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Review

Outdoor air pollution and cystic fibrosis

Rossa Brugha *, Claire Edmondson, Jane C. Davies

Gene Therapy, National Heart and Lung Institute, Imperial College London, Emmanuel Kaye Building, Manresa Road, London SW3 6LR, United Kingdom

Educational aims

On reading this article the reader will:

- Understand the major sources and constituents of outdoor air pollution
- Appreciate the methodologies used to attribute exposures to individuals
- Have covered the key studies regarding cystic fibrosis and air pollution
- Be able to give advice to patients and families about reducing exposure to air pollution

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SUMMARY

Outdoor air pollution is increasingly identified as a contributor to respiratory and cardiovascular disease. Pro-inflammatory particles and gases are inhaled deep into the lungs, and are associated with impaired lung growth and exacerbations of chronic respiratory diseases. The magnitude of these effects are of interest to patients and families, and have been assessed in studies specific to CF. Using systematic review methodology, we sought to collate these studies in order to summarise the known effects of air pollution in cystic fibrosis, and to present information on decreasing personal air pollution exposures.

INTRODUCTION

The World Health Organisation estimates that globally 1 in 8 deaths (approximately 7 million people in 2012) are attributable to air pollution, of which over half are due to outdoor pollutants (both urban and rural) [1]. 92% of the world's population live in areas where air quality fails to meet WHO targets [2] and it is estimated that outdoor particulate air pollution is responsible for the loss of 69.7 million disability-adjusted life years worldwide [3]. Recent Supreme Court cases in the United States of America [4] and the United Kingdom [5], have increased public awareness of polluted air. Google news returns for "air pollution" have increased by a factor of 919 between 2006 and 2016 (in comparison, returns for "cystic fibrosis" have increased by a factor of 298). Air pollution is associated with a host of communicable and non-communicable diseases including pneumonia [6], cancer, asthma, stroke and heart disease, diabetes and dementia, although evidence for the strength of these associations varies [7]. Anecdotally, in our clinic, patients, and parents of children with cystic fibrosis (CF) are concerned about the effects that polluted air may have on their lungs.

AIR POLLUTION

What pollutes our air?

Modern urban air pollution is dominated by vehicle emissions [8]. Urban air pollution consists predominantly of particles and gases arising from the combustion of fossil fuels in engines (petrol/gasoline and diesel) and in power stations (coal). These are then mixed, in turn, with dust from brakes, fragments of tyre rubber, as well as dust from construction, mould spores, pollen, bacteria [9], industrial emissions following national and trans-national airflows, emissions from shipping (in coastal areas), sand or soil particles ("crustal matter") and sea salt. In parts of the world, a significant proportion of pollutants are generated by burning biomass – either deliberately (wood or dung for cooking and

Abbreviations: PM, particulate matter; Pa, *Pseudomonas aeruginosa*; Bcc, Burkholderia cepacia complex.

* Corresponding author.
E-mail addresses: r.brugha@imperial.ac.uk (R. Brugha), c.edmondson@imperial.ac.uk (C. Edmondson), j.c.davies@imperial.ac.uk (J.C. Davies).

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heating homes, burning crop stubble in fields) or natural events such as seasonal forest fires. Classifying this complex mixture of species is fraught with difficulty, and has historically been driven by the available methods used to directly quantify pollutants, either by collecting particles suspended in the air (particulate matter; PM) or by analysing pollutant gases.

PM is defined by particle size. The fraction of PM particles with an aerodynamic diameter small enough to penetrate a 10 micron filter is termed PM_{10} (or "coarse" PM), the fraction of these which can penetrate a 2.5 micron filter is termed $PM_{2.5}$ ("fine" PM), and particles smaller than 0.1 microns are termed $PM_{<0.1}$ or "ultrafine" particles. In context, a human hair is approximately 50–70 microns in diameter and a *Pseudomonas aeruginosa* (*Pa*) bacterium is between 1 to 5 microns in length; fine particles smaller than bacteria are able to deposit deep in the lungs and potentially exert toxic effects on the epithelium. Urban PM in cities is composed predominantly of incompletely combusted particles from lorries, buses and cars [8,9]. These particles consist of a core of elemental carbon, carrying an adsorbed mixture which may include heavy metals, lipopolysaccharide, sulphates, ammonium nitrate and polyaromatic hydrocarbons [10].

