to increased respiratory tract oxidative stress potentially through changes in antioxidant enzyme concentrations within the lungs (11) as well as inflammation related injury via alterations in cell proliferation (12) in O_3 exposed neonate rodents.

Few studies have further investigated subgroups who may be more vulnerable to potential effects of O_3 exposure on lung function. While associations between $PM_{2.5}$ and lung function may be stronger among boys (13), findings for O_3 are more mixed; some found an association among girls but not boys and posited differences in lung volumes and hormones, as well as differential behaviors related to ambient exposure as potential explanations for these findings (14,15). Early life respiratory infection, including bronchiolitis in infancy, may increase vulnerability to effects of ambient pollutants (16,17) via disruption of the lung epithelium (18,19) as well as dysregulation of immune response and inflammation (18,20). Allergic sensitization may also contribute to vulnerability to effects of air pollution exposure (21) through eosinophilic airway inflammation (22).

This study examined associations between long-term postnatal O_3 exposure and lung function in middle childhood. In secondary models, we assessed associations with O_3 exposure averaged within several shorter windows during childhood. We also investigated several potential effect modifiers of this relationship, including bronchiolitis in the first year of life, allergen sensitization, and child sex. We hypothesized that higher long-term O_3 exposures would be associated with worse lung function, particularly for the lifetime average and the later postnatal windows. We further hypothesized that this association would be more pronounced in some groups, including children with bronchiolitis in early life and children with allergic sensitization.

2. METHODS

2.1 Study Population

A total of 648 participants were drawn from the Conditions Affecting Neurocognitive Development in Early Childhood (CANDLE) study, one of three cohorts in the ECHO-PATHWAYS Consortium (23). CANDLE has been described in detail previously (23,24). Women aged 16–40 years and in the second trimester with singleton, low-medical-risk pregnancies were recruited between 2006 and 2011. A combination of clinic and community-based recruitment was used for this population-based sample in Shelby County (Memphis), Tennessee. Participants were included in the analytic sample if the child completed spirometry at the age 8–9 follow-up study visit, had a valid and complete address history during the exposure window, and had a gestational age at birth of at least 32 weeks.

2.2 Air Pollution Exposures

We estimated O_3 (ppb) exposure using predictions of outdoor pollutant concentrations at residential locations using a validated regionalized national spatiotemporal model (25–27). In brief, a combination of 4891 research campaign and regulatory monitors across three United States regions were utilized to predict point-based O_3 concentrations with a spatiotemporal model via the decomposition of the space-time field. The three regions were defined to include locations where previous research monitoring campaigns had been conducted. Hundreds of geographic covariates measured at monitoring locations across the contiguous United States were included in the models using dimension reduction via partial least squares. A spatiotemporal generalization of universal kriging applied to time trends estimated from observed time series was also utilized in the construction of the models.

For estimation of the temporal trend, data was included from monitors with sufficiently complete time series given the length of time the monitor was running (e.g. >70% coverage per week over 10 years). Monitors that were not included in temporal trend estimation were used in estimating the beta-fields but were not used during validation. Model performance was good, with a cross-validated R^2 of 0.737 and 0.834 for the long-term spatial and temporal estimates, respectively. Bi-weekly averages representing 24-hour mean pollutant concentrations were estimated at residential locations for each child and averaged from the date of birth to the eighth birthday to calculate a long-term (8 year) O_3 exposure for each participant. The same methods were used to derive NO_2 (ppb) and $PM_{2.5}$ ($\mu g/m^3$) estimates for inclusion in multipollutant models. Secondary exposure windows included birth-1 year, 1–5 year, and 5–8 year to capture infancy, early childhood, and middle childhood O_3 exposures, respectively.

2.3 Child Lung Function

Pulmonary function testing (PFT) was performed at the age 8 visit using Breezesuite™ software and American Thoracic Society (ATS) guidelines (28). In brief, trained staff administered a calibrated spirometer to assess lung function using a minimum of 3 and a maximum of 8 attempts for each child. Participants reporting respiratory infections, difficulty breathing, or use of asthma/wheeze rescue medication in the three days prior to the exam, or more than one nighttime asthma attacks in the past 4 weeks, had their test rescheduled. After caregiver consent, children with valid spirometry and without any cardiovascular-related disorders were administered albuterol and post-bronchodilation spirometry was measured 10 minutes later. All PFT results were reviewed by a pediatric pulmonologist for quality control and those deemed an unacceptable effort were removed from the dataset (N=59).

Three spirometry measures are used as outcomes in this analysis. Forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC) prior to bronchodilator administration were considered as primary outcomes. Forced expiratory flow between 25% and 75% of the vital capacity ($FEF_{25–75}$) was considered a secondary outcome. Post-bronchodilation FEV_1, FVC, and $FEF_{25–75}$ were considered in sensitivity analyses in the subset of participants who consented to albuterol administration.

