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Air pollution and lung function in children

Erika Garcia, PhD[a], **Mary B Rice, MD, MPH**[b], **Diane R Gold, MD, MPH**[c,d]

[a]Department of Preventive Medicine, University of Southern California, Los Angeles, USA

[b]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA

[c]Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

[d]Channing Division of Network Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA.

Abstract

In this narrative review we summarize the literature and provide updates on recent studies of air pollution exposures and child lung function and lung function growth. We include exposures to outdoor air pollutants that are monitored and regulated through air quality standards, and air pollutants that are not routinely monitored or directly regulated, including wildfires, indoor biomass and coal burning, gas and wood stove use, and volatile organic compounds. Included is a more systematic review of the recent literature on long-term air pollution and child lung function since this is an indicator of future adult respiratory health and exposure assessment tools have improved dramatically in recent years. We present "summary observations" and "knowledge gaps." We end by discussing what is known about what can be done at the individual/household, local/regional, and national level to overcome structural impediments, reduce air pollution exposures and improve child lung function. We found a large literature on adverse air pollution effects on children' lung function level and growth; however, many questions remain. Important areas needing further research include: whether early life effects are fixed or reversible; and what are windows of increased susceptibility, long-term effects of repeated wildfire events, and effects of air quality interventions.

Keywords

Children; lung function; FEV1; FVC; air pollution; indoor pollution; wildfire; gas stoves; biomass

Erika Garcia, PhD, Keck School of Medicine of USC, Department of Preventive Medicine, 2001 N. Soto Street, SSB1 Rm 225F MC 9237, Los Angeles, CA 90089-9237, Phone: (323) 442-1092, garc991@usc.edu.

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INTRODUCTION

The adverse acute effects of ambient air pollution from traffic, fossil fuel combustion, industrial facilities, and other sources on child respiratory health have been well-documented in decades of research. This research has directly informed national ambient air quality standards for ground-level ozone (O_3), fine particulate matter ($PM_{2.5}$) and other criteria pollutants regulated by the United States Environmental Protection Agency (US EPA)[1] per the Clean Air Act, which mandates that the standard be designed to protect sensitive subpopulations including children. In the 1980s and 90s child lung function was assessed as a subclinical marker of acute pollution health effects in panel studies of children with and without asthma, and short-term decrements in lung function were observed with short-term increases in ambient air pollution.[2–4] These early panel studies contributed biologic plausibility to the time-series studies of clinically-sensitive children that demonstrated short-term increases in air pollution to related with increases in adverse clinical events (e.g., urgent care visits and hospitalization for respiratory illnesses).[5, 6] Air pollution and lung function studies also have direct clinical import for stepwise management of childhood asthma, since level of forced expiratory volume in one second (FEV_1) and FEV_1/ forced vital capacity (FVC) percent predicted are used in assessment of level of asthma severity.[7]

In addition to studies showing acute effects of air pollution on lung function, a growing number of longitudinal studies have suggested adverse effects of early-life or life-time long-term air pollution exposures on lung function growth during childhood. In contrast to lung function level, which is assessed at a single point in time, lung function growth is assessed based on repeated measurements with the difference between first and last lung function measure (size of increase) often used as a proxy for lung function development. As a body of evidence, these studies suggest that long-term childhood air pollution exposures may shift the entire population distribution of childhood lung function and lung function growth downward. This is portrayed in the hypothetical child lung function growth trajectories (Figure 1),[8–10] where air pollution exposures in the prenatal period or during early childhood could result in reduced lung function growth (Figure 1: scenarios b or d). Persistent or additional exposures could compound the injury by increasing the risk of early, and potentially steeper lung function decline after the plateau in early adulthood (Figure 1: scenarios c or e). The consequence of either scenario could be lung function that is below the threshold for chronic obstructive pulmonary disease (COPD; post-bronchodilator FEV_1/FVC below 0.70) in later adulthood.

We provide a narrative review of air pollution exposures and their associations with child lung function and lung function growth in general pediatric populations. We primarily focus on ambient air pollutants that are primary and secondary products of fossil fuel combustion and regulated by the US EPA (e.g., particulate matter <2.5 μm [$PM_{2.5}$] and <10 μm [PM_{10}], nitrogen dioxide [NO_2], ozone [O_3]), reporting results separately for short- and long-term exposures. We include a more systematic review of the recent literature on long-term exposure to ambient air pollution and child lung function. We also include separate summaries of the literature on air pollution that is not currently regulated or covered by the Clean Air Act but may have adverse child lung function effects. Specifically, we focus on air pollution from wildfires, indoor biomass and coal burning, gas and wood stove use, and

volatile organic compounds (VOCs) from household products. Exposure data and research on child lung function outcomes are much sparser for these pollutants compared with the large body of evidence on the outdoor criteria pollutants. For each section we provide boxed statements of “summary observations” and “knowledge gaps”.

While some families may have a few options to improve their children’s health by reducing air pollution exposures at home and during the school day, for consequential exposure reduction across the population structural changes and regulations at national, regional, and local levels are required. As neighbors and citizens, individual families can influence structural change and regulation, for example by advocating for electric buses, traffic-free zones, wildfire mitigation strategies, or public housing upgrades (e.g., ventilation, new stoves)—we acknowledge, however, that not all are empowered to do so. In the final segment of this review, we share summary observations (and knowledge gaps) about what can be done at the individual/household, local/regional, and national level to reduce air pollution exposures and improve child lung function, thereby improving child and subsequent adult respiratory health. Additionally, suggestions for future research are made.

We briefly describe our review methods. We searched the database PubMed with combinations of the following search terms: “‘lung function,” “pulmonary function,” “pollution,” “pollutant,” “traffic,” “child,” “children,” “childhood,” “adolescent,” “adolescence,” “in utero,” “prenatal,” and “early life.” We also searched using the following MeSH Terms in combination: “lung function test,” “air pollutants, environmental,” and “children.” Studies not in English were excluded, but we did not restrict by country—the scope was global. We conducted our search on October 15, 2020. We also reviewed the most recent US EPA Integrated Science Assessments (ISAs) for NOx, PM, O_3 for additional citations.[11–13] The ISAs were also helpful in providing context for interpretation of individual citations, as they provided a committee-based comprehensive review of experimental, toxicologic, and epidemiologic data to evaluate the specificity, temporality, and plausibility of associations of specific pollutants with a large range of child and adult health outcomes. Studies of household air pollution and wildfire smoke are not consistently reported as studies of pollution, and therefore we extracted studies from the above PubMed search and performed additional targeted literature searches using the terms “wildfire,” “smoke,” “household air pollution”, “gas stove,” “wood stove,” “biomass burning,” and “volatile organic compounds” to review the sparser literature on household/indoor and wildfire pollution and child lung function. In select cases where epidemiologic evidence is scant and toxicologic data was compelling to us (e.g., O_3 effects on lung development relevant to growth), we drew from the toxicology literature. We provide a complete summary of all studies found in our search that were published 2018 or later only for long-term ambient air pollution exposure and lung function level or growth because long-term exposure assessment has improved in the past several years due to satellite data availability, child lung function level and growth is a key indicator of future adult respiratory health, and these most recent studies have not previously been included in prior reviews.