Gaseous air pollutants include nitrogen dioxide (NO_2) and other oxides of nitrogen (termed NO_x) predominantly from vehicle engines, sulphur dioxide (from contaminated fossil fuels, including emissions from coal-fired power stations), and ozone (O_3). Ground level ozone is generated via the photochemical reaction of NO_2 with oxygen, driven by the generation of reactive oxygen species via the action of sunlight on oxygen molecules. As these species mix the result is the reddish (nitrogen dioxide) haze (from particles) seen on the horizon in major cities across the globe: photochemical smog (Fig. 1). PM, NO_x and ozone levels are legislated for in many developed countries (Table 1), and WHO guidelines exist for benzene levels, other gaseous pollutants including other volatile organic compounds (VOCs) may not be legislated for.

How air pollution is measured in research studies

Long-term randomised trials of exposures to individual air pollutants have not been conducted. Short-term "natural experiments", such as the imposition of vehicle restrictions during the 2008 Beijing Olympics, give insights about the effect of cleaner air on markers of airway inflammation [11,12]. In general, efforts to delineate the separate effects of the constituent species in polluted air on health (in order to inform policy makers, and fuel and vehicle manufacturers) are hampered by the common origin of many of the pollutants – vehicle engines - and the relative paucity of air pollution monitors in many cities. Ideally, a study looking to quantify associations between air pollution and health outcomes would involve large numbers of people carrying cheap, small, light, accurate monitors that would contemporaneously record and relay exposure data for multiple pollutants, while mapping exposures to activities and location in real time. While this technology may exist in the future, at present there are no monitors that match all of these specifications, and so current studies depend on classifying individuals' pollution exposures by either (a) modelled air pollution data using complex dispersion models, (b) simplified land-use regression models, or (c) proxy estimates (which classify exposures by the data recorded by the nearest air pollution monitor – which may be many miles away). Each of these methods bring benefits and limitations [13] and it is important to view studies on air quality and health with these factors in mind.

Fig. 1. Photochemical smog on the horizon in London. The haze is caused by particulate matter and the red-brown colour is nitrogen dioxide. View looking East from Albert Bridge towards the City of London, 8th June 2016. Annual mean daily NO_2 for the nearby King's Road, Chelsea in 2016 was 77.8 $\mu g/m^3$ (www.londonair.org.uk/london/asp/datadownload.asp), which compares to recommended levels of 40 $\mu g/m^3$ (http://www.londonair.org.uk/london/asp/publicstats.asp).

Measuring doses in vivo

After inhalation, PM is carried deep into the lungs where it is phagocytosed by airway macrophages (AM) [14]. Sampling AM by either broncho-alveolar lavage [14] or sputum induction [15] allows investigators to calculate an internal "dose" of PM by measuring the surface area of black carbon particles visible in the macrophages [16], and in children this has been shown to correlate with lower spirometry scores in healthy controls, [15] and with asthma severity [17]. This approach is unfeasible for studies of large numbers of individuals as it is time consuming. Recently, a non-invasive sampling approach to assessing *in* vivo black carbon has been reported; detecting urinary black carbon using white-light generation under femtosecond pulsed laser illumination [18], which in a study of 289 children was associated with black carbon exposures at home, and was raised in children living close to a major road. This raises the possibility of quantifying pollution exposures both in large numbers of individuals to assess health risk, but also intra-individual after interventions designed to decrease exposures [19].

Controlled pollution exposure studies in humans

Breathing diesel exhaust fumes results in airway and systemic inflammation. Controlled exposure studies (with healthy volunteers exposed to engine exhausts in closed exposure chambers) have demonstrated increased peripheral leucocyte counts [20], increased broncho-alveolar lavage eosinophil counts, and increased expression of vascular cell adhesion molecule-1 and P-selectin in bronchial mucosa biopsy samples [21]. Diesel exhaust increases gene expression in oxidative stress and coagulation pathways [22] and in a controlled exposure to a mixture of diesel exhaust and ozone, possible synergistic effects were seen with suppression of IFN-γ and TNF-α, and increased peripheral blood neutrophil counts [23]. Individuals working as diesel engine testers show greater levels of markers associated with DNA damage when matched to controls [24], and "genomic instability" induced by particulate matter may contribute to cases of lung cancer in non-smokers [25]. Together these studies demonstrate activation of inflammatory pathways triggered by pollution exposures in controlled environments.