Z-scores for FEV_1 and FVC were calculated using the 2022 Global Lung Institute (GLI) race-neutral reference equations (GLI-Global 2022) (29). Z-scores for $FEF_{25–75}$ were calculated using the 2012 GLI-Other reference equation (30) because $FEF_{25–75}$ was not included in the recent GLI update. In our primary analysis, we used the global reference equations which are calculated using the inverse probability weighted average of coefficients by race/ethnicity from the original GLI dataset for FEV_1 and FVC (GLI-Global) while $FEF_{25–75}$ utilizes the race/ethnicity weighted average of race/ethnicity specific coefficients (GLI-Other). In a sensitivity analysis, we used the race/ethnicity-specific reference equations to calculate z-scores for each spirometry measure.

2.4 Covariates

Confounders and precision variables were selected *a priori* due to being known risk or protective factors for airways related detriments. Child factors include the age at spirometry assessment (years), height at spirometry assessment (cm), sex (male or female), race (reported by the parent as American Indian/Alaska Native, Asian, Black, Native Hawaiian/other Pacific Islander, White, other, or multiple), date of birth (natural splines with 1 degree of freedom for each year), and report of recent medication use for asthma exacerbation in the past 12 months (binary). Child race was collapsed into three categories (Black, White, or other) based on cohort composition due to small sample sizes in some groups and was included as a proxy for disparities in both exposures to environmental hazards such as air pollution (31,32), and access to health-promoting resources, resulting from systemic racism and leading to higher rates of asthma and worse lung function among Black children relative to other groups in the United States (33). Maternal factors include modified Organization for Economic Co-operation and Development (OECD) adjusted household income (USD) (OECD Equivalence Scales (34)) and maternal education at the age 8–9 study visit (less than high school, high school, some college, 4-year college degree, or post-graduate degree), and maternal history of asthma (a binary composite based on self-report at either the age 4 and age 8–9 follow-up study visits). Additional factors include maternal smoking during pregnancy (assessed as yes/no based on a combination of mid-pregnancy urinary cotinine [>200 mg] and self-report of smoking during pregnancy), preterm birth (<37 weeks), duration of breastfeeding (never, less than 6 months, or at least 6 months), and exposure to furry pets during the first year of life (binary). Exposure to postnatal environmental tobacco smoke (ETS) was defined based on report at three timepoints: during the first year of life, at age 4, and at age 8. This variable was categorized as yes if ETS exposure was reported at any visit; if no ETS was reported at 2 visits and data from the third visit was missing, the participant was considered to have no ETS exposure. The Neighborhood Deprivation Index (NDI) was calculated from five census tract variables and averaged over each participant's residential history (35,36).

Additional covariates and sample characteristics were considered in sensitivity analyses. O_3 exposure was averaged over the prenatal residential history and assessed during the two-weeks prior to the spirometry exam. $PM_{2.5}$ and NO_2, derived from separate regionalized national spatiotemporal models utilizing a near identical methodology as the O_3 model, were averaged over the same exposure windows as O_3 (25–27). The amount of time the child spends outdoors was reported at the age 8–9 study visit in response to the question "How many hours per day was your child at home outside during the past 7 days?" Time outdoors was dichotomized as >2 hours per day versus ≤2 hours per day.

2.5 Potential Effect Modifiers

Potential effect modifiers were explored in this analysis, selected based on *a priori* hypotheses about susceptible subgroups: child sex, history of bronchiolitis during infancy, and allergen sensitization, and current asthma. A history of bronchiolitis was defined as 'yes' to *During the first 12 months of [child's name] life, did a doctor or health care provider diagnose him or her with bronchiolitis, wheezing, or "RSV" (respiratory syncytial virus)?* asked retrospectively at age 8–9. Blood samples were obtained at the age 8–9 study visit

and allergic sensitization was determined using a multiallergen screen for aeroallergens (Phadiatop, mix proprietary) and food allergen mix (chicken egg, cow's milk, peanut, soybean, codfish and wheat). Samples were analyzed following the ImmunoCAP 250 Specific IgE Procedure developed by Johns Hopkins University (37–40). A value greater than 0.35 kUA/l on either the aeroallergen or food allergen IgE screen was considered sensitized.

2.6 Statistical Analysis

Descriptive statistics were used to calculate the distribution of exposures, outcomes, and covariates. Linear regression with robust variance estimators was used to examine associations between lifelong O_3 exposure and continuous lung function z-scores. Secondary exposure windows were assessed using the same methods. A staged modeling technique was utilized for covariate adjustment. A minimally adjusted model included: child sex, child height, child age, and date of birth splines. While child age, sex, and standing height at time of pulmonary function testing were used to derive z-scores, these z-scores were normed in a separate population, allowing the possibility of residual correlation between these variables and spirometry outcomes in our sample; therefore, we included sex, age, and height as covariates in our regression models. Our primary model additionally adjusted for household income, maternal education, NDI, child race, postnatal ETS exposure, maternal smoking during pregnancy, preterm birth, maternal history of asthma, and recent asthma medication use by the child. An extended model further adjusted for length of breastfeeding and furry pets in the home.

