Effects of Long-Term Exposure to Traffic-Related Air Pollution on Lung Function in Children

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters

| Citation         | Schultz, Erica S., Augusto A. Litonjua, and Erik Melén. 2017. “Effects of Long-Term Exposure to Traffic-Related Air Pollution on Lung Function in Children.” Current Allergy and Asthma Reports 17 (6): 41. doi:10.1007/s11882-017-0709-y. http://dx.doi.org/10.1007/s11882-017-0709-y. |
|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Published Version| doi:10.1007/s11882-017-0709-y                                                                                                                                                                                                                                                                                                           |
| Citable link     | http://nrs.harvard.edu/urn-3:HUL.InstRepos:33439352                                                                                                                                                                                                                                                                                   |
| Terms of Use     | This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA                                                                                     |
Effects of Long-Term Exposure to Traffic-Related Air Pollution on Lung Function in Children

Erica S. Schultz 1 · Augusto A. Litonjua 2 · Erik Melén 1,3,4

Published online: 27 May 2017
© The Author(s) 2017. This article is an open access publication

Abstract Lung function in early life has been shown to be an important predictor for peak lung function in adults and later decline. Reduced lung function per se is associated with increased morbidity and mortality. With this review, we aim to summarize the current epidemiological evidence on the effect of traffic-related air pollution on lung function in children and adolescents. We focus in particular on time windows of exposure, small airway involvement, and vulnerable sub-groups in the population. Findings from studies published to date support the notion that exposure over the entire childhood age range seems to be of importance for lung function development. We could not find any conclusive data to support evidence of sup-group effects considering gender, sensitization status, and asthma status, although a possibly stronger effect may be present for children with asthma. The long-term effects into adulthood of exposure to air pollution during childhood remains unknown, but current studies suggest that these deficits may be propagated into later life. In addition, further research on the effect of exposure on small airway function is warranted.

Keywords Adolescence · Asthma · Cohort · Epidemiology · Sensitization · Small airways · Spirometry

Introduction

Air pollution (outdoor and indoor) is a global problem and one of the most important environmental determinants for human health. About 300 million children worldwide breathe highly toxic air, defined as levels six or more times exceeding international guidelines [1]. Indoor and outdoor air pollution is linked to 1 in 10 deaths in children under 5 years of age, and out of these, about 20% are attributable to outdoor air pollution levels [2]. The most important process contributing to levels of ambient air pollution in urban settings relates to the combustion of fuels. Due to the proximity between people and sources, road traffic is particularly important for the population exposure to ambient air pollution in developed countries.

Lung development starts in utero, and exposure to air pollution prenatally has been shown to negatively affect respiratory health [3]. Considerable maturation of the lungs continues after birth, which makes the lungs potentially vulnerable to the effects from exposure to air pollution also postnatally. Infants are relatively immobile and are often in a pram during outdoor transportation, at the level of motor exhaust emissions. Infants and children may also be more exposed to air pollution compared to adults relative to their size, due to higher ventilation per minute. In addition, the immune system of infants and young children is not fully developed, which may contribute to an increased vulnerability to the effects of exposure to air pollution [4].

Lung function in early life has been shown to be an important predictor for peak lung function in adults and later decline [5, 6]. Reduced lung function per se is associated with increased morbidity and mortality, even among healthy non-
smoking individuals with only modestly reduced lung function [7, 8]. Longitudinal studies have revealed that, taking height and gender into consideration, the deviation of an individual’s value of lung function from the population average remains rather constant independent of age. This is known as tracking of lung function, and a person is said to follow his or her own trajectory if crude lung function values are increasing as expected, relative to age, height, and gender [5, 9]. From a public health perspective, it is therefore of great interest to evaluate the effect of modifiable environmental factors such as pre- and postnatal air pollution exposure on children’s lung function, given the potential long-term effects.

With this review, we aim to summarize the current epidemiological evidence on the effect of traffic-related air pollution on lung function in children and adolescents. We will particularly focus on time windows of exposure, small airway involvement, and vulnerable sub-groups in the population.

Search strategy and selection criteria

We searched the PubMed databases for publications from Jan 2006 to March 2017, with the search terms (TRAP OR (traffic AND pollut* OR emission* OR PM OR NO OR particle*)) AND (“Lung function” OR spirometry OR “pulmonary function” OR “forced expiratory” OR “FEV*” OR “Impulse oscillometry” OR “forced oscillat* techniq*” OR “FOT” OR “lung volume” OR “small airway*” OR “peripheral airway”) AND (Children* OR “school-age” OR “pre-school*” OR infant* OR adolescence*), as well as (TRAP OR traffic OR pollut* OR emission* OR PM OR NO OR particle*)) AND (“Impulse oscillometry” OR “small airway*” OR “peripheral airway*”).

From PubMed search, 258 articles were identified. We also identified references from the bibliographies of these publications and from a review article by Gotschi et al. from 2008 [10].

Included articles had longitudinal air pollution data (about 1-year estimates or proxies for long-term traffic-related air pollution (like traffic counts/density). In summary, 32 articles with cross-sectional lung function data (Table 1) were included, as were 12 articles with longitudinal lung function data (Table 2).

Air Pollution Exposure

Ambient (outdoor) air pollution constitutes a complex mixture of compounds, which vary in concentration depending on sources, geography, topography, wind direction and speed, temperature, ultraviolet radiation, and relative humidity. The concentrations of pollutants may be correlated both in time and space, because they come from the same sources and are distributed similarly. Therefore, in studies of health effects, it may be difficult to discern the importance of one pollutant from the other.

Ambient air pollution consists of organic and inorganic liquid and solid particles suspended in air (particulate matter—PM), as well as different types of gases such as ozone ($O_3$), nitrogen oxides ($NO_x$), and carbon monoxide (CO), as well as vapors, as volatile organic carbons (VOCs) [55]. Classification of particles is often according to size, and this provides information about possible health effects. For example, particulate matter with an aerodynamic diameter of less than 10 $\mu$m (PM$_{10}$) is inhalable and reaches the lower airways and is subdivided into PM$_{coarse}$ (PM with a diameter between 2.5 and 10 $\mu$m), which reach the proximal airways, and PM$_{2.5}$ (PM $< 2.5$ $\mu$m), which reach the more peripheral regions of the lungs where gas exchange occurs. Ultrafine particles consist of those with a diameter of less than 0.1 $\mu$m, which contribute little to the total mass but are higher in numbers, have a large surface area, and are suggested to reach past the alveolar wall into the blood circulation [56].

Proposed Mechanisms Related to Health Effects

The exact mechanisms by which air pollution affects the lungs and airways are not known. It has been hypothesized that oxidative stress and airway inflammation are important processes [57]. It has for example been suggested that inhaled particles provoke the generation of reactive oxygen species. This, as well as direct damage by highly oxidative gases such as ozone and NO$_2$, induces oxidative stress and inflammatory responses [55]. Epigenetics has been proposed as one of the links between exposure to air pollution and respiratory health effects, for example through methylation of genes involved in immune-mediated inflammatory response [58, 59]. In studies of human histological lung tissue, correlations have been observed between exposure to high PM levels and small airway remodeling by greater amounts of fibrous tissue and smooth muscle cells [60].

Studies investigating exhaled nitric oxide in humans support the notion that inflammatory processes may play a role for the observed respiratory health effects by exposure to air pollution [61]. Nitric oxide is an established biomarker of airway inflammation, and several studies show a relation between exposure to air pollution and increased levels of the exhaled fraction of nitric oxide (FeNO). This has been observed for short-term exposures, long-term exposures, markers of traffic-related air pollution, and even in children with no history of airway damage [61].