Table 1
Air quality limits for selected countries and World Health Organisation recommended limits.

Pollutant (μg/m^3)	European Union	United States	Canada (2020 standards)	Australia	World Health Organisation
PM2.5	25	35*	8.8	8†	10
PM10	40	150*	-	50	20
NO2	40	101.4**	-	57	40
SO2	125	199.6***	-	53.2	20
O3	120	139.7****	123	199.6	100‡

PM, particulate matter; NO2, nitrogen dioxide; SO2, sulphur dioxide; O3, ozone. All limits as average over 1 year except; Ozone: maximum daily hour mean, Sulphur dioxide: average over 24 h. *24 h average **US NO2 limit is 53 ppb, converted to μg/m^3 using a conversion factor of 1 ppb = 1.9125 μg/m^3 at 20 °C at 1013 mb. ***1 h daily maximum concentration using a conversion factor of 1 ppb = 2.6609 μg/m^3 at 20 °C at 1013 mb. ****Annual fourth-highest daily maximum 8-h concentration using a conversion factor of 1 ppb = 1.9957 μg/m^3 at 20 °C at 1013 mb. †Maximum ambient concentration over 1 year. ‡8-h mean.
Sources (accessed 26th March 2018):
http://ec.europa.eu/environment/air/quality/standards.htm
https://www.epa.gov/criteria-air-pollutants/naaqs-table
https://www.ccme.ca/en/resources/air/pm_ozone.html
http://www.who.int/mediacentre/factsheets/fs313/en/
Conversion factors available at https://uk-air.defra.gov.uk/assets/documents/reports/cat06/0502160851_Conversion_Factors_Between_ppb_and.pdf

Mechanisms and effects on CF epithelium in vitro

Particulate matter has been shown to enhance mitochondrial-signalled CF bronchial epithelial cell apoptosis *in vitro* via caspase-9 and Bcl family proteins, at lower levels of exposure compared to healthy controls [26], and it has been postulated that this may impair pathogen clearance [27]. Ozone-induced stress decreases the transcription of CFTR, via phosphorylation of STAT-1, in human bronchial epithelial cells, resulting in a reduced CFTR-mediated chloride current [28]. Ozone-induced oxidative stress is enhanced in CF versus non-CF cells in air-liquid interface cultures [29]. Short term exposures to gasoline exhaust, somewhat counter-intuitively, result in decreased IL-6 and IL-8 production and decreased MCP-1 release in CF bronchial epithelial cells, whereas non-CF cells increase the production of these pro-inflammatory mediators [30]. In summary, the CF airway epithelium, at least in experimental models, appears particularly vulnerable to inhaled toxins.

HEALTH OUTCOMES

Air pollution and association studies

There is consensus in the scientific literature that polluted air impairs lung growth in healthy children. Many of the key publications in this field arise from the Children's Health Study [31–33], where repeated measures of lung function on repeated cohorts of children and adolescents in Southern California demonstrated decreased FEV_1 growth associated with higher levels of particulates and nitrogen dioxide. A recent meta-analysis estimates that the magnitude of NO_2 exposure on children's lung function is similar to that of environmental tobacco smoke [34].

In adults, the Six Cities study [35] followed cohorts for between 14 and 16 years across the 1970s and 1980s in cities across the US and demonstrated increased mortality in populations exposed to higher levels of fine particulate matter. Effects may begin *in utero* [36]. The impact of outdoor air pollution on asthma has recently been reviewed [10], with data from 10 European cities suggesting that exposure to roads with high vehicle traffic accounts for 14% of all asthma cases in children [37].