We utilized multiplicative interaction terms in the primary model to assess effect modification. For the analysis of effect modification by history of bronchiolitis, which was defined based on report of bronchiolitis before age 1, we used a slightly different exposure metric to ensure that the effect modifier was not a causal intermediate between the exposure and outcome of interest. In this particular analysis, O_3 exposure was averaged between age 1 and age 8 rather than between birth and age 8. Other effect modification analyses used O_3 exposures averaged from birth to age 8 as in the primary analysis.

Several sensitivity analyses were conducted using the primary model. Recent exposure to O_3 (2-weeks prior to spirometry exam date) was additionally adjusted for to account for O_3-related exacerbations or acute short-term effects of O_3 on lung function prior to the spirometry exam. Prenatal exposure to O_3 was also adjusted for to address potential confounding related to correlations between prenatal and postnatal pollutant concentrations. For analyses of age 0–1, 1–5, and 5–8 exposure windows, a mutually-adjusted model was run in which the model was adjusted for all of the other postnatal exposure windows, as well as for prenatal O_3 exposure. To better approximate exposure to mixtures of air pollutants, we examined models adjusted for NO_2 and $PM_{2.5}$ along with O_3 in each exposure window. A fifth sensitivity analysis aimed to reduce potential exposure misclassification due to O_3 exposure estimates reflecting outdoor concentrations; the analytic sample was restricted to those who spend more time outdoors (defined as >2 hours per day). The relationship between O_3 and post-bronchodilation z-scores was explored to assess lung function after removing any reversible obstruction. The primary analysis was repeated using the race/

ethnicity-specific reference equations for each participant to facilitate comparisons to prior literature. Lastly, generalized additive models (GAMs) were used to explore non-linear associations between O_3 and lung function. All analyses were conducted using R 4.2.2.

3. RESULTS

Our sample included 648 participants who completed a spirometry exam at the age 8–9 year visit, had a valid residential history from birth to age 8, a gestational age >32 weeks at birth, and were not missing covariates for the primary analysis. Participant composition was near equally assigned male at birth (50.9%), predominantly Black (63.7%), had an average age and height at spirometry of 8.6 (SD: 0.7) years old and 135.0 (7.8) centimeters, respectively (Table 1). Mean household income adjusted for household size was $17,957 (SD $13,788) USD and the largest share of mothers had some college or technical school education (40.3%).

Mean (SD) z-scores calculated using the GLI Global reference equation were −0.42 (1.05) for FEV_1 and −0.36 (1.05) FVC (Table 2). Mean (SD) z-scores for $FEF_{25–75}$ –derived using the GLI Other reference equation due to no Global reference equation available for this outcome—were −0.31 (1.06).

Mean O_3 exposure averaged over the residential history between birth and age 8 was 26.6 ppb (SD 1.1) (Table 3). Mean exposure levels in secondary windows were also modest with limited variability. A map illustrating the spatial distribution of O_3 in the study area, using the modeled annual average O_3 concentrations for 2014, is included in supplementary materials (Supplemental Figure 1). Concentrations of other pollutants can be found in Supplemental Table 1. In this sample, there are 167 (25.8%) participants who live near a major roadway (within 150m of a roadway classified as an A1, A2, or A3). O_3 was negatively correlated with NO_2 (Pearson correlation of −0.78, Supplemental Table 2), $PM_{2.5}$ (Pearson correlation of −0.45) and the neighborhood deprivation index (Pearson correlation of −0.52) in the primary age 0–8 window as well as with NO_2 and $PM_{2.5}$ in all secondary exposure windows.

The majority of effect estimates were statistically significant in the un-hypothesized direction within the minimal models (Table 4). However, these associations were attenuated with further covariate adjustment and confidence intervals included the null in our primary models for our primary outcomes. In our primary model, a 2 ppb higher O_3 exposure from birth to age 8 was associated with a 0.12 (95% CI: −0.04, 0.29) units higher z-score for FEV_1, a 0.03 (95% CI: −0.13, 0.19) higher FVC, and 0.17 (95% CI: 0.01, 0.34) higher $FEF_{25–75}$. None of the secondary exposure windows were significant for either FEV_1 or FVC, however, those with 2 ppb higher O_3 in the age 1–5 exposure window had an average of 0.19 (95% CI: 0.03, 0.36) higher z-score of $FEF_{25–75}$. The extended model yielded similar estimates to the primary model.

No effect modification was detected for associations with exposure within the primary exposure window (Figure 1). A statistically significant interaction by child sex was determined in the age 0–1 window for both FEV_1 (female: −0.04 (95% CI: −0.11, 0.20),

male: 0.15 (95% CI: −0.01, 0.31)) and FVC (female: −0.11 (95% CI: −0.26, 0.04), male: 0.11 (95% CI: −0.40, 0.25). No other combination of outcomes or exposure windows had significant interactions by child sex. There was no significant effect modification of history of bronchiolitis, or allergic sensitization status detected for any outcomes in any exposure windows.