SHORT-TERM AMBIENT AIR POLLUTION EXPOSURE AND CHILD LUNG FUNCTION

A large literature indicates that short-term air pollution exposures can acutely reduce lung function in children. This literature has been previously reviewed[11–16] and we will briefly summarize the findings here, focusing on studies of acute effects of ambient gases and particles in general pediatric populations. It is important to recognize that in panel studies of children—as well as any observational air pollution study—, inhalation exposure is to a mixture of air pollutants, thus the responses being measured are responses to that mixture. Air pollutant mixtures, however, may be dominated by one pollutant, or another, depending on the source of the mixture and whether the pollutant mixture is dominated by local sources (e.g., local traffic or nearby industries with ground-level emissions of primary pollutants), or regional pollution, with exposure to transported primary and secondary pollutants. Nevertheless, below we report a summary of studies that focused on specific pollutants, sometimes interpretable as representing sources or mixtures, and their acute influences on children's lung function.

Higher O_3 exposure has been linked with lower levels of lung function (both FEV_1 and FVC) in healthy children and those with asthma, with much evidence coming from panel studies of children attending schools or summer camps.[12, 14, 17–20] Short-term $PM_{2.5}$ exposure has been associated with acute decrements in lung function, including lower FEV_1/FVC, in healthy pediatric populations.[13, 21] Short-term PM_{10} exposure has also been linked with acute lung function decrements in children.[22, 23]

Epidemiologic studies have found associations between higher short-term ambient NO_2 (often considered as an indicator of exposure to traffic-related air pollution) with acute lung function decrements in children,[11, 16, 24, 25] although not all studies support this relation.[26, 27] For observed NO_2 associations, there is uncertainty as to whether NO_2 is the causal factor, there is confounding by correlated pollutants (e.g., $PM_{2.5}$), or NO_2 serves as a representation of a pollution mixture (e.g., traffic pollution) that is the causal factor.[11]

Often at significantly higher levels of exposure than in the U.S., recent panel studies of schoolchildren from sub-Saharan Africa, Bangladesh, and China add supporting evidence for acute lung function impacts of NO_2[28] and $PM_{2.5}$[29–31] and PM_{10}.[29, 31] Air pollution concentrations at study locations are important to consider (i.e., whether concentrations are below or well above recommended US EPA/European standards). In settings of low air pollution levels greater sample size is needed to detect associations should they exist.

Wildfires

Air quality regulations, technological advances such as improved catalytic converters, and a transition away from coal burning in many regions of Europe and the US have contributed to a downward trend in outdoor PM pollution. Despite these advances, in the Northwestern US and Northern California, air quality has in fact *worsened* between 1988 and 2016 as a result of wildfire activity in the US and Canada.[32] In the US, wildfires have become the #1 single

source of PM and contribute more than a third of the total annual burden of $PM_{2.5}$ in the atmosphere according to the US EPA Emissions Inventory.[33]

North America has experienced a sharp increase in the frequency of large, devastating wildfires as a result of longer, hotter fire seasons due to climate change, and years of fire suppression that have led to an over-accumulation of fire-prone organic matter.[34] Many other parts of the world, including Australia, Brazil, Southeast Asia, and Russia, are also grappling with increased wildfire activity—a worrisome trend that will continue globally due to climate change.

The composition of wildfire smoke varies depending on the type of fuel burned (e.g., forests, grasslands, peat bogs, human-made structures). Wildland smoke includes not only high levels of particles from organic sources, but also gases such as carbon monoxide (CO), nitrogen oxides (NOx; that also lead to O_3 formation), and volatile organic compounds including carcinogens such as benzene, benzo[a]pyrene, formaldehyde, and acetaldehyde.[34, 35] Even though wildfire smoke events may be relatively short in duration (e.g., days to weeks), the pollution levels can be extremely high. For example, $PM_{2.5}$ levels in San Francisco exceeded 200 $\mu g/m^3$ during the Camp Fire, while the average $PM_{2.5}$ level for the city is about 9 $\mu g/m^3$. In addition, smoke travels great distances. Children living in wildfire-prone areas today are exposed to smoke pollution from multiple regional fires during each wildfire season, which now continues for weeks to months longer than the wildfire season of a generation ago.

The respiratory effects of individual wildfire smoke pollutants (e.g., $PM_{2.5}$, NOx, O_3) are likely to be similar to the effects of those pollutants as identified in epidemiologic and mechanistic studies without regard for emission source. However, the composition of $PM_{2.5}$ emitting by burning wildlands is different from $PM_{2.5}$ emitted by fossil fuel combustion, and there are likely to be unique airway toxicities of the complex wildfire-generated smoke mixture of gases and particles. Among children (and adults) with asthma, for example, $PM_{2.5}$ from wildfires appears to be more likely to trigger an asthma exacerbation per unit mass than $PM_{2.5}$ from other sources, suggesting a possible enhanced inflammatory effect of the wildfire smoke mixture on asthmatic airways.[36, 37] There is evidence that healthy children who have smaller airways, as determined by a low ratio of the forced expiratory flow at 25–75% of the pulmonary volume ($FEF_{25–75}$) to the FVC, are more likely to experience respiratory symptoms when exposed to wildfire smoke than children with normal lung function.[38] These findings suggest an acute inflammatory effect of wildfire smoke on small airways.

Relatively few studies have examined the acute effects of short-term exposure to wildfire smoke on child lung function. A panel study measuring daily peak flow among 234 generally healthy schoolchildren aged 6 to 15 exposed to seasonal wildfires in the Brazilian Amazon found that higher levels of PM_{10} and $PM_{2.5}$ in the preceding 5 days were associated with lower peak flow.[39] In this study, younger children (aged 6–8) experienced greater decrements in peak expiratory flow rate (PEFR) in association with wildfire-PM than older children. A panel study of 309 schoolchildren exposed to smoke from biomass burning in the Brazilian Amazon also found associations between short-term $PM_{2.5}$ exposure and daily

PEFR, with greater effects for non-asthmatic children.[40] In one of very few studies of chronic effects of wildfires on child lung function, infants exposed to a 6 week coal mine fire had lower lung reactance as measured by forced oscillation technique at age 3 in association with their level of $PM_{2.5}$ exposure during the fire.[41] A study of rhesus macaque monkeys exposed as infants to ambient smoke from a series of Northern California wildfires in 2008 while housed in an outdoor colony had lower lung function at age 3 compared to unexposed monkeys.[42] These studies suggest that such extreme fire pollution events may have long term sequelae for lung function growth. However, there is a need for more studies on the chronic effects of long-term and repeated exposure to wildfire smoke on child lung function level and lung function growth.