Associations between cystic fibrosis health outcomes and air pollution

Search strategy

In order to identify studies, two authors (RB and CE) adapted the search strategy employed by Guarnieri and Balmes [10] to conduct a systematic review in order to identify studies comparing air pollution exposures with health-associated outcomes in CF. We searched PubMed from Jan 1st, 1980 with the search term "cystic fibrosis" combined with the specific terms "air pollution", "particulate matter", "PM10", "PM2.5", "elemental carbon", "black carbon", "nitrogen dioxide", "nitrogen oxide*", "NO2", "NOx", "ozone", "O3", "traffic", "diesel", "sulphur/sulfur dioxide*", "sulphur/sulfur oxide*". Searches were restricted to humans. In addition we reviewed the references from relevant reviews that mentioned air pollution as part of a wider review of cystic fibrosis and environmental influences on disease progression. Inclusion criteria were population based studies, assessing a health-related outcome in people with CF, compared to measurement of exposures to air pollution. Studies were excluded if they failed to meet the inclusion criteria. 510 studies were identified via the literature search. Two authors separately reviewed the retrieved studies. 11 studies were considered for inclusion after review of titles (see online supplement parts 1 and 2 for full list of retrieved studies with selections by author). 5 were subsequently excluded after abstract review 2 editorials, 2 reviews, 1 study of tobacco smoke) and 1 excluded after manuscript review (a death certificates analysis, see online supplement part 3). Five studies [27,38–41] were identified as relevant to this review (Table 2). One additional study with air pollution data in the supplementary material was identified during peer review [42]. Heterogeneity of the study designs precluded the use of meta-analysis.

Air pollution and CF pulmonary exacerbations

Exacerbations are key events in disease progression and associated with stepwise declines in FEV_1 [43]. Four of the studies identified measured exacerbations as a key outcome. The first published study to associate air pollution with health outcomes was by Goss and colleagues in 2004 [38]. They retrieved clinical data on 10,294 children (aged 6 years and above) and adults with CF from the US Cystic Fibrosis Foundation National Patient Registry (CFFNPR) who lived within range of an air pollution monitoring station. Data was retrieved for 24-h average exposures to particulates ($PM_{2.5}$ and PM_{10}) and annual mean exposures to carbon monoxide, ozone, nitrogen dioxide and sulphur dioxide from readings collected by monitors no more than 30 miles (48 km) from the centre of the residential zip code. The air pollution exposures were compared with data on spirometry and exacerbations using logistic regression. Exacerbations were defined as a course of intravenous antibiotics either in hospital or at home as recorded in the registry. The patients were divided into 0 or 1, or 2 or more exacerbations in 1 year; as expected the patients with 2 or more exacerbations were older (17.4 vs. 20.6 years), had lower percent predicted FEV_1 (mean 59% vs 81% in the 0 or 1 exacerbations

Table 2
Comparison of studies retrieved during systematic review. PM, particulate matter; OR, odds ratio; HR, hazard ratio; IQR, interquartile range.

Study Author, year	Number of participants	Design	Outcome measure	Pollutants	Exposure metric	Reported NO_2 (μg/m^3)	Results
Goss 2004	10,294	Retrospective cohort from national US registry data. All individuals aged 6 years and over	Exacerbations (hospital or home iv antibiotics) FEV_1 decline	Mean 1 h O_3 NO_2 CO 24 h mean PM_{10} 24 h mean $PM_{2.5}$	Residential zipcode/postcode within 30 miles (48.3 km) of monitoring station	Mean 32 s.d. 14	For exacerbations: PM_{10} OR 1.08 (1.02–1.15) $PM_{2.5}$ OR 1.21 (1.07–1.33) O_3 OR 1.10 (1.03–1.17) Others not significant For FEV_1 decline: $PM_{2.5}$ and lung function inversely correlated
Jassal 2013	145	5 year retrospective study at Children's Hospital Los Angeles (CA, USA) Adults and children	Exacerbation requiring iv antibiotic. Participants divided into 2 groups: 0 or 1 exacerbations vs 2 or more	Annual mean $PM_{2.5}$ Max annual 1 h O_3	Proximity to freeways and major arterial roads	Not reported	2 or more exacerbations group had an OR 6.7 (1.23–54.9) if 1000 m nearer major road (p = 0.0420) Not significant for $PM_{2.5}$, O_3 or freeway proximity
Goeminne 2013	215	Retrospective cohort adults and children Lag 0–2 days pollution exposures. Belgium	Exacerbations (iv, oral, or combined iv and oral abx for clinical exacerbation or FEV1 fall. Exacerbations by modified Fuchs criteria)	PM_{10} NO_2 O_3	4x4km modelled grids	Median 24 IQR 17–32	Combined lag day 0 and day 1 For 10ug/m^3 increase in each pollutant OR for exac was: PM_{10} 1.043 (1.004–1.084) NO_2 1.106 (1.05–1.166) O_3 1.034 (1.003–1.067)
Farhat 2013	103	1 year prospective Sao Paulo Children Lag 0–6 days	Exacerbations (Fuchs criteria)	Daily levels 1 h O_3 24 h mean SO_2 1 h NO_2 24 h mean PM_{10} 8 h CO	Nearest monitoring station (average of 14 in city)	Mean 103 s.d. 35	Lag 2 day IQR change in O_3 gave OR 1.86 (1.14–3.02) for exacerbation All other analyses negative
Psoter 2015	3575	Retrospective US registry data 2003–2009 for children aged 0–5 y	First acquisition of *Pseudomonas aeruginosa*	$PM_{2.5}$	Monitor within 10, 30 and 50 miles of residential postcode/zipcode	Not reported	10 μg/m^3 increase in $PM_{2.5}$ exposure associated with HR 1.24 (95%CI 1.01–1.51) for initial *Pseudomonas aeruginosa* infection