Air Pollution Exposure and Lung Function in Children and Adolescents

A number of epidemiological studies have investigated the association between long-term exposure to traffic air pollution and lung function in children and adolescents, and evidence on the negative effects of exposure to air pollution on respiratory health is accumulating. The studies with individual exposure assessment and in case of aggregated data use, studies with at least three communities included are summarized in Tables 1 (cross-sectional studies) and 2 (longitudinal studies).
| Author, year          | Country (cohort name) | N     | Ages (years) | Exposure(s)                                                                 | Outcome(s)                  | Subgroup(s) | Main findings |
|----------------------|-----------------------|-------|--------------|-----------------------------------------------------------------------------|-----------------------------|-------------|---------------|
| Barone-Adesi, 2015   | UK (CHASE)            | 4884  | 9–10         | PM₁₀, PM₂.₅, NOₓ, NO₂, NOₓO₂, O₃ (annual average for current year based on dispersion modeling at home address), traffic-proximity metrics. | FEV₁, FVC, FEF₂₅₋₇₅       | None        | Negative non-significant association between all pollutants (except O₃, traffic proximity) and FEV₁ and FVC. Stronger effect for FVC. |
| Brunekreef, 1997     | Netherlands           | 877   | 7–12         | Distance to motorway, traffic density, school indoor measurements PM₁₀, NO₂ | FEV₁, FVC, PEF, FEF₂₅₋₇₅   | Gender      | Negative association of truck traffic on LF, stronger effects in girls |
| Cakmak, 2016         | Canada                | 1528  | 9–11         | Traffic-counts and PM₂.₅, NO₂, SO₂ (LUR-annual averages)                    | FEV₁, FVC, eNO             | SES         | Effects on FEV₁ and FVC in low-income group |
| Dales, 2008          | Canada                | 1613  | 11           | NOₓ, PM₂.₅, PM₁₀, PM₂.₅ abs, SO₂ (LUR annual average at current address), roadway density | FEV₁, FVC, eNO             | Asthma      | Significant positive effects for roadway density and PM on eNO, stronger in subjects with asthma |
| Dockery, 1989        | USA (The 6 cities study) | 5422  | 10–12        | TSP, PM₁₀, PM₂.₅, SO₂, O₃, and NO₂ (central city monitoring stations, daily, monthly, annual mean) | FEV₁, FVC, FEV₀.₅, and FEF₂₅₋₇₅ | Asthma and wheeze | Null effects for lung function |
| Eeftens, 2014        | Europe (ESCAPE)       | 4659  | 6–8          | PM₁₀ and PM₂.₅; elemental composition (LUR at current addresses)            | FEV₁, FEV₀.₅, FVC, PEF     | Asthma      | Small effects related to nickel and sulfur. Heterogeneity across cohorts. Stronger effects in children with asthma |
| Eenhuizen, 2013      | Netherlands (PIAMA)   | 880   | 4            | NO₂, PM₂.₅ abs (LUR annual averages at birth address)                      | Interrupter resistance (Rₚₑₐₜ) | Gender, Parental allergy | Positive association between air pollution at birth address and Rₚₑₐₜ, no effect modification |
| Frye, 2003           | Germany               | 1911  | 11–12        | Total suspended particles (TSP) and SO₂—daily and annual averages—community monitoring | FEV₁, FVC                  | Gender      | Effects of reduction in TSP and an increase in FVC and possible to a smaller degree in FEV₁, especially in girls |
| Fuertes, 2015        | Germany (LISA and GINI) | 2266  | 15           | NOₓ, PM₂.₅, PM₂.₅,absorbance, O₃ (LUR—annual averages at birth, 10-year and current residential address) | FEV₁, FVC, FEF₂₅, FEF₅₀, FEF₇₅, PEF, < LLN | Gender, Asthma | No convincing overall effects but indications of effects from current exposure in subjects with asthma |
| Gao, 2013            | China                 | 3168  | 8–10         | PM₁₀, SO₂, NO₂, O₃ (lifetime and current annual averages from local monitoring stations) | FEV₁, FVC, FEF₂₅₋₇₅, FEF₇₅ | Gender      | FEV₁, FEF₂₅₋₇₅, and FEF₇₅ were significantly lower in boys in high-pollution district than in low-pollution district |
| Gehring, 2013        | Europe (ESCAPE)       | 5921  | 6–8          | NOₓ, NO₂, PM₁₀, PM₂.₅, PM₁₀ abs, PM₂.₅,absorbance (LUR—annual averages at birth and current address) | FEV₁, FEV₀.₅, FVC, PEF     | Asthma, gender sensitization | Estimated levels of NO₂, NOₓ, PM₂.₅ absorbance, and PM₁₀ at the current address, but not at the birth address, were associated with small decreases in lung function. |
| Gehring, 2015        | Netherlands (PIAMA)   | 3702  | 11–12        | PM constituents, PM₂.₅, PM₁₀ (LUR—annual averages at birth and current address) | FEV₁, FVC, FEF₂₅₋₇₅         | Allergy, SES | Copper and iron (from PM₂.₅) at current address was negatively associated with FEV₁, also FEF₂₅₋₇₅ (with copper from PM₁₀). |
| Author, year | Country (cohort name) | N  | Ages (years) | Exposure(s) | Outcome(s) | Subgroup(s) | Main findings |
|--------------|-----------------------|----|--------------|-------------|------------|-------------|---------------|
| Hirsch, 1999 [23] | Germany | 1137 | 9–11 | NO\textsubscript{2}, NO\textsubscript{2}, CO, benzene, O\textsubscript{3} (modeled previous year averages based on measurements stations—residential and school addresses) | FEV\textsubscript{1}, FEF\textsubscript{25–75}, BHR | None | Null effects for lung function and BHR |
| Hoek, 2012 [24] | Multicenter | 22,809 | 6–12 | PM\textsubscript{10}, NO\textsubscript{2}, and SO\textsubscript{2} from local monitoring stations, approximately 1 year previous spirometry test | FEV\textsubscript{1}, FVC, FEF\textsubscript{25–75}, PEF | Gender, wheeze, sensitization | Null effects in combined analyses on lung function |
| Islam, 2011 [25] | USA (CHS) | 1399 | 11 | NO\textsubscript{x}, NO\textsubscript{2}, NO (LUR at school and resident) | FEV\textsubscript{1}, FVC | Parental stress level, no asthma | Sign negative association of NO\textsubscript{x} and FEV\textsubscript{1}, in high-stress households. Effect remained in non-asthmatics |
| Janssen, 2003 [26] | Netherlands | 1726 | 7–12 | Truck/car traffic counts, PM\textsubscript{2.5}, and NO\textsubscript{2} (estimated averages during previous year based on measurements at schools) | FEV\textsubscript{1}, FVC, FEF\textsubscript{25–75}, BHR | Sensitized, +BHR | Null effects for lung function and BHR |
| Lee, 2011 [27] | Taiwan (TCHS) | 3957 | 12–13 | CO, NO\textsubscript{x}, NO\textsubscript{2}, O\textsubscript{3}, SO\textsubscript{2}, PM\textsubscript{2.5}, PM\textsubscript{10} (community-based monitoring data—annual, and monthly averages) | FEV\textsubscript{1}, FVC, FEF\textsubscript{25–75}, PEF | Gender, asthma | Sign negative association of annual CO, NO\textsubscript{x}, NO\textsubscript{2}, and NO with FVC and FEV\textsubscript{1}, especially in boys |
| Morales, 2015 [28•] | Spain (INMA) | 620 | 4.5 | NO\textsubscript{2} and benzene (LUR; Trimester specific, first year of life, previous year, current (1 week)) | FVC, FEV\textsubscript{1}, PEF, FEF\textsubscript{25–75} < 80% predicted | Gender asthma, SES, allergy | Strongest association on LF after exposure in second trimester of pregnancy, especially among allergic children and those of low SES (negative associations, but not significant for the other time periods) |
| Neophytou, 2016 [29] | USA and Puerto Rico (GALA II and SAGE II) | 1968 | 8–21 | NO\textsubscript{2}, SO\textsubscript{2}, O\textsubscript{3}, PM\textsubscript{2.5}, PM\textsubscript{10} (calculated at residents from 4 monitoring stations. Monthly, annual, and lifetime averages) | FEV\textsubscript{1}, FVC FEF\textsubscript{25–75} | Global genetic ancestry | Lifetime average and first year of life PM\textsubscript{2.5} associated with reduced FEF\textsubscript{25–75} and FEV\textsubscript{1} |
| Nicolai, 2003 [30] | Germany | 904 | 9–11 | Proximity to traffic and traffic counts, benzene, NO\textsubscript{2}, and soot (estimated residential averages during previous year based on measurements stations) | Spirometry | SHS | Null effects for lung function and BHR |
| Nordling, 2008 [31] | Sweden (BAMSE) | 2599 | 4 | NO\textsubscript{2}, PM\textsubscript{10}, SO\textsubscript{2} (first year of life averages based on dispersion model at residential addresses) | PEF | Gender, wheezing | Effects on PEF, most strong for PM\textsubscript{10}. No effect modification |
| Oftedal, 2008 [32••] | Norway | 2307 | 9–10 | NO\textsubscript{2}, PM\textsubscript{10}, PM\textsubscript{2.5} (early life, lifetime, and current annual averages based on dispersion model at residential addresses) | FEV\textsubscript{1}, FVC, FEF\textsubscript{25}, FEF\textsubscript{50}, PEF | Gender, asthma, ethnicity | Negative association between all time periods of exposures and PEF, FEF\textsubscript{25}, and FEF\textsubscript{50} especially in girls. Slightly stronger effect from first year of life |
Table 1 (continued)