LONG-TERM AMBIENT AIR POLLUTION EXPOSURE AND CHILD LUNG FUNCTION

Associations with subsequent level and growth of lung function

We first summarize the literature on long-term air pollution exposure and children's lung function in general pediatric populations and then present the findings from our systematic review of studies since 2018. Studies up to through approximately 2018 have been previously reviewed or summarized.[11–14, 43] A range of exposure windows, both in duration and timing, have been considered in prior studies. In studies of chronic air pollution exposure, lung function outcomes have often been assessed either (1) at a single time point (e.g., at age ~12 years; "lung function level"), or (2) at relatively few repeated time points with the difference (size of increase) between first and last lung function measure sometimes used as a proxy for lung function development (e.g., change in FVC between ages 8 and 16 years; "lung function growth"). We should note, however, that the use of only 2 to 3 repeated measures to represent lung function growth over time may lead to limitations in interpretation of the outcome (see below).

In their recent comprehensive review that extended beyond examination of the literature on traffic exposure and lung function to include pollution exposures from other sources, Schultz et al. concluded that regardless of the timing of exposure early life and school-age exposure to traffic-related air pollution adversely affects children's lung function.[43] The authors did not find firm evidence from the studies evaluated that exposure during certain age windows were more relevant for subsequent lung function. They instead concluded that exposure over the entire childhood period is of importance but suggested that more studies may be needed to define whether children were more vulnerable at specific life-stages.[43]

Defining effects of specific long-term pollutant exposures by particle size fraction, particle component, or level of pollutant gases

A large number of studies provide evidence that that long-term $PM_{2.5}$ is associated with lower lung function levels and slower lung function growth in children.[13] Studies have been conducted in multiple cohorts from several locations, with differing exposure assessment methods and from different time periods, adding to the robustness of the evidence. The evidence for the larger size range of PM_{10}—which includes road dust (tire and brake wear, road salt), wildfires smoke, and aeroallergens—is less robust due to lower availability of

long-term PM_{10} models.[13] Two studies that have been conducted, both in Europe, have found null associations between long-term PM_{10} exposure and child lung function.[44, 45] Recently, there is a renewed interest in the study of the coarse particle fraction (2.5μm-10μm; $PM_{10-2.5}$),[46] which is primarily composed of organic debris, crustal elements, and suspended road dust metals.[47] The effects of particles in this size fraction on child lung function, possibly mediated through their effects on the upper airway, including the nose, is an area of active investigation.[48]

Associations between long-term NO_2 exposure and decrements in lung function levels in children are also well-documented in the epidemiologic literature from studies in various locations with varied follow-up time and using different methods for exposure assessment and lung function measurements.[11] The evidence for adverse NO_2 effects is stronger for FEV_1, representing airway mechanical properties and/or airway caliber, compared with that for FVC, representing lung volume.[11] Uncertainty, however, remains as to whether NO_2 is the causal agent, if results are confounded by copollutant exposure, or if NO_2 represents a source that is the causal factor. Results from NO_2 models with adjustment for $PM_{2.5}$ are mixed, and it is therefore difficult to conclude whether the NO_2 associations with lung function are explained by effects of traffic particles that are imperfectly measured by NO_2 and $PM_{2.5}$[11]

Based on epidemiologic studies previously reviewed, studies with evidence supporting associations of long-term O_3 exposure with lower lung function levels and growth are inconsistent, suggesting perhaps that this pollutant may have its greatest chronic effects in regions of the world where exposure is more constantly elevated and where indoor penetration of outdoor air is greater.[12, 49–55] Toxicologic studies involving rodents and primates, in contrast, provide support of prenatal or early life effects of O_3 exposure on lung development, with suggestive evidence in Shore's rodent models of interactions amongst O_3, diet/obesity, and allergen exposures in their influences on the risk of airflow obstruction.[12, 56–62]

Following up on these prior thorough reviews and summaries, in Table 1 and in the text below we present a summary of recent lung function studies of general pediatric populations and long-term air pollution exposure assessment published since 2018, using the literature search methodology described in the introduction. We defined long-term air pollution exposure as exposure in some earlier time period (i.e., not concurrent, and not only the preceding 12 months). Lung function assessment must have included one of the following measures: FEV_1, FVC, or $FEF_{25–75}$ (the latter being the same as flow mean flow between 25% and 75% of FVC [$MEF_{25–75}$] and maximum mid-expiratory flow [MMEF]). We identified eight studies fitting these criteria. Five of the studies were based in Europe,[44, 48, 63–65] two in Asia,[66, 67] and one in the U.S.[68] Of these eight studies: four included exposure to NO_2 all of which found a negative association with lung function; two included O_3 of which one found a negative association with lung function; one included $PM_{2.5}$ which found a negative association with lung function; and five included PM_{10} of which three found a negative association with lung function. While all studies examined lung function levels and only one study[48] also examined lung function growth. This study, the Dutch Prevention and Incidence of Asthma and Mite Allergy cohort, assessed associations between

air pollution exposure from birth-4 years of age with lung function growth between ages 8 and 16 years in 721 children. They included into their models an exposure-age interaction term—which can be interpreted as the association of pollution exposure with annual rate of change in lung function.[48] They reported that $PM_{2.5}$ exposure was related to reduced FEV_1 growth.[48]

Our review of recent literature highlights the small number of assessments of lung function growth in studies of long-term air pollution at contemporary levels of exposure. As illustrated with hypothetical growth curves in Figure 1, the trajectories of lung function growth can be tracked throughout childhood, with assessment of whether children attain normal peak growth and avoid a steep decline that could lead to COPD or other respiratory deficits shown to be predictive of higher morbidity or mortality (Figure 1). More frequent longitudinal outcome measurements and more precise exposure estimates during critical childhood life stages offer more opportunities for investigators to assess whether and when air pollution perturbs lung function growth, and whether any deficit in growth can be recovered with reduced air pollution exposure (e.g., through regulation to reduce emissions or limit exposure to pollution sources at school, or interventions to purify the air). Single measures of lung function during adolescence are particularly challenging, as estimates of lung function growth during this period need to consider height growth and where the children are in their growth spurt, which differs by sex.[69] While challenging to perform, studies with repeated pulmonary function testing across childhood and adolescence would add important data to the literature by enabling evaluation of more nuanced aspects of the pollution-lung function growth relation, such as pollution effects on lung function growth velocity (i.e., time-varying rate of growth); whether effects are fixed or reversible; or whether effects differ by timing of exposure (e.g., during puberty—a period of great somatic growth related to lung development).