group), and lower weight percentile (23 vs 33.6). In addition, they were more likely to be infected with *Pseudomonas aeruginosa (Pa)* or *Burkholderia cepacia* complex (Bcc) organisms, have a diagnosis of pancreatic insufficiency, and government provided insurance (as a proxy for socio-economic status). Patients with 2 or more exacerbations lived in areas with slightly higher measured levels of both $PM_{2.5}$ (14.2 vs 13.9, $p < 0.001$) and PM_{10} (25.4 vs 25.1, $p < 0.01$), however there was no difference in annual mean CO, SO_2 or NO_2.

After adjusting for gender, age, weight, ethnicity, airway *Pa* and *Bcc*, pancreatic status and insurance status, the investigators reported an odds ratio (OR) of 1.21 (95%CI 1.07–1.33) for 2 or more exacerbations, for a given 10 μg/m^3 increase in PM2.5. PM10 (OR 1.08, 95%CI 1.02–1.15) and ozone (OR 1.10, 95%CI 1.03–1.17) were also associated with an increased number of exacerbations. No significant association was seen with exposures to NO_2, SO_2 or carbon monoxide.

The authors highlight the limitation of registry studies with respect to incomplete data for possible confounders; environmental tobacco smoke exposure and active smoking were not recorded in the CFFNPR. The authors adjusted for socio-economic status, but there remains a risk of residual confounding, with respect to exposure misclassification. For example, annual $PM_{2.5}$ levels in London range from 8 to 22 μg/m^3 [44] in a city approximately 16 miles in diameter; it may be that the actual air pollution exposures encountered by individuals in this study were markedly different to those measured at a mean distance of 11.5 miles (sd 7.9 miles) but this limitation is difficult to overcome given the extent of air pollution monitoring data available to the investigators at the time. This may be a factor in the absence of a measured association with nitrogen dioxide; given their common source the NO_2 findings would be expected to correlate with $PM_{2.5}$.

As traffic is the major source of small particles and NO_2, Jassal et al. [39] compared residential proximity to freeways and major roads, in addition to maximum annual 1-h O_3 and annual mean $PM_{2.5}$, with CF exacerbations in 145 patients cared for at Children's Hospital Los Angeles (CHLA), including those who had transitioned to adult services. This was a retrospective longitudinal study over 5 years (2004–2008). Exacerbations were defined as a change in respiratory status requiring intravenous antibiotics, and/or an encounter recorded as a pulmonary exacerbation on the CFFPR, and as per the study by Goss et al. [38], the groups were classified as 0 or 1 vs 2 or more exacerbations. Via logistic regression, no association was seen with O_3 or $PM_{2.5}$ exposure and exacerbation status, which could represent a type 2 error given the power in this smaller study if looking to replicate the effect sizes described in the previous registry study by Goss et al. [38]. No association was seen with residential proximity to freeways (OR 1.12, 95%CI 0.30–66.53), however a positive association was seen for straight line distance to a "major road" (which was defined as a "major arterial route"), with OR 6.7 (95% CI 1.23–54.49) for exacerbation status associated with living 1000 m closer to a major road. The authors also highlight the limitation of no recorded data on smoking or tobacco smoke exposure, as well as the possible confounding by socio-economic status, as people living closer to main roads may

have poorer health outcomes due to a range of factors including income and access to health care. In order to adjust for this, insurance status was corrected for in their model.