In general, results from other sensitivity analyses were similar to the primary analysis (Supplemental Table 3). Further adjustment for O_3 exposure in the two-weeks prior to spirometry examination slightly attenuated estimates in the age 0–8 window. Additional adjustment for prenatal O_3 exposure almost uniformly slightly shifted all estimates away from the null and did not alter the main findings. In a mutually-adjusted model for other exposure windows, point estimates for age 0–1, 1–5, and 5–8 exposure windows shifted slightly and confidence intervals widened to include the null. Co-pollutant adjustment for NO_2 and $PM_{2.5}$ in the same exposure window generally had a minimal impact on O_3 effect estimates. There was a shift in magnitude of estimates in the 0–1 exposure window for all outcomes, although all confidence intervals include the null. Restricting the study population to those who spent more time outdoors (>2 hours per day, N=412) increased the magnitude of estimates in the non-hypothesized direction, although confidence intervals were similarly widened. When the sample was restricted to the subset of participants with post-bronchodilation spirometry outcomes (N=510), estimates of associations of O_3 with spirometry before and after bronchodilation were similar. Estimates were nearly identical to the primary model when the GLI race/ethnicity-specific z-scores were utilized in the 0–8 exposure window. Overall, there was little evidence of non-linear O_3 response although there may be some suggestion of a non-linear relationship of $FEF_{25–75}$ with exposure in the age 1–5 window (Supplementary Figure 2).

4. DISCUSSION

In this study sample, we did not find evidence of a detrimental impact of long-term postnatal O_3 exposure and child lung function at age 8–9 years. Confidence intervals included the null for estimates of associations with FEV_1 and FVC; we observed borderline associations with $FEF_{25–75}$, a secondary outcome, in the opposite of the hypothesized direction. We did not observe strong evidence for effect modification of associations with lifetime average O_3 by child sex, history of bronchiolitis, or allergic sensitization.

A systematic review of studies from 2013–2021 highlighted accumulating evidence of associations between O_3 and lung function (1). Our findings are in contrast to several prior studies which identified associations between higher O_3 and worse child lung function (4–6). For example, a study of children (n=1016) ages 6–15 in Taiwan found that higher lifetime exposure to O_3 was associated with a 0.93% decrease (95% CI: −1.53, −0.34) in FEV_1 per 1 ppb O_3 (4). A study of 6740 children ages 7–14 years in 7 cities in China found adverse associations between O_3 and lung function measures, with the largest effect estimates among obese and overweight participants, though interaction by BMI was not statistically significant (6,7). A study of 1811 children ages 5–7 in eight communities in southern California found a 3.1% lower FEV_1 (95% CI: −5.2, −0.9) with 22.7 ppb higher O_3 levels averaged over six years (5). A study centered on two cities in Greece that

supplemented fixed site and modeled O_3 estimates with personal campaign measures found that a difference in 10 μg/mL O_3 over one year was associated with reduced FVC by 17 mL (95% CI: 5–28) and reduced FEV_1 by 13 mL (95%CI: 3–21) (41). While some of these studies had mean exposures comparable to those in our study (4,5), others had exposures that were substantially higher (6,7,41); additionally, multi-city studies had greater variability in exposures than we observed in our sample within a single urban area.

While the use of spatiotemporal modeling in our study improves upon prior approaches such as using a central fixed site monitor, the modest exposure levels and limited exposure variability in our study sample likely hindered our ability to detect any associations. In contrast to other criteria pollutants, O_3 is a secondary pollutant and concentrations are typically lower in urban centers and near major roads; negative correlations between O_3 and traffic-related air pollutants are observed particularly with NO_2, which also exhibits fine-scale variability and high concentrations around major roads. We adjusted for $PM_{2.5}$ and NO_2 in a sensitivity analysis, but the high degree of correlation with our primary exposure limits our ability to separate out the effects of each pollutant, which is a limitation of this study. Future work should apply advanced approaches to mixtures, including the pollutants considered here, as well as additional air pollutants. O_3 is also a seasonal pollutant with higher concentrations in the summer and lows in the winter in TN, and with annual average concentrations that have remained relatively stable over the past decade. While previous literature suggests that cumulative exposure over long time frames may be relevant for child lung function, long-term exposure averages in our single-site study were less variable than short-term exposures that capture seasonal variation. For example, findings from panel studies indicate a detriment to lung function associated with short-term exposure to O_3 (42,43) and highlight the importance of adjusting for short-term effects in studies of long-term exposures. Future work in samples with larger variability in long-term exposures could additionally assess the potential for threshold effects of O_3 on lung impairment.