Studies evaluating effect of air pollutant mixtures

Continued child lung function research should consider the context of air pollution mixtures when examining health effects. Such considerations can refer to a number of different research questions, such as: Which pollutant is the causal agent in this mixture? Do pollutants interact in their health effect? What is the overall effect of the mixture?[70] Air pollution studies often examine one pollutant at a time due to statistical realities regarding multi-collinearity for highly correlated pollutants. Some studies of child lung function have implemented multi-pollutant models examining the effects of multiple pollutants in a single model (e.g., $PM_{2.5}$ and NO_2 together as explanatory variables in a single model), often just two pollutants,[25, 71, 72] although some studies have included more.[49] This type of approach is often used to answer the first question above, which is the causal agent or dominant mixture/cluster associated with the adverse outcome?[70] There have been several recent advancements in mixture model approaches[70, 73, 74]—a research area of great interest in environmental epidemiology—that could be implemented in studies of child lung function to improve understanding of air pollution effects. Overall, however, disentangling the effects of individual pollutants is challenging and often not possible in observational studies in children, as compared to toxicologic studies and controlled human exposure studies in adults, which themselves have limitations in terms of size, generalizability, and potential to

measure long-term as opposed to short-term exposure responses. Nevertheless, complementary studies from these and other fields will continue to be needed to evaluate causality and understanding potential biologic mechanism. In some cases, removing or reducing the exposure and witnessing the improvement in health has been the strongest evidence for causality.

INDOOR SOURCES OF AIR POLLUTION AND CHILD LUNG FUNCTION

Young children often spend most of their time at home, where they are exposed to household air pollution (from household sources such as cooking and heating) and ambient pollution (from outdoor sources) that penetrates inside the home. Here, we review the literature on three major sources of household air pollution—biomass burning, gas stove use, and VOCs—and child lung function.

Indoor Biomass and Coal Burning

In low- and middle-income countries, biomass burning for cooking or heating is a major source of air pollution inside the home, and in the neighborhood if vented to the outdoors. The few studies of indoor biomass or coal burning for cooking or heating have generally found that these exposures are associated with lower lung function in children.[75–80] The largest of these followed more than 3,000 children aged 6–13 with repeated lung function measures in four Chinese cities and found that use of coal as a household fuel was associated with a 16.5 (95% CI −23.6, to −9.3) mL/year lower annual growth of FEV_1, and a 20.5 (95% CI-28.3 to −12.7) mL/year lower growth of FVC.[78] This study also found that household ventilation improved lung function growth. A small number of intervention studies in low-income countries have examined the effect of placing clean cookstoves in homes to improve indoor air quality. Most of these have examined childhood pneumonia as the primary outcome, with mixed results.[81] The RESPIRE trial placed clean chimney stoves in households with pregnant women and infant children in Guatemala either at baseline or 18 months later. Among the 440 children with longitudinal spirometry testing, delayed (18 month) chimney stove placement was associated with slower PEF growth of 173 mL/min/year (95% CI −341 to −7) and slower FEV_1 growth of 44 mL/year (95% CI −91 to 4).[82] This suggests an effect of early life indoor air quality on lung function growth that may not be fully reversible with a subsequent air quality intervention, and that household air quality interventions during infancy may have lasting lung function benefits.

Indoor biomass burning is not only a phenomenon in low- and middle-income countries. Wood-burning stoves are a common source of heating in many high-income countries. In the US, wood stove use has been increasing over the past two decades, and it has been estimated that 11 million households and more than three million children are exposed to higher levels of indoor particulate matter due to the use of wood-burning stoves for heating.[83] In a recent narrative review of 36 studies conducted in developed countries on the pediatric health effects of wood smoke exposure, estimated community-level wood smoke exposure was consistently associated with child respiratory symptoms, while findings on wood stove use were less consistent.[84] There are few studies of wood stove use and child lung function. The recent review identified a single study, which was conducted in Turkey among 617

schoolchildren aged 9–12 years and found lower average child lung function among those living in households using wood stoves.[85] Pediatric research on wood stove use has relied on self-reported questionnaire data, and there is a clear need for studies that measure wood smoke pollution in the home to arrive at a more precise estimate of household air pollution exposure.[84]

Gas Cooking

Gas cooking is a common source of indoor NO_2 in low-, middle-, and high-income countries, with peak indoor NO_2 levels during cooking far exceeding exposure to NO_2 from outdoor sources that penetrates indoors.[86] In fact, it has been estimated that more households are exposed to indoor NO_2 levels above the 1-hour US EPA national ambient air quality standard for NO_2 due to use of unvented gas stoves than NO_2 emitted by outdoor pollution sources that enters the home.[87] While controlled human exposure studies have yielded inconsistent results regarding the acute effects of NO_2 gas alone on lung function at typical outdoor NO_2 exposure concentrations (up to 20 ppb), indoor NO_2 concentrations can exceed 100 ppb (especially in the absence of outdoor kitchen ventilation),[87] and among adults such concentrations have been linked to oxidative stress and acute decrements in lung function.[88] Numerous individual studies have examined whether gas stove cooking is associated with lower lung function in children, with inconsistent findings.[89, 90] Inconsistencies may vary in part by whether the gas stove has a continuously burning pilot light, whether it is vented to the outdoors, whether it is used for heating the home, and also by the amount of air exchange in the home. A meta-analysis combining data from 24,000 children in Europe and North America concluded that gas stove cooking is associated with a small but significant reduction in FEV_1 (0.7%) and FVC (0.6%), with evidence of greater effect sizes among children with atopy.[91] This suggests a reduction in average lung function among healthy children with gas stoves in the home, and that children with allergic phenotypes may be more susceptible. If true, this would add to a very long and complicated literature on the effect of gas stove use on risk of childhood asthma and respiratory symptoms among children with asthma or atopy.[92, 93]

There is also some evidence that gas stove ventilation can mitigate the effect of gas stoves on lung function: in NHANES III girls living in households with gas stoves using ventilation had higher FEV_1 and FEV_1/FVC than those with gas stoves and no ventilation.[94] This suggests an opportunity to improve child lung function through household interventions such as improved ventilation or replacement of gas stoves with electric models.