These two studies suggest an association between outdoor air pollution and CF exacerbation, but are limited by the methods used to classify exposures. Given the *in vitro* evidence that particles exert a direct effect on the airway epithelium, short term deteriorations in air pollution may be triggers for exacerbation. Goeminne et al. [40] used a case-crossover model comparing daily air pollution exposures (rather than annual means) to explore associations between short-term rises in pollutants and subsequent exacerbations of CF in 215 patients, looking retrospectively at hospital records between 1998 and 2010. In contrast to the studies outlined previously, exacerbations were defined as the use of home or hospital oral or intravenous antibiotics. Air pollution exposures for PM_{10}, NO_2 and ozone were calculated using modelling which provided data for 4 km grid squares, for 2 days prior, 1 day prior and on the day of exacerbation onset. NO2 and PM10 exposures were positively correlated ($r = 0.67$, $p < 0.0001$). The investigators found significant associations between 10 $\mu g/m^3$ increases in all three measured air pollutants and same-day exacerbations. Averaging exposure for the preceding day, and the day of the exacerbation resulted in PM_{10} OR 1.043 (95%CI 1.004–1.084), ozone OR 1.034 (95%CI 1.003–1.067) and NO_2 1.106 (95%CI 1.050–1.166). The study is limited by not including $PM_{2.5}$ as a specific measurement (although the $PM_{2.5}$ fraction will be captured in the PM_{10} data as it will pass through the filters); this was because $PM_{2.5}$ was not measured until 2009, and the local PM_{10} and $PM_{2.5}$ levels are strongly correlated (they report correlation coefficients of 0.94–0.98). The authors also highlight the risk of bias from the retrospective study design where a complete data set may not be recorded contemporaneously. A strength of the study is the case-crossover design; patients act as their own controls which minimises potential confounders such as socio-economic status. It is worth noting that the reported air pollution for their region of Belgium was lower than that in the previous US study by Goss et al. [38], with median NO_2 24 (IQR 17–32) 10 $\mu g/m^3$ vs mean NO_2 32 (sd 14) $\mu g/m^3$, this may have reduced the effect sizes observed and a replicate study in a highly polluted city may show greater effects.

Farhat and colleagues [41] used a prospective design in a highly polluted city (Sao Paulo, Brazil) to look at exacerbations in 103 children with CF over a period of 12 months. Exacerbations were defined as the presence of three or more of: fever, increased sputum production or cough intensity, change in sputum colour, worsening dyspnoea, loss of appetite, >10% decrease in FEV_1 or weight loss. These were compared to daily records of ozone, SO_2, NO_2, PM_{10} and carbon monoxide obtained from an average of the state environmental agency monitoring stations based within the city. Children were reviewed a mean (SD) of 4 (1.7) times over the study period, and the lag air pollution for each pollutant was calculated for 6 days pre-exacerbation. For an interquartile range increase in ozone two days before the onset of an exacerbation, an increased relative risk (RR 1.86, 95%CI 1.14–3.02) was observed. For the 34 other analyses (5 pollutants, 7 days) no positive results emerged. In summary, each study outlined shows an association between at least one pollutant and CF exacerbations, with relatively similar estimates for effect sizes.

Air pollution and lung function

FEV_1 is a key predictor of mortality in CF [45]. One study [38] assessed the effect of pollutants on FEV_1. Goss et al. showed a negative linear association between FEV_1 and both PM_{10} and $PM_{2.5}$ after adjusting for age, gender and height. A 10 $\mu g/m^3$ increase in PM2.5 was associated with a 155 ml (95%CI 115–194 ml) decrease in FEV_1, and when calculated by percent predicted FEV_1 this equated to a 0.5% (95%CI 0.3–0.9%) decrease per 10 $\mu g/m^3$ increase in $PM_{2.5}$. No associations were found with the other recorded pollutants.