| Author, year | Country (cohort name) | N  | Ages (years) | Exposure(s) | Outcome(s) | Subgroup(s) | Main findings |
|--------------|-----------------------|----|--------------|-------------|------------|-------------|---------------|
| Peters, 1999 [33] | USA | 3293 | 9–16 | NO\textsubscript{2}, PM\textsubscript{10},O\textsubscript{3}, acid vapor (12 communities—local monitoring stations during yrs. 1986–1990, and year 1994) | FEV\textsubscript{1}, FVC, FEF\textsubscript{25–75}, PEF | Gender | exposures. Stronger PM, and weaker NO\textsubscript{2} effects in asthmatics. Effects on FEV\textsubscript{1}, FVC, and FEF\textsubscript{25–75} in girls. Stronger effects from current exposure |
| Raizenne, 1996 [34] | USA and Canada | 10,251 | 8–12 | Particles and gaseous pollutants. Community level; previous year averages based on measurements | FEV\textsubscript{1}, FVC, FEV\textsubscript{0.75}, FEF\textsubscript{25–75}, FEF\textsubscript{75–75}, PEF, FVC < 85% predicted | Gender | Effects on FEV\textsubscript{1}, FVC and FEF, especially strong in association with particle acidity. No gender difference. |
| Rice, 2016 [35] | USA (Project Viva) | 614 | 8 | Proximity to major road, PM\textsubscript{2.5} (hybrid model) and BC (LUR: LUR and hybrid model: first year of life, life time, previous year | FEV\textsubscript{1}, FVC, bronchodilator response | Gender, SES, SHS, asthma | Prior year and lifetime PM and BC—significant with FVC (and none significant with FEV\textsubscript{1}), also higher OR of <80% predicted. No effect modification by asthma, gender or SHS. Stronger effects in high-income households |
| Schultz, 2012 [36] | Sweden (BAMSE) | 1924 | 8 | PM\textsubscript{10}, NO\textsubscript{2} (first year of life, 1–4 years, and 4–8 years averages based on dispersion modeling (DM at addresses) | FEV\textsubscript{1}, FEV\textsubscript{0.65}, FVC, < 80%, < 85% predicted | Gender, sensitization | Associations between first year of life exposure and mainly FEV\textsubscript{1} |
| Schultz, 2016 [37*] | Sweden (BAMSE) | 2415 | 16 | PM\textsubscript{2.5}, NO\textsubscript{2} (first year of life, previous year averages based on DM at addresses) | Impulse oscillometry measurements | Gender, asthma, sensitization, | Associations between first year of life exposure and indices related to function in the small airways, especially in those with asthma |
| Schwartz, 1989 [38] | USA | 3922 | 6–24 | TSP, O\textsubscript{3}, NO\textsubscript{2}, SO\textsubscript{2} (community-level annual averages) | FEV\textsubscript{1}, FVC, PEF | No | Effects on lung function from all pollutants (except SO\textsubscript{2}). Threshold effects for TSP and O\textsubscript{3}. |
| Sugiri, 2006 [39] | Germany | 2574 | 5–7 | TSP and SO\textsubscript{2}—daily and annual averages—community monitoring (background levels), and residential distance to major road | TLC, airway resistance | No | Better total lung capacity (TLC) when TSP decreased, but not related to distance from traffic |
| Svendsen, 2012 [40] | USA | 1529 | 10 | NO\textsubscript{2} and diesel-related compounds (LUR at school and residential address) | FEV\textsubscript{1}, FVC, < 85% predicted | Gender, Asthma, SHS | Negative associations between NO\textsubscript{2} and FVC. Increased OR of <85% predicted FEV\textsubscript{1} and FVC. Stronger effect in children not exposed to SHS |
| Wang, 2015 [41] | The Netherlands (PIAMA) | 1058 | 8 | NO\textsubscript{2}, PM\textsubscript{2.5}, PM\textsubscript{10}, PM\textsubscript{2.5} soot (LUR and DM—birth and current address) | FEV\textsubscript{1}, FVC, PEF | No | Negative associations all pollutants and FEV\textsubscript{1} and FVC, not PEF |
| Wjst, 1993 [42] | Germany | 4320 | 9–11 | Traffic-density in school district (as a proxy for long-term exposure—minimum of 5 years at current residence) | FEV\textsubscript{1}, PEF, FEF\textsubscript{25}, FEF\textsubscript{50}, FEF\textsubscript{75} | No | Effects on PEF and FEF\textsubscript{25}, and FEF\textsubscript{50}. |
| Author (year)       | Country (cohort) | Number | Age at start (follow-up time) | Exposure(s)                                                                 | Outcome(s)                        | Subgroup(s)       | Main findings                                                                 |
|--------------------|------------------|--------|-------------------------------|-----------------------------------------------------------------------------|-----------------------------------|-------------------|-------------------------------------------------------------------------------|
| Avol, 2001 [43]    | USA (CHS)        | 110    | 10 (5)                        | PM$_{10}$, NO$_x$, O$_3$ (annual averages from community monitoring stations) | FEV$_1$, FVC, FEF$_{25-75}$, PEF  | No                | LF (not FVC) lowered when subjects moved to high PM$_{10}$ level areas and increased when moving to low PM$_{10}$ areas. |
| Gauderman, 2000 [44]| USA (CHS)        | 3035   | Fourth, 7th and 10th graders (4) | PM$_{10}$, PM$_{2.5}$, PM$_{coarse}$, NO$_x$, O$_3$, O$_2$, inorganic acid vapor (annual averages from community monitoring stations) | FEV$_1$, FVC, FEF$_{25-75}$, FEF$_{75}$ | Gender, Asthma | Most effects in fourth graders: deficits in LF growth related to increase in all pollutants (except O$_3$). No effect modification by asthma or gender. |
| Gauderman, 2002 [45]| USA (CHS)        | 1678   | Fourth graders (4)            | PM$_{10}$, PM$_{2.5}$, PM$_{coarse}$, NO$_x$, O$_3$, inorganic acid vapor, elemental carbon (annual averages from community monitoring stations) | FEV$_1$, FVC, FEF$_{25-75}$, FEF$_{75}$ | Gender, Asthma | Replication but less strong effects of results from Gauderman 2000. Effects from O$_3$. No effect modification by asthma or gender. |
| Gauderman, 2004 [46•] | USA (CHS)        | 1759   | 10 (8)                        | PM$_{10}$, PM$_{2.5}$, PM$_{coarse}$, NO$_x$, O$_3$, inorganic acid vapor, elemental carbon (annual averages from community monitoring stations) | FEV$_1$, FVC, FEF$_{25-75}$, FEF$_{75}$, FEV$_1 < 80%$ predicted | No Asthma, No smoking | Effects of NO$_2$, acid vapor, EC, and PM$_{2.5}$ on LF. Increased OR of <80% predicted if high exposed. Effect remained in non-asthmatics and non-smokers. |
| Gauderman, 2007 [47]| USA (CHS)        | 3677   | 10 (8)                        | Proximity to traffic, regional measurements                                  | FEV$_1$, FVC, FEF$_{25-75}$, FEF$_{75}$, FEV$_1 < 80%$ predicted | Gender, No asthma, No smoking | Effects on FEV$_1$ and FEF$_{25-75}$ growth independently for proximity to traffic and regional levels. Effects mainly in boys. Effect remained in non-asthmatics and non-smokers. |
| Gauderman, 2015 [48•] | USA (CHS)        | 2120   | 11 (4)                        | PM$_{10}$, PM$_{2.5}$, PM$_{coarse}$, NO$_x$, O$_3$ (annual averages from community monitoring stations) | FEV$_1$, FVC, < 90%, <85%, and <80% predicted | Gender, Asthma status | Improvements in FEV$_1$ and FVC growth related to declining levels of PM$_{10}$, PM$_{2.5}$, and NO$_x$. Stronger effects in boys. |
| He, 2010 [49]      | China            | 1983   | 8–10 (0.5)                   | PM$_{10}$, SO$_2$, NO$_x$ (lifetime and current annual averages from local monitoring stations) | FEV$_1$, FVC, FEF$_{25-75}$, FEF$_{75}$ | Gender | Children living in high polluted district showed significant deficits in FEV$_1$, FEF$_{25-75}$, and FEF$_{75}$ growth. No effect modification by gender. |
| Horak, 2002 [50]   | Austria          | 860    | 6 (3)                        | PM$_{10}$, NO$_x$, O$_3$ (6-month averages from community monitoring stations in proximity to school) | FEV$_1$, FEF$_{25-75}$ | Asthma, ETS | Effects of NO$_2$ and O$_3$ on FVC and FEV$_1$. Summer PM$_{10}$ was negatively associated with growth of FEV$_1$ and FEF$_{25-75}$. No clear effect modification. |
| Mölter, 2013 [51•] | UK (MAAS)        | 1185   | 3 (8)                        | PM$_{10}$ and NO$_x$ (different time windows over the life course and previous year, individual estimates by micro-environmental model based on LUR) | sRAW, FEV$_1$, bronchodilator | No | Small but significant deficits in growth of FEV$_1$. Stronger effects after bronchodilator treatment, especially in relation to early life exposures. |
| Neuberger, 2002 [52]| Austria          | 3451   | Elementary school age (5)    | NO$_x$, SO$_2$, TSP (calculated at school addresses from regional monitoring stations) | FEV$_1$, FVC, FEF$_{25-75}$, FEF$_{75}$ | No | Faster FEF$_{25-75}$ and FEF$_{75}$ growth in areas with NO$_2$ level reductions. |
| Rojas-Martinez, 2007 [53]| Mexico       | 3170   | 8 (3)                        | FEV$_1$, FVC, FEF$_{25-75}$ | Gender | | |
Most studies report of lung function data from a single point in time (see Table 1; 32 cross-sectional studies vs. 12 with longitudinal data). The most commonly reported index is forced expiratory volume in 1 s (FEV$_1$), representing mainly the mechanical properties of the large and medium-sized airways, followed by the forced vital capacity (FVC), reflecting lung size. Linear statistical models are generally used. Studies have compared lung function levels in children living in different communities with varying levels of ambient air pollution measured at central monitoring stations or at schools [15, 18, 27, 30, 33, 34, 38, 39, 43–45, 46–49, 50, 52, 53]. Traffic measurements such as traffic density or proximity to highways have also been used as exposure estimates [12, 14, 26, 30, 39, 42], as well as modeling individual data using land use regression (LUR) models [13, 14, 16, 17, 19, 22, 25, 28–35] or dispersion models (DMs) [31, 32–36, 37–41, 54]. Most but not all studies [15, 23, 26, 30] have observed negative impact from traffic-related air pollution on lung function.