Other studies identified suggestive associations in the hypothesized direction, but did not reach statistical significance (44–46). For example, Usemann *et al.* identified suggestive but not statistically significant associations with lifetime average exposures to O_3, in a cohort of children in Switzerland with a sample size of 202 and a mean age of 6 (3). Our results are similar to those found in a cohort study in London of 4884 children (mean age 9.9 years), which found no associations between O_3 and either FEV_1 or FVC (47). Mean exposure in this study (19.1 ppb) was lower than that in our study sample (26.6 ppb). Other studies have identified associations with lung function growth, even when cross-sectional associations were null or with effect estimates in the opposite of the hypothesized direction at a single time point (48,49). This is an important area for future research with longitudinal outcome measures to assess lung function growth.

Differences in spirometry reference equations used across studies limit our ability to directly compare lung function across study samples. Only Usemann *et al.* used the GLI 2012 race/ethnicity-specific reference equations and had similar lung function z-scores and, as noted above, had null associations between long-term O_3 and both FEV_1 and FVC (3). In contrast, those reporting significant associations with O_3 and reduced lung function had higher raw lung function compared to the CANDLE cohort, although comparing non-reference

equation adjusted spirometry values may reflect differences in examination procedures and not baseline lung function in a cohort (4–7). When compared to the reference population utilized to derive the GLI 2022 Global reference equations, lung function in the CANDLE cohort is modestly below the z-score of zero which reflects the mean of the reference population (29). Further detriment from environmental factors may not be present due to other non-environmental sources dominating the causes of lower lung function in the cohort, limiting our ability to see an adverse association with higher O_3 exposures.

Contrary to our hypothesis, higher O_3 in the age 0–8 window was associated with higher lung function for our secondary outcome of $FEF_{25–75}$. However, protective associations lack biological plausibility and null associations were found with this measure in previous literature (4,6–7). This result may be due to residual confounding or it could be a spurious association, due to chance. Additionally, the negative correlation between O_3 and NO_2 and $PM_{2.5}$ as well as the attenuation of the association after co-adjustment for the other pollutants may indicate that higher exposure to O_3 is serving as a proxy for low exposure to near-roadway traffic-related air pollutants, which are more established risk factors for decreased lung function (2). Another possibility for this unexpected finding is the use of the GLI Other reference equation, in which the race-unweighted average of the 2012 GLI equations were utilized for all participants, that may introduce bias from the demographic composition of the reference population. However, no weighted reference equation for the $FEF_{25–75}$ measure is currently available through the GLI. $FEF_{25–75}$ was considered as a secondary outcome because this measure is more variable within an individual than FEV_1, particularly for children, and only suggestively indicates severity of disease among children with asthma (50,51); the clinical use of this measure provides minimal improvement to asthma diagnoses over the use of FEV_1 and FVC in general populations (52,53).

Some studies have observed a more pronounced association of air pollution exposure with lung function among vulnerable subgroups such as children with lower respiratory tract infections in early life, allergic sensitization, or asthma (21,54), though few have investigated such subgroups in relation to O_3 exposure. In our study, we did not observe statistically significant effect modification by history of bronchiolitis in infancy or positive IgE screen. Others have also identified sex-specific effects, including a detriment to lung function with higher O_3 exposure only for girls during the summer season (14). Our study also observed inverse associations between O_3 and both FEV_1 and FVC only among females, though effect modification was only statistically significant for a secondary exposure window, from birth to age 1. Future work could consider exploration of additional effect modifiers, such as childhood obesity.

Several limitations may explain our findings in this study. Due to the COVID-19 pandemic and restrictions on human subjects research, we were limited to a single study site which was able to complete spirometry in children ages 8–9 prior to the pandemic. There was also some loss to follow-up, reducing the sample size, which may have further limited our ability to identify associations. Overall, exposures in this sample were generally low with limited variability in long-term O_3 that diminished our ability to detect an adverse association. Additionally, while our research question was focused on the potential effect of long-term chronic exposure, a limitation of this approach is that it assumes a constant

lag-response, though shorter windows of exposure may have been causally associated with child lung function. Furthermore, moderate correlations between O_3 concentrations in our shorter secondary exposure windows complicates interpretation of mutually-adjusted models. Future work could consider exploring smaller windows of exposure using flexible modeling techniques. A further challenge of assessing exposure to O_3 was that children may spend variable amounts of time outside, resulting in some exposure misclassification using ambient O_3 levels. We relied on spatiotemporally modeled O_3 estimates at the residential location, rather than personal monitoring, which has limited feasibility for long follow-up times and our focus on long-term averages. In a sensitivity analysis, we did not see associations when the sample was restricted to those reporting at least two hours outside per day in the past week. However, this measure was referenced to the week prior to spirometry and may not be reflective of overall patterns of behavior across all of childhood. It may be further complicated if healthier children were more likely to spend time outdoors. A further limitation of this analysis is the potential for collider bias due to adjustment for preterm birth in the primary model. In the case where prenatal O_3 exposure predicts both preterm birth and postnatal O_3 exposure, and unmeasured factors predict both preterm birth and child lung function, it is possible for preterm birth to act as a collider and induce an association between prenatal O_3 and unmeasured factors when included in the model. However, adjustment for prenatal O_3 in a sensitivity analysis produced similar results to our main model.