Air pollution and respiratory infection

Infection with *Pseudomonas aeruginosa* early in life is associated with increased morbidity and mortality [46]. In a murine model [47], prolonged diesel exhaust exposures (6 h per day for 6 months) impaired clearance of *Pa* infection, associated with inflammatory changes on histology and a decrease in ciliated bronchial epithelium, and urban particulate matter increases binding of *Streptococcus pneumoniae* to primary bronchial epithelial cells [48]. In an *in vitro* exposure model, *Staphylococcus aureus* and *Streptococcus pneumoniae,* common pathogens found early in CF, when exposed to black carbon show altered responses to antibiotics, and changes in biofilm structure [49]. These findings imply that air pollution exposures may increase susceptibility to initial bacterial infection, similar to the observed effect of indoor air pollution and pneumonia in children [50,51].

Psoter et al. [27] hypothesised that pollution exposure early in life might associate with an increased risk of early infection with *Pa*. They used a similar methodology to the study of Goss et al. [38] by conducting a retrospective analysis of US registry data over a 7-year period, limiting their analysis to children aged below 6 years, comparing air pollution exposures with age of first diagnosed *Pa* infection. Exposures were again determined using data from monitors within a 30 mile radius, and limited to $PM_{2.5}$ only. 3575 children were included in the analysis of whom 1,711 (48%) acquired *Pa*. Of the 2861 children who lived within 30 miles of a monitor, an increase of 10 $\mu g/m^3$ in $PM_{2.5}$ was associated with a hazard ratio (HR) of 1.24 (95%CI 1.01–1.51) for initial *Pa* infection. For context, the mean (sd) background $PM_{2.5}$ for this group in the study was 12.3 (2.7) $\mu g/m^3$. In a replicated cohort study, Collaco and colleagues [42] estimated $PM_{2.5}$ exposures in US CF patients enrolled in the CF Twin and Sibling Study using methodology comparable to that of Goss et al. [38], and in a univariate regression model including data on 677 subjects showed that higher levels of $PM_{2.5}$ were associated with a greater risk of *Pa* infection.

WHAT CAN PEOPLE WITH CF DO TO DECREASE THEIR AIR POLLUTION EXPOSURE?

Evidence in this area is limited. A study in adults with asthma demonstrated the benefits of walking through an urban green space in contrast to walking along a polluted thoroughfare [52], as asthmatic patients experienced a fall in FEV_1 that persisted into the following day after a 2-h walk along Oxford Street in London, UK. Using small, handheld personal monitors, we have previously shown that micro-environmental exposures to "peaks" of air pollution may be equivalent in cities with markedly different background levels of $PM_{2.5}$ [53], and that the majority of a child's daily exposure occurs on the school run. In adults, exposures depend on what you do and where you do it. In a short experiment giving pollution monitors to different individuals, an ambulance driver (who sits in an enclosed space) had greater air pollution exposure than a cycle courier (who can move quickly through polluted air) [7]. It makes sense to avoid air pollution by taking traffic-free routes to and from school, but it may be counter-intuitive to realise that walking along a roadside can expose a child to less pollution than being in a car on the same road. Studies into the magnitude of air pollution exposures along different school routes are ongoing [54], and have included "citizen scientist" approaches [55]. It is possible to reduce exposures to indoor air pollutants (including volatile organic compounds, and particles generated by cooking) by ensuring adequate ventilation and using the extractor fan when cooking [7] – these small changes increment over

time. Cycling or walking to work or school decreases both your air pollution exposure and the amount of air pollution you generate for others to breathe, and is beneficial for your health even after taking into account the risk of accidents [56]. Air pollution exposures are not simply a matter for individuals – they depend on trans-national legislation, with transport and energy policies that focus on reducing the generation of toxic gases and particles into our environment. Adults caring for children with lungs that appear particularly vulnerable to polluted air need to advocate for these changes.

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DIRECTIONS FOR FUTURE RESEARCH

- Use new and emerging monitoring technologies to accurately quantify pollution exposures
- Exploit large datasets on pollution exposures generated by citizen science projects to generate evidence-based advice on how to avoid polluted air
- Establish the direct effect of air pollution on host airways and on pathogens

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.prrv.2018.03.005.

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