A general finding seems to be a larger effect estimate observed for FEV$_1$ than for FVC. This pattern has been observed in studies from Austria [52], China [20], the USA [25, 44, 45, 47, 48], Puerto Rico [29], Sweden [36, 54], and Norway [32], even though many of these studies observed the strongest effect estimate for mid-expiratory flows (FEF 25–75). However, FVC has in some studies shown stronger associations than FEV$_1$ [33, 35, 40, 41, 53].

The effect estimates across studies, i.e., change in mean values of lung function, are not always straightforward to compare and interpret, as the exposure usually differs between studies. For example, the mixture of components may differ between the studies due to differences in car fleet, road wear, use of studded tires, and fuel composition. Most epidemiological studies using modeled exposures cannot separate the different components of the emissions effectively [16, 22]. Because of the diversity across studies, we desist from reporting quantitative summary of effects. However, when reduction in lung function is reported in association with traffic-air pollution exposure, it is usually with deficits of a few percent (0.5–3%) [10, 11, 21].

An average reduction in lung function of a few percent has from an individual perspective likely only minor physiological effects. A small shift in the population distribution of lung function may, however, increase the prevalence of subjects presenting lung function values below clinical thresholds, as seen in studies that show increased risk of having less than 80 or 85% of the predicted FEV$_1$ and/or FVC values [28–36, 40], or less than the lower limit of normal (<−1.645 SD) [54]. A substantial improvement in public health may subsequently follow decreased air pollution levels, and this effect was recently seen in a publication from the Children’s Health Study in California. In this study, Gauderman and colleagues initiated and followed three cohorts during separate calendar periods, at the same time as air pollution levels improved [48].
The authors observed that the risk of exhibiting FEV\textsubscript{1} values below 80% of predicted at 15 years of age declined from 7.9 to 6.3 to 3.6% across the three time periods, indicating a substantial improvement in public health following decreased levels of air pollution.

### Timing of Air Pollution Exposure

Although several studies highlight the importance of exposures prenatally or during infancy for subsequent respiratory health [9, 62, 63], until recently, only a few studies had investigated exposure during the infancy period in relation to lung function in children [31, 32] and none in adolescents. The majority of published cross-sectional and longitudinal studies have only investigated later life exposures (usually around school ages, see Tables 1 and 2), and the potential dynamic changes of exposure to air pollution during the life-course and subsequent influences on lung function growth remain largely unknown.

To date, there are eight studies that have reported on the relative impact of early life vs. current exposure to traffic-related air pollution. A Norwegian cohort study of 2307 9- and 10-year-olds showed that both early life and lifetime exposure to PM\textsubscript{10} and NO\textsubscript{2} were negatively associated with lung function [32], even though early life exposure had slightly stronger effects. A meta-analysis of five European birth cohorts within the ESCAPE collaboration showed associations mainly with exposures at the current address and lung function at 6–8 years of age, while no significant association was seen with exposures at the address at birth [21]. Mölter and colleagues have followed 1185 children from birth to 11 years of age within the MAAS cohort [51] and observed strong effects mainly from exposure to PM\textsubscript{2.5} and black carbon were all negatively associated with mainly FVC (not as strongly with FEV\textsubscript{1}), but that only the latter two time periods were statistically significant [35]. Studies from the Swedish birth cohort BAMSE report associations mainly from first year of life exposure to PM\textsubscript{10} and/or NO\textsubscript{x} with FEV\textsubscript{1} at 8 years of age [36], at 16 years of age [54], and with impulse oscillometry measurements at 16 years of age [37].