Volatile Organic Compounds

VOCs include wide range of chemicals, and while emission sources are numerous and varied most are emitted from indoor sources such as paints and floor coverings, building materials and furnishings, and consumer products (e.g., cleaning supplies, air fresheners, hobby supplies).[95–97] Outdoor sources (e.g., industrial facilities, dry cleaners, gasoline stations) and attached garages can also contribute to residential VOC exposure.[96, 98] Concentrations of many VOCs are often higher indoors compared with outdoors levels.[96, 99]

Adverse effects of VOCs children's respiratory health have been reported,[100–102] but there are very few studies examining associations with lung function in children.[103–106] A Canadian study measured 84 VOCs in residential indoor air and report that among the 709 participants aged 6–16 years there were significant reductions in lung function observed for nine VOCs.[103] The largest associations were a 9.0% (95%CI: −15.4, −2.6) decrease in FEV_1, associated with an IQR change in nonanal, and a 5.1% (95%CI: −9.2, −1.0) change in FEV_1 associated with an IQR change 2-furancarboxaldehyde.[103] A study of 772 Mexican preschoolers examined prenatal VOC exposure and lung function measured with forced oscillation tests at 36, 48, and 60 months of age.[104] Negative associations between prenatal exposure to xylene and respiratory reactance were reported, but null associations for benzene and toluene were found.[104] Data from a South African birth cohort with lung function measured at 6–10 weeks of age among 645 infants demonstrated higher levels of household benzene to be associated with lower early lung function as measured by the forced oscillation technique.[105] Higher levels of prenatal exposure to benzene were associated with clinically significant deficits in FEV_1 among 620 Spanish preschoolers (aged 4.5 years); however, this study used estimates of outdoor (not indoor) benzene levels at residential address.[106] Given the expansive sources of VOCs and their ubiquitous presence in the air, especially indoors, coupled with this small literature, their effects on child lung function merit further research.

WHAT CAN BE DONE?

There are several actions that can be taken to reduce children's exposure to air pollution, implemented at a range of control levels from individuals and families to national policies (Figure 2). Interventions at higher levels (e.g., national air quality standards) would impact a larger number of people compared with actions taken at smaller scales (e.g., an air filtration unit will only reduce exposure for those within the household). To be clear we are not recommending each of the interventions, instead when there is sufficient or reasonable evidence then such interventions could be considered and implemented.

Individual and Household Interventions

Several studies of air pollution interventions at the household and individual levels have identified subsequent improvements in child respiratory health (though not always including lung function as an outcome). As discussed above, improved kitchen ventilation and placement of clean cookstoves appear to benefit child lung function, especially if done early in life. Short-term use of indoor air purifiers has been found to lower airway resistance in adults[107] and appears to improve asthma symptoms,[108] but any long-term benefits of indoor air filtration on child lung function or lung function growth remains unknown.

National and Local Policies to Improve Outdoor Air Quality

Several studies have taken advantage of changes—usually reductions—in air pollution levels to investigate subsequent impacts on children's lung function. These studies add to the evidence of a causal relationship between air pollution and respiratory health, directly relating to the "experiment" viewpoint of the Bradford Hill criteria for causality.[109] If lung function is adversely impacted by higher air pollution exposure—and these relations are

truly causal—then it is expected in situations of improved air quality benefits in lung function would be observed. Here we provide a brief review of studies that have used this approach.

During the 1990s the reunification of Germany saw marked declines in air pollution levels, including for total suspended particles and sulphur dioxide, and several studies of schoolchildren from East and West Germany reported associated improvements in lung function primarily based on consecutive cross-sectional surveys between 1992 and 1999.[110, 111] Using multiple prospective cohorts consecutively recruited in the 1990s and early 2000s in the Southern California Children's Health Study (CHS), studies have reported observed improvements in air quality to be associated with improved lung function in schoolchildren.[50, 52, 55, 112] In the most recent of these CHS studies, which combined data from three cohorts spanning a 13-year period of air quality improvement, lower concentrations of NO_2, $PM_{2.5}$, and PM_{10} across cohorts were related with improved lung function growth between the ages of 11 and 15 years.[52] An evaluation of the Oxford Transport Strategy (implemented in 1999 to reduce city center congestion) did find improvements in lung function in schoolchildren as measured by peak expiratory flow (PEF) after its implementation, but these improvements were not related to observed changes in traffic exposure.[113] A 5-year study of London's low emission zones (implemented in 2008, restricts vehicle entry in urban areas and applies penalties on polluting vehicles) found reduced NO_2 and NOx concentrations, although not PM_{10}, and that annual NO_2 and PM_{10} exposures were inversely associated with FVC in 8–9 year old children; however, no change was observed in the proportion of children with small lung volumes for their age over the study period.[114] Adoption of clean air technologies and fuels in school buses were found to reduce $PM_{2.5}$ and ultrafine PM in buses, and ultralow-sulfur diesel adoption was associated with improved changes in FVC and FEV_1 school bus riders (aged 6–12 yrs).[115] Other interventions that have been found to improve health (though child lung function was not a measured outcome) include public guidance for low-pollution walking/biking routes,[116–119] idle-free zones,[120] and complete streets programs.[121] Increasing neighborhood green space[122] and the building of affordable "healthy housing"[123] may also reduce indoor and outdoor air pollution exposures. Future lung function research should continue to take advantage of "natural experiments" to improve understanding of the air pollution impacts on children's respiratory health.

It is important to acknowledge that individuals may be limited in their ability to engage in pollution exposure reduction activities and advocacy due structural or social constraints (Figure 2), which could lead to further disparities in pollution exposure. For example, individual families may not have the financial resources to undertake interventions such as replacement of stoves or installation of air purifiers, and instead structural changes (e.g., in public and private housing, insurance coverage) would be needed to bring about such interventions. Some U.S. communities have suffered an overt expression of structural racism through historical "redlining", leading to the siting of communities, their homes, and their schools nearer to highways and sources of air pollution, which in turn have public health effects.[124–126] Lastly, just as people are exposed to air pollutants as a mixture, people are exposed to several factors concurrently when one considers the wider realm of exposures, including other environmental exposure, individual characteristics including heritable

factors, diet/nutrition, psychosocial stressors, structural racism, etc., which can interact to either adversely or beneficially impact health outcomes such as lung function.[53, 127–130]

CONCLUSION

There is a large literature supporting the link between air pollution exposure and adverse effects on children' lung function level and growth; however, many questions remain, some relating to more nuanced understanding of air pollution effects and others to new or less studied exposures. Studies of repeated measures of pulmonary function in children as they grow—including into adulthood—would provide significant opportunity to expand our understanding of air pollution effects on children's lung function. Important areas needing further study include identification of windows of increased susceptibility, whether early life effects are fixed or reversible, evaluating the long-term effects of repeated wildfire events on child lung function, and the effect of air quality interventions at the individual, household, and local level on child lung function and respiratory health. As additional studies are conducted to improve scientific knowledge about the adverse effects of air pollutants on children, simultaneous efforts at the individual, local/city, state and national level can be made to improve indoor and outdoor air quality, with assessment of the short and long-term benefits to children and their families. Citizen and community engagement on the need for improved air quality and environmental justice may inspire ground-breaking policy changes with lasting health benefits.