Our study also had several strengths. The racially and sociodemographically diverse CANDLE cohort has been well-characterized and thus we were able to account for important potential confounders. While many prior studies have relied on a single fixed site monitor per city to characterize exposure, we used a well-validated highly-resolved air pollution model to estimate long-term childhood exposures to ambient O_3 concentrations. Spirometry provided objective and continuous measures of lung function in this sample of children and we were further able to conduct a suite of secondary and sensitivity analyses.

5. CONCLUSIONS

Examining the burden of disease associated with childhood exposure to O_3 is important to improving public health. We did not observe associations between lifetime O_3 exposure and lung function in middle childhood in this single-city sample with low exposure levels. We additionally did not identify enhanced vulnerability to exposure among pre-specified subpopulations. However, we were limited by restricted variability in, and generally low levels of, long-term O_3 exposures in Memphis. Furthermore, disentangling effects of O_3 from traffic-related air pollutants remains a challenge. Future work utilizing spatiotemporal model derived air pollution exposure across multiple cities with greater spatial variability in exposures is needed. Additionally, there is a need for research exploring the effect of air pollutant exposures on lung function growth.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability statement

The data utilized for this study are not publicly available but de-identified data may be available on request, subject to approval by the internal review board and under a formal data use agreement. Contact the corresponding author for more information.

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Highlights

Long-term ozone exposure and lung function in middle childhood

- Child FEV_1 and FVC were ascertained via spirometry at age 8–9 in the CANDLE cohort.
- We used a point-based spatiotemporal model to assess lifetime O_3 exposure, age 0–8.
- O_3 exposures in this sample were modest with limited variability.
- No adverse associations were observed between long-term O_3 and lung function.
- No effect modification found by bronchiolitis, allergic sensitization, or child sex.