In summary, the evidence of a particular important air pollution exposure time window for subsequent lung function appears inconclusive, and findings from studies published to date rather support that exposure over the entire age range is of importance. Most longitudinal studies are supporting this observation, with attenuated lung function growth in relation to air pollution exposure during later childhood and adolescence [46, 51, 53] being reported, as well as recovery of previous deleterious effects in subjects moving to less polluted areas [43]. In one study (from the BAMSE cohort), no association was observed for the change of lung function between childhood and adolescence, for any of the explored life-time exposure time windows [54]. The authors highlight the fact that the levels of air pollution decreased during the course of the study, limiting the possibility of discerning the importance of exposure during adolescence. Most studies on lung function growth focus only on exposure during later life [43–45, 46, 49, 50, 53], and the potential impact of exposures during the first year of life in these cohorts is therefore unknown.

### Small Airways

The small airways are by convention defined as those with an airway diameter of 2 mm or less (in adults). This corresponds to approximately airway generation 8 and more distally and comprises the more peripheral conducting airways (up to generation 15), as well as the bronchioles and alveolar regions where gas exchange occurs. For many lung diseases, like chronic obstructive pulmonary disease (COPD) and asthma, the small airways are a major site of pathology [64, 65], and the severity of disease is often rather significant before changes in spirometry measurements appear [66]. As the small airways are relatively difficult to study, they are sometimes referred to as “the quiet zone” of the lung [67].

Most investigations linking air pollution exposure to lung function have employed measurements of total airway resistance and large rather than small airway function measured using spirometry [68]. In experimental studies on mice, small aerosol particles of a size range typical of traffic-related air pollution are deposited in the small airways [69].

There are reports of associations between exposures to air pollution and forced mid-expiratory flows, like FEF\textsubscript{25–75}, suggesting that the results represent small airway effects [22, 44, 49, 50, 52]. Although flows measured in the middle or at the end of a forced expiration generally offer insight of the more peripheral airway, the interpretation has lately been subject to debate [70]. Abnormalities in these flow indices are not specific to small airway disease [71], and it has been suggested that the mid-expiratory flows do not contribute additional information over what is provided by FEV\textsubscript{1} and FVC [68].

An alternative measure of the small airways that may be feasible in an epidemiological setting is assessment of the residual volume (RV) using plethysmography. This index provides sensitive measure of gas trapping and hyperinflation, although not specific to small airway involvement [67]. Inert gas washout and forced oscillation techniques, such as impulse oscillometry (IOS), are methods that may discriminate between large and small airway effects [67, 72, 73]. In recent years, these techniques have become commercially available and easily accessible.
Despite advances with peripheral airway assessment, it is rarely investigated whether exposure to traffic-related air pollution influences small airway function. In a panel study of 163 children aged 7–10 years in Austria, IOS indices related to peripheral airway resistance was increased in relation to short-term exposure to air pollution [74]. Following 174 adults exposed to dust/fume from the World Trade Center collapse with airway symptoms and normal spirometry revealed abnormal posed to dust/fume from the World Trade Center collapse with airway symptoms and normal spirometry revealed abnormality in the peripheral airways assessed with IOS in 68% of the subjects [75]. In the same group of individuals, RV/total lung capacities was elevated in approximately 33% of subjects, also indicative of small airway involvement. In 2415 children from the Swedish BAMSE cohort, NOx-exposure from the first year of life was associated with increased resistance in indices related to peripheral airway function also assessed with IOS at 16 years of age [37*].

To summarize, few studies have addressed small airway disease in relation to air pollution exposure to date, although associations between exposure and small airway involvement have been reported. Given the importance of small airway function in asthma and COPD, further studies are warranted.

Susceptible Subgroups

In our modern society, everybody is more or less exposed to air pollution. However, certain people or subgroups in the population may be more susceptible to negative outcomes following exposure. For the studies included in the present review, we have focused on sub-analyses with respect to asthma, sensitization, and gender status.

Gender Differences

Gender differences on lung function in response to air pollution or other environmental stimuli may be present due to inherited differences in lung and airway development. For example, surfactant production starts earlier in the lungs of neonatal females than males [76], which may be one reason why infant females have lower airway resistance and higher air-flow rates compared to infant males [77]. In addition, males present already at birth with a higher total number of alveoli and alveolar surface area than females do, but at the same time, the growth of the airways lags behind, resulting in relatively more narrow airways in infant to adolescent males compared with females (known as dysanaptic growth) [76]. Males may, therefore, during infancy, childhood, and early adolescence have a pulmonary phenotype more susceptible to the deleterious effects of air pollution exposure [78].

During puberty, however, the risk in males compared with females may become reversed as several studies indicate influence by estrogens (female sex hormone) on increased incidence and severity of asthma [79]. Thus, a gender-related vulnerability to the detrimental effects from exposure to air pollution may be influenced by age.

Several of the published epidemiological studies within the area of this review have presented stratified analyses based on gender, but results have not been consistent. Six studies show stronger effect of air pollution exposure in males compared with females [20, 27, 37*, 47, 48*, 54••]. There are almost as many reporting stronger effects in girls [12, 18, 32••, 33] and a majority showing no differences in associations [17, 34, 40, 44, 45, 49, 53]. In addition, the mixed results regarding the role that gender has in relation to air pollution—lung function association is not obviously explained by age, as the observed differences in results cover the entire age range. Based on the published studies to date, there seems to be no conclusive evidence regarding gender-pollution interaction effects on lung function.

Asthma

Data regarding asthma as an effect modifier for the association between traffic air pollution and lung function are accumulating, although still limited. The majority of reports from the Children Health Study in the USA show no effect modification by asthma [25, 44, 45, 46••, 47, 48••]. Additional studies also show no differences in relation to asthma status: Svendsen and colleagues including 1529 10-year-olds in El Paso, Texas [40]; Schultz and colleagues from the 16-year BAMSE cohort [54••]; and Rice and colleagues in 614 children aged 8 years [35]. Stronger effects in those with asthma are, however, suggested from several studies [14, 19, 32••, 37•]. For example, Eeftens report from the ESCAPE collaboration small effects from nickel and sulfur (part of the air pollution mixture) on lung function especially in children with asthma [16]. Dales et al. observed stronger associations between roadway density and particles on the exhaled nitrogen oxide in children with asthma, indicative of increased airway inflammation [14]. Stronger association for children with asthma was also seen in the BAMSE cohort for small airway indices assessed with IOS [37•] (but not for FEV1 [54••]).

There is a risk that many studies are underpowered to detect significant effect modification by asthma status, which may explain some of the null findings. Weaker effects in children with asthma is, to our knowledge, seldom reported [32••], which may support the conclusion that if effect modification by asthma exists, it points towards an increased effect in children with asthma.

Sensitization

Effect modification of air pollution-lung function associations by sensitization has not been well investigated in epidemiological studies. In one study, Morales and colleagues found stronger associations on FEV1 in allergic (allergic asthma,
atopic dermatitis, eczema, or allergic rhinitis) 4.5-year-olds exposed to air pollutants during pregnancy and lifetime, compared with non-allergic children [28••]. Janssen and colleagues reported that associations between truck-traffic counts and respiratory symptoms were only observed among children with bronchial hyper-responsiveness and/or sensitization [26], indicating a sensitive subgroup. However, no associations were observed in the same study regarding spirometry outcomes. In studies from Schultz et al. from the BAMSE cohort, the results from subgroup analyses differed depending on whether the outcome was assessed at 8 or 16 years of age. A stronger association between the first year of life exposure to PM\textsubscript{10} and FEV\textsubscript{1} at 8 years of age was suggested in those sensitized than not sensitized. However, the effect modification was not statistically significant [36]. At 16 years of age, no association difference between sensitized vs non-sensitized subjects was seen [54••]. As part of the ESCAPE project, stratified analyses based on sensitization status for the relation between air pollution exposure and lung function at 6–8 years of age did not reveal evidence of any effect modification [21•].

Evidence supporting sensitization as an effect modifier comes from a high-risk cohort study, where the authors observed that early exposure to allergens in combination with secondhand smoke exposure increased the risk for incident asthma, compared with having neither of the exposures [80]. Such findings are supported by controlled exposure studies [81, 82•].