The rate of lung function decline and level of lung function in later adulthood are strong predictors of overall morbidity and mortality. If reduction of air pollution exposures improves lung function growth, maximizes the peak lung function children attain as young adults, and minimizes population decline in lung function in adulthood, this will have significant long-term benefits for the health of the next generation.[131]

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ABBREVIATIONS:

CO	Carbon monoxide
COPD	Chronic obstructive pulmonary disease
$FEF_{25–75}$	Forced expiratory flow at 25–75% of the pulmonary volume
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
ISA	Integrated Science Assessments
$MEF_{25–75}$	Mean flow between 25% and 75% of FVC
MMEF	Maximum mid-expiratory flow

NO_2	Nitrogen dioxide
NO_3-	Nitrate
NOx	Nitrogen oxide
O_3	Ozone
PEF	Peak expiratory flow
PEFR	Peak expiratory flow rate
PM	Particulate matter
PM_{10}	Particulate matter <10 μm
$PM_{2.5}$	Particulate matter <2.5 μm
SO_2	Sulfur dioxide
US EPA	United States Environmental Protection Agency

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What Do We Know?

- Short-term exposure to ozone, nitrogen dioxide, and particle pollution have been associated with lower child lung function
- Fine particulate matter levels can reach extreme concentrations during wildfires, and are associated with acute decrements in peak expiratory flow
- Long-term early childhood exposure to ambient pollutants, especially nitrogen dioxide and fine particulate matter, are associated with subsequent children's lung function level
- Children worldwide are often highly exposed to smoky household air pollution at a very critical age of lung development

What Is Still Unknown?

- Long-term consequences of repeated exposure to wildfire smoke on child lung function
- Whether timing or cumulative period of exposure influences if pollution effects are fixed or reversible over time, as children reach adulthood
- Long-term consequences of air pollution on reduced lung function development in childhood are not fully understood. Studies need to investigate impacts of childhood exposures on lung function trajectories and later respiratory health in adulthood
- Need to understand (i) who is more susceptible to the adverse lung function effects of gas stove pollution and (ii) the extent to which gas stove-related lung function decrements are improved or prevented with improved kitchen ventilation
- What factors, in trials for homes with biomass or coal burning cookstoves, are responsible for the inconsistencies in effects of provision of clean stoves and improved indoor ventilation on child lung function

Box 1.

Why Study Effects of Ambient Air Pollution on Lung Function in Children?

Why children

- More susceptible to pollution effects due to developing physiology
- Increased exposure due to size and behavior

Why lung function

- Subclinical marker with short- and long-term clinical implications for lung health across the lifespan
- Clinical outcome measure in children with asthma, cystic fibrosis, and other chronic lung diseases

Box 2.

Short-term Ambient Air Pollution Exposure and Children's Lung Function

Summary observations

- Short-term exposure to O_3 and particle pollution ($PM_{2.5}$ and PM_{10}) have been associated with lower lung function, including lower FEV_1, FVC, and FEV_1/FVC, in generally healthy children and in those with asthma
- Large wildfires are occurring at increasing frequency and are a major source of PM and other pollutants
- $PM_{2.5}$ levels during wildfires can reach extreme concentrations that far exceed air quality standards and are associated with acute decrements in peak expiratory flow
- Short-term elevations NO_2 levels outdoors and indoors have been associated with reduction in child lung function

Knowledge gaps

- Need to improve understanding of the extent to which observed acute effects of NO_2 on child lung function are causal, due to confounding by correlated pollutants (e.g., $PM_{2.5}$), or represents a pollution mixture that is causal (e.g., traffic pollution)
- Need to evaluate the long-term consequences of repeated exposure to wildfire smoke on child lung function

Box 3.

Long-term Ambient Air Pollution and Children's Lung Function

Summary observations

- A large number of studies support a relation between early-life or long-term air pollution exposures and subsequent children's lung function level, with the most epidemiologic evidence for $PM_{2.5}$ and NO_2
- There is inconsistent evidence of an effect of early-life or long-term exposure to O_3 on subsequent children's lung function, although animal model studies suggest pre-natal or early-life O_3 effects on lung development
- Associations with long-term exposures are more consistent for FEV_1 compared with for FVC, which may indicate greater impacts on airway caliber/airflow obstruction than overall lung size or growth

Knowledge gaps

- While there is evidence that air pollution exposure at all ages in childhood can have adverse lung function effects, few studies have evaluated whether timing or cumulative period of exposure influences whether pollution effects are fixed or reversible
- Long-term consequences of air pollution on reduced lung function development/growth/trajectories in childhood are not fully understood; studies need to investigate impacts of childhood exposures on lung function in adulthood as well as risk for later respiratory health, such as chronic obstructive pulmonary disease, emphysema, fibrosis, or pulmonary vascular disease
- Need to further assess the toxicity of specific PM components and sources on lung function

Box 4.

Indoor Sources of Air Pollution and Children's Lung Function

Summary observations

- Worldwide, young children are often highly exposed to smoky household air pollution from biomass burning for heating and cooking at a very critical age when their lungs are developing
- There are a few trial studies providing evidence that installation of clean chimney stoves in infancy may lead to more rapid lung function growth
- Installation of clean stoves can improve indoor air pollution, but levels of indoor/outdoor pollution may remain elevated (though lower than previously) and these reductions are inconsistently associated with improvements in lung function

Knowledge gaps

- Gas stoves.
  - Need to understand who is more susceptible to the adverse lung function effects of gas stove pollution
  - Need to understand the extent to which gas stove-related lung function decrements are improved or prevented with improved kitchen ventilation
- Biomass and coal burning cook stoves
  - Need to assess what additional exposures or factors in the use of multiple fuel sources or lack of stove maintenance are responsible for the inconsistencies in effects of provision of clean stoves and improved indoor ventilation on child lung function
- Additional research is needed on the effects of VOCs on child lung function to corroborate the few existing studies which provide evidence of adverse effects