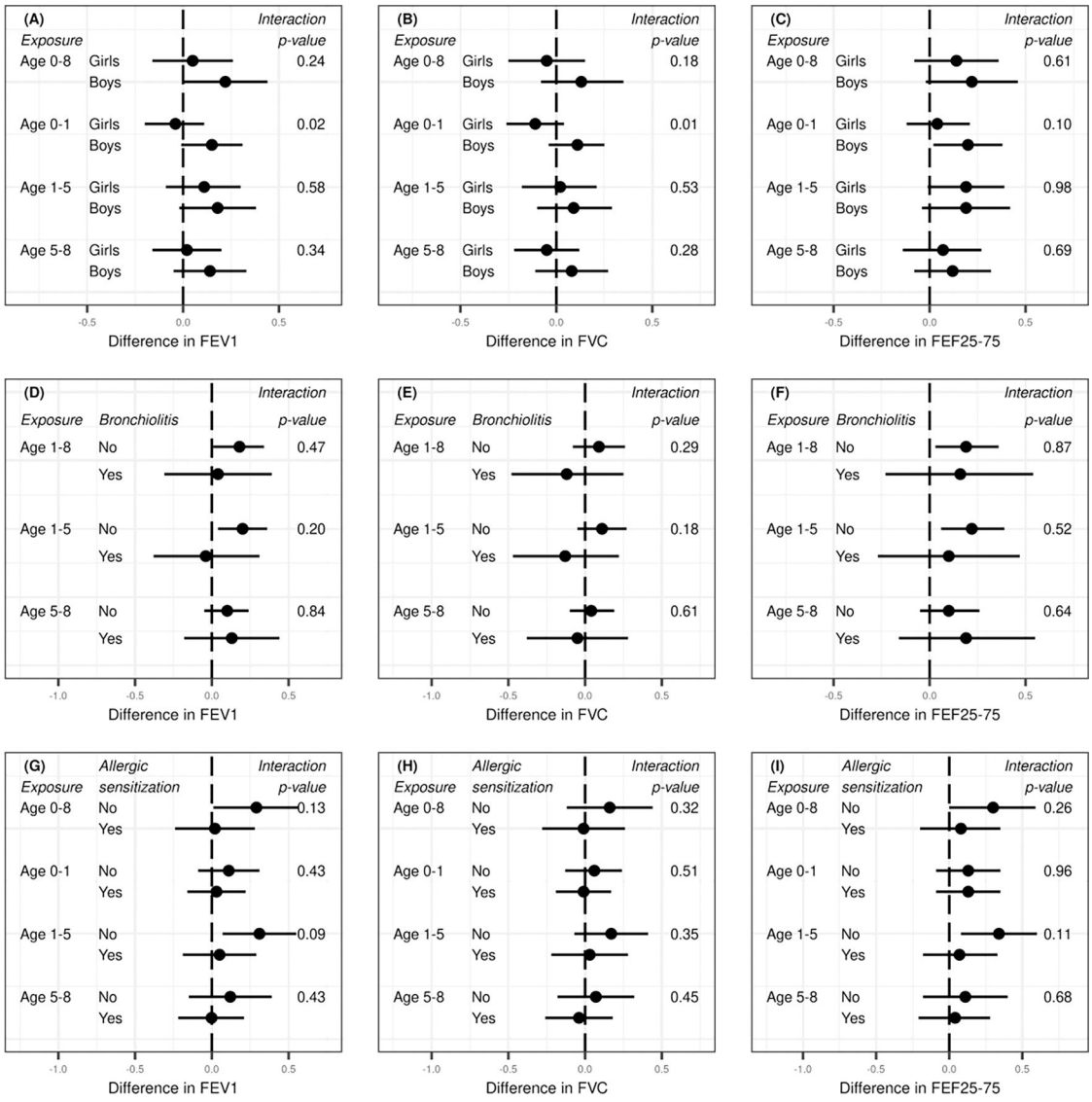

Figure 1.

Effect modification of associations between ozone exposures and child lung function. Panels A-C show effect modification by child sex (n=330 female, 318 male), panels D-F show effect modification by history of bronchiolitis in infancy (n=109 yes and 532 no), and panels G-H show effect modification by allergic sensitization (IgE screen >0.35, n=248 yes and 196 no). Estimates of difference in lung function and 95% confidence intervals are shown per 2 ppb higher ozone. All models were adjusted for child sex, age and height at the spirometry examination, splines for date of birth (1 degree of freedom per year), household income, maternal education, neighborhood deprivation index, child race, postnatal environmental tobacco smoke exposure, maternal smoking during pregnancy, preterm birth, maternal history of asthma, and recent asthma medication use by the child.

Abbreviations: FEV_1=forced expiratory volume in the first second; FVC=forced vital capacity; $FEF_{25–75}$=forced expiratory flow between 25% and 75% of the vital capacity

Table 1.

Sample Characteristics (N=648)

	N[a] or mean	% or SD
Child age at spirometry exam (years)	8.6	0.7
Child height at spirometry exam (cm)	135	7.8
Female	330	50.9%
Male	318	49.1%
Child race		
Asian	4	0.6%
Black	413	63.7%
Multiple race	35	5.4%
Other	7	1.1%
White	189	29.2%
Preterm birth		
Yes	57	8.8%
No	631	91.2%
Breastfeeding duration		
None	218	33.6%
< 6 months	255	39.5%
≥ 6 months	174	26.9%
Postnatal exposure to environmental tobacco smoke		
Yes	248	43.8%
No	400	61.7%
Furry pets in the home during first year of life		
Yes	284	43.9%
No	363	56.1%
Child asthma medication use in past year		
Yes	81	12.5%
No	567	87.5%
Maternal education		
<High school	30	4.6%
High school	102	15.7%
Some college or technical school	261	40.3%
4-year degree	136	21.0%
Graduate or professional	119	18.4%
Maternal history of asthma		
Yes	104	16.0%
No	544	84.0%
Maternal smoking during pregnancy		

	N[a] or mean	% or SD
Yes	77	11.9%
No	571	88.1%
Household income (USD) adjusted for household count [b]	17957	13788
Neighborhood Deprivation Index (NDI) [c]	0.29	0.76
Time spent outdoors (per day in the last week)		
≤2hrs	231	35.9%
>2hrs	412	63.1%
Potential effect modifiers		
Bronchiolitis in early life		
Yes	109	17.0%
No	532	83.0%
Positive IgE screen (>0.35 kUA/I)		
Yes	248	55.9%
No	196	44.1%

[a] Number missing: 1 breastfeeding, 1 furry pets, 5 time outdoors, 7 bronchiolitis, and 204 IgE screen.

[b] Annual household income (in US dollars) ascertained at child age 8 and adjusted for household count using OECD equation.

[c] NDI averaged over residential history from birth to age 8.

Table 2.

Child lung function measured via spirometry at the age 8–9 year study visit.

Spirometry Measure and Reference Equation	Mean	SD	Min.	Q1	Median	Q3	Max.
Pre-bronchodilator (N=648)							
FEV_1							
GLI-Global z-score (primary)[a]	−0.42	1.05	−3.32	−1.12	−0.44	0.24	−3.07
Race/ethnicity-specific z-score[b]	0.29	1.01	−2.84	−0.34	0.31	0.96	3.25
GLI-Other z-score [c]	0.04	1.19	−3.57	−0.77	−0.01	0.83	4.09
Raw (L)	1.66	0.30	0.78	1.45	1.64	1.84	2.72
FVC							
GLI-Global z-score (primary)[a]	−0.36	1.05	−3.36	−1.10	−0.40	0.34	2.72
Race/ethnicity-specific z-score[b]	0.40	0.99	−2.57	−0.28	0.39	1.05	3.45
GLI-Other z-score[c]	0.20	1.25	−3.43	−0.71	0.19	1.08	4.05
Raw (L)	1.91	0.36	1.07	1.64	1.90	2.12	3.11
$FEF_{25–75}$							
GLI-Other z-score[c]	−0.31	1.06	−3.67	−1.00	−0.32	0.38	3.12
Race/ethnicity-specific z-score[b]	−0.15	0.96	−3.23	−0.77	−0.18	0.43	3.03
Raw (L/second)	1.93	0.54	0.52	1.55	1.89	2.27	3.85
Post-bronchodilator (N=510)							
FEV_1							
GLI-Global z-score [a]	−0.17	1.13	−5.16	−0.90	−0.18	0.53	3.49
FVC							
GLI-Global z-score [a]	−0.23	1.08	−3.50	−0.96	−0.30	0.52	3.30
$FEF_{25–75}$							
GLI-Other z-score [c]	0.22	1.19	−4.10	−0.46	0.24	1.02	3.96