The mechanisms behind a potential effect modification are not clear, but it has been suggested that genetically susceptible children more often present with impaired epithelial barrier function, which subsequently increases the airway’s vulnerability to early life air pollution exposure [83]. Epigenetic effects on DNA have been proposed as a potential link by which sensitization-pollution interaction influences the lung function [84]. Based on the identified epidemiological studies included in this review, evidence for effect modification by sensitization status of the relation between air pollution exposure and lung function remains inconclusive.

**Conclusions and Future Directions**

As much as 85% of the world’s population live in cities with outdoor air pollution levels exceeding the WHO Air Quality Guidelines for PM\textsubscript{10} [2]. The trend towards global urbanization implies that more and more people will become highly exposed if further control of emissions is not applied. We conclude that early life and school-age exposure to air pollution has a negative impact on lung function, at least up to adolescence (Fig. 1). Whether these lung function deficits persist into adulthood, and subsequently result in a reduced maximally attained lung function, or a shortened growth phase, remains unknown. However, based on prior studies of lung function changes over time, these studies suggest that these affected children will continue to have lower lung function than those who were exposed to lower levels of pollutants, especially if they continue to be exposed. There is therefore a need to follow pregnancy and birth cohorts with air pollution data up to adulthood when the plateau of lung function is reached. The relative impact of pregnancy vs. early life

---

**Fig. 1** A schematic illustration of effects on lung function from long-term traffic-related air pollution (TRAP) exposure. The Y-axis corresponds to lung function and the X-axis corresponds to time (age). The blue line illustrates normal lung function growth and decline, with a maximum in young adulthood. The dark red line illustrates lung function growth slightly less than normal due to exposure of traffic-air pollution. The long-term effect of air pollution exposure during childhood remains largely unknown.

- Negative effects of TRAP-exposure over the entire age-range suggested.
- Possibly stronger effects in children with asthma.
- Long-term effects into adulthood of childhood exposure still unknown.
- Further studies of effects on small airway function is warranted.
exposure is sparsely investigated and when initiating new cohorts, efforts should be made to capture both pregnancy and lifetime exposures and measure lung function already in infancy. Findings from studies published to date support that exposure over the entire childhood age range seems to be of importance for lung function development. In this review, we have also evaluated potential effect modification by gender, asthma status, and sensitization but could not find any conclusive data to support evidence of specific sup-group effects. Most studies have used spirometry indices to evaluate lung function in relation to air pollution exposure. A handful of recent studies have used other methods such as impulse oscillometry techniques to also assess small airway involvement, and further research in this area is warranted.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

• Of major importance

1. UNICEF Clear the air for children: the impact of air pollution on children. Edited by. NewYork: UNICEF; 96. [UNICEF (Series Editor); 2016.

2. World Health Organization. Ambient air pollution: a global assessment of exposure and burden of disease. WHO report. 2016. Retrieved from http://apps.who.int/iris/bitstream/10665/250141/1/9789241511353-eng.pdf.

3. Korten I, Ramsey K, Latzin P. Air pollution during pregnancy and lung development in the child. Paediatr Respir Rev. 2017;21:38–46.

4. Holt PG, Jones CA. The development of the immune system during pregnancy and early life. Allergy. 2000;55:688–97.

5. Stern DA, Morgan WI, Wright AL, Guerra S, Martinez FD. Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. Lancet. 2007;370:758–64.

6. Lange P, Celi B, Agusti A, Boje Jensen G, Divo M, Faner R, Guerra S, Marott JL, Martinez FD, Martinez-Cambil P, et al. Lung-function trajectories leading to chronic obstructive pulmonary disease. N Engl J Med. 2015;373:111–22.

7. Schunemann HJ, Dorn J, Grant BJ, Winkelstein W Jr, Trevisan M. Pulmonary function is a long-term predictor of mortality in the general population: 29-year follow-up of the Buffalo Health study. Chest. 2000;118:656–64.

8. Young RP, Hopkins R, Eaton TE. Forced expiratory volume in one second: not just a lung function test but a marker of premature death from all causes. Eur Respir J. 2007;30:616–22.

9. Stocks J, Hislop A, Sonnappa S. Early lung development: lifelong effect on respiratory health and disease. Lancet Respir Med. 2013;1:728–42.

10. Gotschi T, Heinrich J, Sunyer J, Kunzli N. Long-term effects of ambient air pollution on lung function: a review. Epidemiology. 2008;19:690–701.

11. Barone-Adesi F, Dent JE, Dajnak D, Beever S, Anderson HR, Kelly FJ, Cook DG, Whincup PH. Long-term exposure to primary traffic pollutants and lung function in children: cross-sectional study and meta-analysis. PLoS One. 2015;10:e0142565.

12. Brunekreef B, Janssen NA, de Hartog J, Harssema H, Knape M, van Vliet P. Air pollution from truck traffic and lung function in children living near motorways. Epidemiology. 1997;8:298–303.

13. Cakmak S, Hebbeln C, Cakmak JD, Vanos J. The modifying effect of socioeconomic status on the relationship between traffic, air pollution and respiratory health in elementary schoolchildren. J Environ Manag. 2016;177:1–8.

14. Dales R, Wheeler A, Mahmud M, Frescura AM, Smith-Doiron M, Nethery E, Liu L. The influence of living near roadways on spirometry and exhaled nitric oxide in elementary schoolchildren. Environ Health Perspect. 2008;116:1423–7.

15. Dockery DW, Speizer FE, Stam DO, Ware JH, Spengler JD, Ferris BG Jr. Effects of inhalable particles on respiratory health of children. Am Rev Respir Dis. 1989;139:587–94.

16. Eeftens M, Hoek G, Gruzieva O, Molter A, Agius R, Beelen R, Brunekreef B, Custovic A, Cyrys J, Fuertes E, et al. Elemental composition of particulate matter and the association with lung function. Epidemiology. 2014;25:648–57.

17. Eenhuizen E, Gehring U, Wijga AH, Smit HA, Fischer PH, Brauer M, Koppelman GH, Kerkhof M, de Jongste JC, Brunekreef B, et al. Traffic-related air pollution is related to interrupted resistance in 4-year-old children. Eur Respir J. 2013;41:1257–63.

18. Frye C, Hoelscher B, Cyrys J, Wijst M, Wichmann HE, Heinrich J. Association of lung function with declining ambient air pollution. Environ Health Perspect. 2003;111:383–7.

19. Fuertes E, Bracher I, Flexeder C, Markevych I, Klumper C, Hoffmann B, Kramer U, von Berg A, Bauer CP, Koletzko S, et al. Long-term air pollution exposure and lung function in 15-year-old adolescents living in an urban and rural area in Germany: the GINplus and LISAplus cohorts. Int J Hyg Environ Health. 2015;218:656–65.

20. Gao Y, Chan EYY, Li LP, He QQ, Wong TW. Chronic effects of ambient air pollution on lung function among Chinese children. Arch Dis Child. 2013;98:128–35.

21. Gehring U, Gruzieva O, Agius RM, Beelen R, Custovic A, Cyrys J, Eeftens M, Flexeder C, Fuertes E, Heinrich J, et al. Air pollution exposure and lung function in children: the ESCAPE project. Environ Health Perspect. 2013;121:1357–64. A well-designed study with harmonized and standardized air pollution data from several European birth cohorts, showing that exposure to air pollution at the current address may result in reduced lung function in school-aged children.

22. Gehring U, Beelen R, Eeftens M, Hoek G, de Hoogh K, de Jongste JC, Keuten M, Koppelman GH, Meliefste K, Oldenwening M, et al. Particulate matter composition and respiratory health the PIAMA birth cohort study. Epidemiology. 2015;26:300–9.

23. Hirsch T, Weiland SK, von Mutius E, Safaei AF, Grafe H, Csaplovics E, Duhme H, Keil U, Leupold W. Inner city air pollution and respiratory health and atopy in children. Eur Respir J. 1999;14:669–77.
24. Hoek G, Pattenden S, Willers S, Antova T, Fabianova E, Braun-Fahrlander C, Forastiere F, Gehring U, Luttman-Gibson H, Grize L, et al. PM10, and children’s respiratory symptoms and lung function in the PATY study, Eur Respir J. 2012;40:538–47.