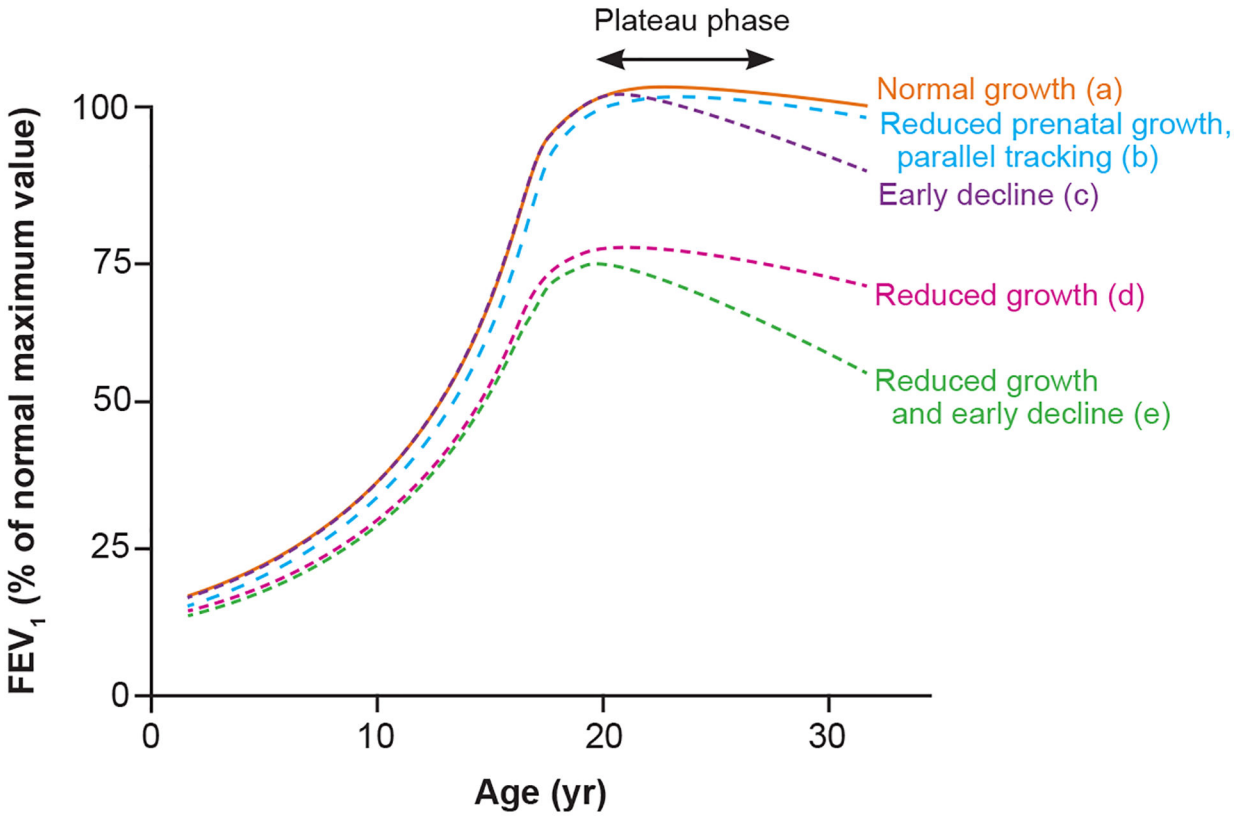

FIGURE 1.

Hypothetical lung function trajectories depicting normal and reduced growth and early decline (figure adapted from McGeachie et al[9]).[8, 10] (a) Normal pattern of lung function growth. (b) Reduced prenatal growth with postnatal growth tracking at a fixed percent predicted lower than normal. (c) Normal growth until late teen years, when peak lung function growth is reduced, and lung function begins to decline early. (d) Reduced growth and (e) reduced growth with early decline. Both (d) and (e) can result in levels of lung function consistent with diagnosis of chronic obstructive lung disease.

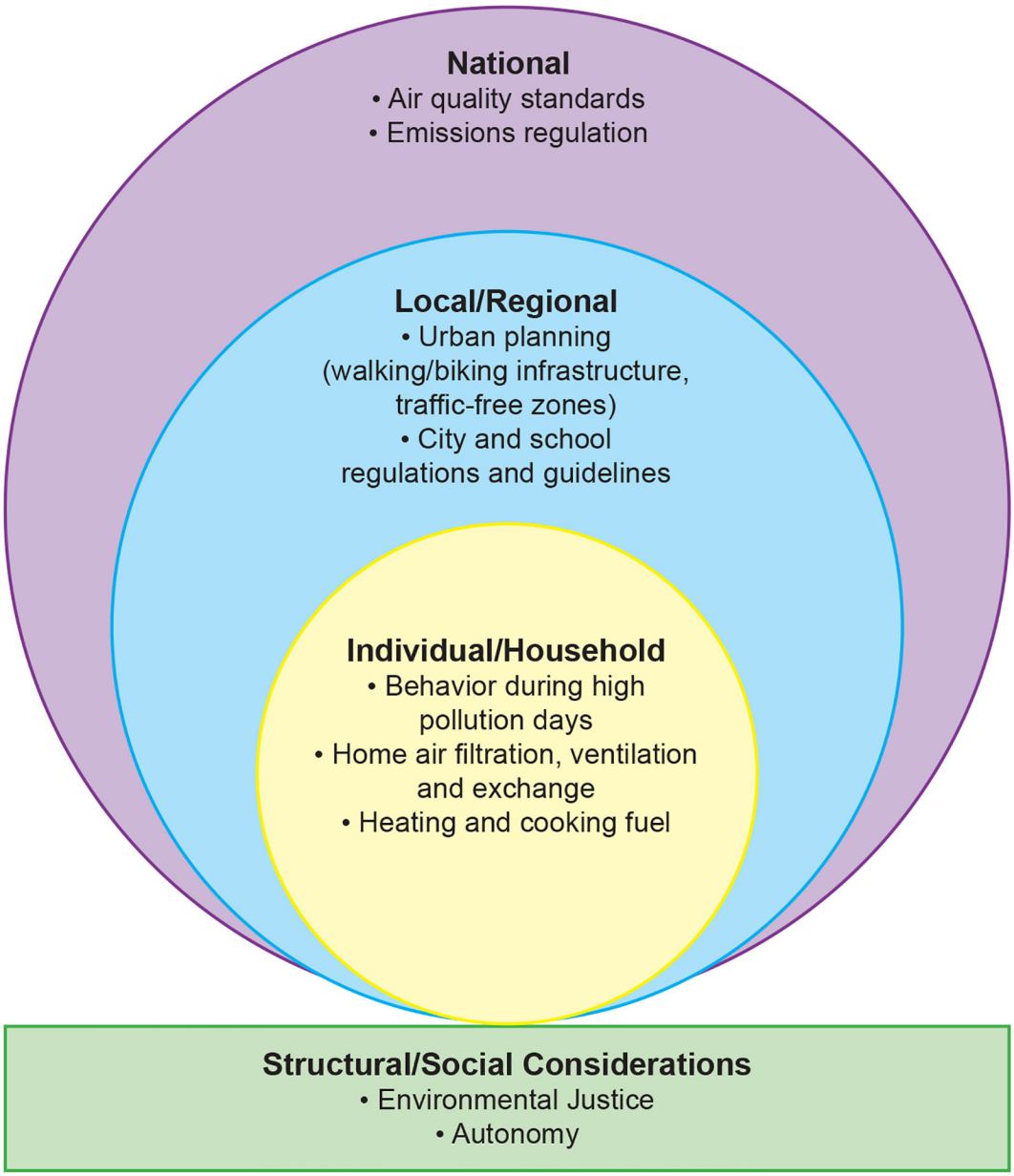

FIGURE 2.
Examples of current or potential air pollution interventions at various intervention levels.