[a]GLI-Global calculated from race-neutral spirometry reference equations derived in Bowerman 2023 (29).

[b]Race/ethnicity-specific z-scores calculated from race and ethnicity-specific reference equations derived in Quanjer 2012 (30).

[c]GLI-Other z-scores calculated by using the Other reference equation derived in Quanjer 2012 (30) for all participants.

Abbreviations: FEV_1=forced expiratory volume in the first second; FVC=forced vital capacity; FEF25–75=forced expiratory flow between 25% and 75% of the vital capacity

Table 3.

Ozone exposures (ppb) in the study sample (N=648).

Exposure window	Mean	SD	Min.	Q1	Median	Q3	Max.
Age 0–8	26.6	1.1	24.4	25.7	26.3	27.3	30.9
Age 0–1	26.9	1.7	22.8	25.6	26.9	28.0	32.3
Age 1–5 [a]	26.8	1.2	23.8	25.9	26.7	27.5	31.8
Age 5–8	26.2	1.2	22.9	25.3	25.9	27.0	31.4
2 weeks prior to spirometry exam [a]	25.6	5.5	14.6	21.2	25.5	29.4	40.4
Pregnancy [a]	26.8	2.4	21.3	25.0	26.8	28.6	32.9

[a]Participants were required to have 95% address coverage during window of interest, leading to small differences in sample sizes across windows: N=4 (0.8%) missing for age 1–5,N=23 (3.5%) missing average for two-week prior to spirometry exam and N=1 (0.1%) missing pregnancy average.

Table 4.

Associations between childhood exposure to ozone and lung function in middle childhood.

Exposure Window	FEV_1	FVC	$FEF_{25–75}$
	Difference (95% CI)[a]	*Difference (95% CI)*[a]	*Difference (95% CI)*[a]
Age 0–8			
Model 1 [b]	0.36 (0.20, 0.51)	0.32 (0.17, 0.47)	0.19 (0.04, 0.34)
Model 2 [c]	0.12 (−0.04, 0.29)	0.03 (−0.13, 0.19)	0.17 (0.01, 0.34)
Model 3 [d]	0.14 (−0.03, 0.30)	0.05 (−0.11, 0.21)	0.17 (0.00, 0.34)
Age 0–1			
Model 1	0.19 (0.05, 0.34)	0.16 (0.03, 0.29)	0.14 (0.00, 0.28)
Model 2	0.05 (−0.08, 0.19)	−0.003 (−0.13, 0.12)	0.12 (−0.03, 0.26)
Model 3	0.06 (−0.08, 0.19)	0.01 (−0.12, 0.13)	0.12 (−0.02, 0.27)
Age 1–5			
Model 1	0.35 (0.20, 0.50)	0.30 (0.16, 0.45)	0.21 (0.06, 0.36)
Model 2	0.14 (−0.01, 0.29)	0.05 (−0.10, 0.21)	0.19 (0.03, 0.36)
Model 3	0.15 (0.00, 0.30)	0.07 (−0.08, 0.22)	0.19 (0.02, 0.35)
Age 5–8			
Model 1	0.28 (0.14, 0.41)	0.25 (0.12, 0.38)	0.12 (−0.02, 0.26)
Model 2	0.07 (−0.07, 0.22)	0.01 (−0.13, 0.15)	0.09 (−0.06, 0.24)
Model 3	0.08 (−0.06, 0.23)	0.02 (−0.11, 0.16)	0.09 (−0.07, 0.24)

[a] Estimates (difference in lung function and 95% confidence intervals) are reported per 2 ppb higher ozone.

[b] Model 1 was considered the minimally-adjusted model and included adjusted for child sex, age and height at the spirometry examination, and splines for date of birth.

[c] Model 2 was considered the primary model and additionally adjusted for household income, maternal education, neighborhood deprivation index, child race, postnatal environmental tobacco smoke exposure, maternal smoking during pregnancy, preterm birth, maternal history of asthma, and recent asthma medication use by the child.

[d] Model 3 was considered the extended model and additionally adjusted for furry pets in the first year of life, duration of breastfeeding, and season of outcome measurement.

Abbreviations: FEV1=forced expiratory volume in the first second; FVC=forced vital capacity; FEF25–75=forced expiratory flow between 25% and 75% of the vital capacity