25. Islam T, Urman R, Gauvderman WJ, Mihal J, Lurmann F, Shankardass K, Avol E, Gilliland F, McConnell R. Parental stress increases the detrimental effect of traffic exposure on children’s lung function. Am J Respir Crit Care Med. 2011;184:822–7.

26. Janssen NA, Brunekreef B, van Vliet P, Aarts F, Meliefste K, Harssema H, Fischer P. The relationship between air pollution from heavy traffic and allergic sensitization, bronchial hyperresponsiveness, and respiratory symptoms in Dutch schoolchildren. Environ Health Perspect. 2003;111:1512–8.

27. Lee YL, Wang WH, Lu CW, Lin YH, Hwang BF. Effects of ambient air pollution on pulmonary function among schoolchildren. Int J Hyg Environ Health. 2011;214:369–75.

28. Morales E, Garcia-Esteban R, de la Cruz OA, Basterrechea M, Lertxundi A, de Dicastro MD, Zabaleta C, Sunyer J. Intrauterine and early postnatal exposure to outdoor air pollution and lung function at preschool age. Thorax. 2015;70:64–73. The first study that explored air pollution exposure both in pregnancy and in early life, showing the strongest association for exposure during the 2nd trimester of pregnancy with lung function in 4.5 yr olds.

29. Neophytou AM, White MJ, Oh SS, Thakur N, Galanter JM, Ofstedal B, Brunekreef B, Nystad W, Madsen C, Walker SE, Nafstad P. Association between all time periods of exposure and lung function in the PATY study. Eur Respir J. 2012;40:538–47.

30. Nicolai T, Carr D, Weiland SK, Duhme H, von Ehrenstein Oftedal B, Brunekreef B, Nystad W, Madsen C, Walker SE, Nafstad P. The association between air pollution and lung function in minority youth with asthma in the GALA II (genes-environments and admixture in Latino Americans) and SAGE II (study of African Americans, asthma, genes, and environments) studies. Am J Respir Crit Care Med. 2016;193:1271–80.

31. Nicolai T, Carr D, Weiland SK, Duhme H, von Ehrenstein O, Wagner C, von Mutius E. Urban traffic and pollutant exposure related to respiratory outcomes and atopy in a large sample of children, Eur Respir J. 2003;21:956–63.

32. Nordling E, Berglind N, Melén E, Emenius G, Hallberg J, Nyberg P, Pershagen M, Wickman M, Bellander T. Traffic-related air pollution and childhood respiratory symptoms, function and allergies. Epidemiology. 2008;19:401–8.

33. Ofstedal B, Brunekreef B, Nystrøm W, Madsen C, Walker SE, Naftad P. Residential outdoor air pollution and lung function in schoolchildren. Epidemiology. 2008;19:129–37. The first study to investigate the association between early life exposure to air pollution and school-age lung function, showing negative association between all time periods of exposure and lung function.

34. Peters JM, Avol E, Baumgartner WJ, Linn WS, Navidi W, London SJ, Margolis H, Rappaport E, Vora H, Gong H Jr, et al. A study of twelve Southern California communities with differing levels and types of air pollution. II. Effects on pulmonary function. Am J Respir Crit Care Med. 1999;159:768–75.

35. Raizenne M, Neas LM, Damokosh AI, Dockery DW, Spengler JD, Koutrakis P, Ware JH, Speizer FE. Health effects of acid aerosols on north American children: pulmonary function. Environ Health Perspect. 1996;104:506–14.

36. Rice MB, Rinas-Shiman SL, Litonjua AA, Oken E, Gillman MW, Klocq I, Luttman-Gibson H, Zanobetti A, Coull BA, Schwartz J, et al. Lifetime exposure to ambient pollution and lung function in children. Am J Respir Crit Care Med. 2016;193:881–8.

37. Schulz ES, Gruzieva O, Bellander T, Bottai M, Hallberg J, Kull I, Svartengren M, Melén E, Pershagen G. Traffic-related air pollution and lung function in children at 8 years of age: a birth cohort study. Am J Respir Crit Care Med. 2012;186:1286–91.

38. Schwartz J. Lung function and chronic exposure to air pollution: a cross-sectional analysis of NHANES II. Environ Res. 1989;50:309–21.

39. Sugiri D, Ranft U, Schikowski T, Kramer U. The influence of large-scale airborne particle decline and traffic-related exposure on children’s lung function. Environ Health Perspect. 2006;114:282–8.

40. Svendsen ER, Gonzales M, Mukerjee S, Smith L, Ross M, Walsh R, Rhoney S, Andrews G, Ozkaynak H, Neas LM. GIS-modeled indicators of traffic-related air pollutants and adverse pulmonary health among children in El Paso, Texas. Am J Epidemiol. 2012;176:S131–41.

41. Wang M, Gehring U, Hoek G, Keuken M, Jonkers S, Beelen R, Eeftens M, Postma DS, Brunekreef B. Air pollution and lung function in Dutch children: a comparison of exposure estimates and associations based on land use regression and dispersion exposure modeling approaches. Environ Health Perspect. 2015;123:847–51.

42. Wjs M, Reitmeir P, Dold S, Wulff A, Nicolai T, von Loefhelzol-Corber EF, von Mutius E. Road traffic and adverse effects on respiratory health in children. BMJ. 1993:307:596–600.

43. Avol EL, Gauvderman WJ, Tan SM, London SJ, Peters JM. Respiratory effects of relocating to areas of differing air pollution levels. Am J Respir Crit Care Med. 2001;164:2067–72.

44. Gauvderman WJ, McConnell R, Gilliland F, London S, Thomas D, Avol E, Vora H, Berhane K, Rappaport EB, Lurmann F, et al. Association between air pollution and lung function growth in southern California children. Am J Respir Crit Care Med. 2000;162:1383–90.

45. Gauvderman WJ, Gilliland GF, Vora H, Avol E, Strat D, McConnell R, Thomas D, Lurmann F, Margolis HG, Rappaport EB, et al. Association between air pollution and lung function growth in southern California children: results from a second cohort. Am J Respir Crit Care Med. 2002;166:76–84.

46. Gauvderman WJ, Avol E, Gilliland F, Vora H, Thomas D, Berhane K, McConnell R, Kuenzli N, Lurmann F, Rappaport E, et al. The effect of air pollution on lung development from 10 to 18 years of age. N Engl J Med. 2004;351:1057–67. The first longitudinal study to follow children over a 8-year period up to young adulthood. The authors could demonstrate associations between current levels of air pollution and attenuated lung function growth.

47. Gauvderman WJ, Vora H, McConnell R, Berhane K, Gilliland F, Thomas D, Lurmann F, Avol E, Kunzli N, Jerrett M, et al. Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study. Lancet. 2007;369:597–71.

48. Gauvderman WJ, Urman R, Avol E, Berhane K, McConnell R, Rappaport E, Chang R, Lurmann F, Gilliland F. Association of improved air quality with lung development in children. N Engl J Med. 2015;372:905–13. A very important longitudinal study, following three cohorts consecutively over a 13-year-period, showing that improvements in air quality were associated with positive effects on 4-year lung function growth.

49. He QQ, Wong TW, Du L, Jiang ZQ, Gao Y, Qu H, Liu WJ, Wu JG, Wong A, Yu TS. Effects of ambient air pollution on lung function growth in Chinese schoolchildren. Respir Med. 2010;104:1512–20.

50. Horak F, Studnicka M, Gartner C, Spengler JD, Tauber E, Urbanek R, Veiter A, Frischer T. Particulate matter and lung function growth in children: a 3-year follow-up study in Austrian schoolchildren. Eur Respir J. 2002;19:838–45.