Table 1.

Summary of studies on long-term air pollution and lung function in healthy or population-based children published since 2018.

Reference	Population (location, cohort name)	Study design	Exposure focus	Exposure Assessment	Lung function Assessment	Results
Cai et al. 2020[44]	5,276 children at age 8 years, 3,446 children at age 15 years (Avon in southwest England, ALSPAC)	Prospective birth cohort	Prenatal and childhood air pollution	PM_{10} during each trimester, 0–6 months, 7–12 months, and up to age 15 years	FEV_1% predicted and FVC% predicted at ages 8 and 15 years	• At age 8 years PM_{10} was associated with lower FEV_1% predicted and FVC% predicted • At age 15 years no observed adverse association with lung function
Usemann et al. 2019[63]	232 children at age 6 years (Bern, Switzerland, BILD)	Prospective birth cohort	Low-to-moderate air pollution levels, from pregnancy until school-age	NO_2, O_3, PM_{10} during each pregnancy, 1st year of life, 6th year of life, and birth until follow-up	FEV_1, FVC, FEV_1/FVC ratio, and $FEF_{25–75}$ measured at age 6 years	• NO_2 exposure during pregnancy and 1st year of life was associated with decreased FEV_1 • Null associations observed for O_3 and PM_{10}
He et al. 2019[66]	2,942 children at age ~17.5 years (Hong Kong, “Children of 1997” cohort)	Prospective birth cohort	Prenatal and childhood air pollution	NO, NO_2, PM_{10}, and SO_2 during pregnancy, age 0–2 years, and age 2–8 years	FEV_1, FVC, $FEF_{25–75}$, and FEV_1/FVC ratio measured at age ~17.5 years	• Higher NO and NO_2 in utero, age 0–2 years and age 2–8 years were consistently associated with lower FEV_1, FEV_1/FVC and $FEF_{25–75}$% in multi-pollutant analysis • SO_2 and PM_{10} were not associated with lung function
Milanzi et al. 2018[48]	915 children for the age 8–16 years growth analysis, 721 for the age 16 years analysis (The Netherlands, PIAMA)	Prospective birth cohort	Air pollution exposure from birth	NO_2, $PM_{2.5}$, PM_{10}, and PM coarse during preschool, primary school, and secondary school time windows	FEV_1 and FVC measured at age 16, and FEV_1 and FVC growth from ages 8 to 16 years based on repeated measures at ages 8, 12, and 16 years	• Exposure during the preschool period was associated with reduced FEV_1 growth for all pollutants • No association with FVC growth, except for a positive association with $PM_{2.5}$ • Across pollutants and time periods, higher air pollution was associated with lower FEV_1 at age 16 • Inverse associations were also observed for FVC at age 16, but these were not statistically significant
Tsui et al. 2018[67]	1,016 children age 6–15 years (Taiwan)	Nationwide, cross-sectional, school-based survey	Lifetime residential exposure to air pollution	PM_{10}, O_3, SO_2, NO_2, and CO during 1st year of life, age 2–6 years, and lifetime	FEV_1, FVC, $FEF_{25–75}$, and FEV_1/FVC ratio measured once among children at mean age 11.9 years (standard deviation: 2.4)	• Lifetime PM_{10} and O_3 was associated with lower FEV_1, FVC, and $FEF_{25–75}$ • NO_2 was associated with FEV_1 and FVC in all exposure windows examined • CO showed some association with lower lung function

Reference	Population (location, cohort name)	Study design	Exposure focus	Exposure Assessment	Lung function Assessment	Results
						• SO_2 was not associated with lung function
Bougas et al. 2018[64]	788 children age 8–9 years (Paris, France, PARIS)	Prospective birth cohort	Traffic-related air pollution	NOx during each trimester and entire pregnancy, 1st year of life, and lifetime	FEV_1, FVC, and $FEF_{25–75}$ measured at age 8–9 years	• Prenatal NOx exposure during the entire pregnancy was associated with a lower $FEF_{25–75}$, but there were no significant associations with FEV_1, FVC, or FEV_1/FVC ratio • Associations were similar for NOx exposure during the second trimester, but associations were null for the first and third trimester • Null associations for 1st year of life and lifetime exposure
Bose et al. 2018[68]	191 children age 5–8 years (Boston, USA, ACCESS)	Prospective birth cohort	Prenatal NO_3- exposure	NO_3- during pregnancy by gestational week	FEV_1, FVC, $FEF_{25–75}$, and FEV_1/FVC ratio measured once among children at mean age 7.0 years (standard deviation: 0.89)	• No statistically significant sensitive window was identified in the overall population • Shape of the associations across gestation suggests an early window in pregnancy during which higher exposure to nitrates may be associated with reduced FEV_1 • Cumulative effect over entire gestation suggested an inverse association, but results were not statistically significant
Bergstra et al. 2018[65]	424 children age 7–13 years (East Vlissingen in southwest of The Netherlands)	Cross-sectional study	Long-term air pollution from heavy industry	$PM_{2.5}$ and NOx during prior five years	FVC, FEV_1, PEF, $FEF_{25–75}$, FEV_1/FVC ratio measured once among children between the ages of 7 and 13 years	• $PM_{2.5}$ and NOx were associated with lower PEF • Higher NOx was associated with lower FVC and FEV_1

Abbreviations:

CO: Carbon monoxide

$FEF_{25–75}$: Forced expiratory flow at 25–75% of the pulmonary volume

FEV_1 : Forced expiratory volume in 1 second

FVC: Forced vital capacity

NO_2: Nitrogen dioxide

NO_3-: Nitrate

NOx: Nitrogen oxide

O_3: Ozone

PEF: Peak expiratory flow

PM_{10}: Particulate matter <10 μm

SO_2: Sulfur dioxide

$PM_{2.5}$: Particulate matter <2.5 μm