51. Molten A, Agius RM, de Voigt F, Lindley S, Gerrard W, Lowe L, Belgrave D, Custovic A, Simpson A. Long-term exposure to PM10 and NO2 in association with lung volume and airway resistance in the MAAS birth cohort. Environ Health Perspect. 2013;121:1232–8. A well-designed longitudinal study, improving the individual
air pollution exposure assessment by including a micro-environmental model. One of few studies to include bronchodilator response. The study found deficits in lung function growth in relation to early life exposure. Stronger effects after bronchodilator treatment.

52. Neuberger M, Moshammer H, Kundi M. Declining ambient air pollution and lung function improvement in Austrian children. Atmos Environ. 2002;36:1733–6.

53. Rojas-Martinez R, Perez-Padilla R, Olaz-Fernandez G, Mendoza-Alvarado L, Moreno-Macias H, Fortoul T, McDonnell W, Loomis D, Romieu I. Lung function growth in children with long-term exposure to air pollutants in Mexico City. Am J Respir Crit Care Med. 2007;176:377–84.

54. Schulz ES, Halberg J, Bellander T, Bergström A, Bottai M, Chiesa F, Gustafsson PM, Grzuieva O, Thunqvist P, Pershagen G, et al. Early-life exposure to traffic-related air pollution and lung function in adolescence. Am J Respir Crit Care Med. 2016;193:171–7. The first study to follow children with life-time air pollution exposure data up to adolescence. Using advanced life-course statistical approaches, negative association between infancy exposure and lung function at 8 and 16 years of age were shown.

55. Perez L, Rapp R, Kunzli N. The year of the lung: outdoor air pollution and lung health. Swiss Med Wkly. 2010;140:w13129.

56. Brunekreef B, Holgate ST. Air pollution and health. Lancet. 2002;360:1233–42.

57. Romieu I, Garcia-Esteban R, Sunyer J, Rios C, Alcaraz-Zubeldia M, Velasco SR, Holguin F. The effect of supplementation with omega-3 polyunsaturated fatty acids on markers of oxidative stress in elderly exposed to PM(2.5). Environ Health Perspect. 2008;116:1237–42.

58. Grzuieva O, Xu CJ, Breton CV, Annesi-Maesano I, Anto JM, Auffray C, Ballard E, Bellander T, Bousquet J, Bustamante M, et al. Epigenome-wide meta-analysis of methylation in children related to prenatal NO2 air pollution exposure. Environ Health Perspect. 2017;125:104–10.

59. Gref A, Merid SK, Grzuieva O, Ballard E, Becker A, Bellander T, et al. Genome-wide interaction analysis of air pollution exposure and childhood asthma with functional follow-up. 2017;195:1373–83.

60. Churg A, Brauer M, del Carmen A-CM, Fortoul TI, Wright JL. Chronic exposure to high levels of particulate air pollution and small airway remodeling. Environ Health Perspect. 2003;111:714–8.

61. Annesi-Maesano I, Dinh-Xuan AT. Is exhaled nitric oxide a marker of a air pollution effect? Eur Respir J. 2016;47:1304–6.

62. Tumovska TH, Marinov BI. The influence of air pollution during intrauterine development and early childhood on respiratory function at later age. Int J Hyg Environ Health. 2009;212:519–32.

63. Moshammer H, Hoek G, Luttmann-Gibson H, Neuberger MA, Antova T, Gehring U, Hrubu F, Pattenden S, Rudnai P, Slachtaova H, et al. Parental smoking and lung function in children: an international study. Am J Respir Crit Care Med. 2006;173:1255–63.

64. van der Wiel E, ten Hacken NH, Postma DS, van den Berge M. Small-airways dysfunction associates with respiratory symptoms and clinical features of asthma: a systematic review. J Allergy Clin Immunol. 2013;131:646–57.

65. Lipworth B, Manoharan A, Anderson W. Unlocking the quiet zone: the small airway asthma phenotype. Lancet Respir Med. 2014;2:497–506. An excellent review on small airway function and respiratory disease.

66. Shi Y, Aledia AS, Tatavosian AV, Vijayalakshmi S, Galant SP, George SC. Relating small airways to asthma control by using impulse oscillometry in children. J Allergy Clin Immunol. 2012;129:671–8.

67. McNulty W, Usmani OS. Techniques of assessing small airways dysfunction. Eur Clin Respir J. 2014;1.

68. Quanjer PH, Weiner DJ, Pretto JJ, Brazzale DJ, Boros PW. Measurement of FEF25–75% and FEF75% does not contribute to clinical decision making. Eur Respir J. 2014;43:1051–8.

69. Kuehl PJ, Anderson TL, Candelaria G, Gershman B, Harlin K, Hesterman JY, Holmes T, Hoppin J, Laekas C, Noreenberg JP, et al. Regional particle size dependent deposition of inhaled aerosols in rats and mice. Inhal Toxicol. 2012;24:27–35.

70. Berend N. Contribution of air pollution to COPD and small airway dysfunction. Respirology. 2016;21:237–44.

71. Pellegrino R, Vieggi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinsen CP, Gustafsson P, Hankinson J, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26:948–68.

72. Goldman MD, Saadeh C, Ross D. Clinical applications of forced oscillation to assess peripheral airway function. Respir Physiol Neurobiol. 2005;148:179–94.

73. Foy BH, Kay D. A computational comparison of the multiple-breath washout and forced oscillation technique as markers of bronchoconstriction. Respir Physiol Neurobiol. 2017;240:61–9.

74. Moshammer H, Hutter HP, Hauck H, Neuberger M. Low levels of air pollution induce changes of lung function in a panel of schoolchildren. Eur Respir J. 2006;27:1138–43.

75. Oppenheimer BW, Goldring RM, Herberg ME, Hofer IS, Reyfman PA, Lautaud S, Rom WN, Reibman J, Berger KJ. Distal airway function in symptomatic subjects with normal spirometry following World Trade Center dust exposure. Chest. 2007;132:1275–82.

76. Carey MA, Card JW, Volk TJ, Arbes SJ Jr, Germolec DR, Korach KS, Zeldin DC. It’s all about sex: gender, lung development and lung disease. Trends Endocrinol Metab. 2007;18:308–13.

77. Doershuk CF, Fisher BJ, Matthews LW. Specific airway resistance from the perinatal period into adulthood. Alterations in childhood pulmonary disease. Am Rev Respir Dis. 1974;109:452–7.

78. Hsu HH, Chiu YH, Coull BA, Kloog I, Schwartz J, Lee A, Wright RO, Wright RJ. Prenatal particulate air pollution and asthma onset in urban children. Identifying sensitive windows and sex differences. Am J Respir Crit Care Med. 2015;192:1052–9.

79. Keselman A, Heller N. Estrogen signaling modulates allergic inflammation and contributes to sex differences in asthma. Front Immunol. 2015;6:568.

80. Carlsten C, Brauer M, Dimich-Ward H, Dybunco A, Becker AB, Chan-Yeung M. Combined exposure to dog and indoor pollution: incident asthma in a high-risk birth cohort. Eur Respir J. 2011;37:324–30.

81. Jorres R, Nowak D, Magnusson H. The effect of ozone exposure on allergen responsiveness in subjects with asthma or rhinitis. Am J Respir Crit Care Med. 1996;153:56–64.

82. Carlsten C, Blomberg A, Paal M, Sandstrom T, Wong SW, Alexis N, Coates A, van der Grinten CP, Gustafsson P, Hankinson J, et al. Regional particle size dependent deposition of inhaled aerosols in rats and mice. Inhal Toxicol. 2012;24:27–35.

83. Holgate ST. The sentinel role of the airway epithelium in asthma pathogenesis. Immunol Rev. 2011;242:205–19.

84. Clifford RL, Jones MJ, MacIsaac JL, McEwen LM, Goodman SJ, Mostafavi S, Kobor MS, Carlsten C. Inhalation of diesel exhaust and allergen alters human bronchial epithelium DNA methylation. J Allergy Clin Immunol. 2016;