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Air pollution exposure is associated with MRSA acquisition in young U.S. children with cystic fibrosis

Kevin J. Psoter[1*], Anneclaire J. De Roos[2], Jon Wakefield[3], Jonathan D. Mayer[4] and Margaret Rosenfeld[5]

Abstract

Background: The role of air pollution in increasing susceptibility to respiratory tract infections in the cystic fibrosis (CF) population has not been well described. We recently demonstrated that chronic $PM_{2.5}$ exposure is associated with an increased risk of initial *Pseudomonas aeruginosa* acquisition in young children with CF. The purpose of this study was to determine whether $PM_{2.5}$ exposure is a risk factor for acquisition of other respiratory pathogens in young children with CF.

Methods: We conducted a retrospective study of initial acquisition of methicillin susceptible and methicillin resistant *Staphylococcus aureus* (MSSA and MRSA), *Stenotrophomonas maltophilia* and *Achromobacter xylosoxidans* in U.S. children <6 years of age with CF using the CF Foundation Patient Registry, 2003–2009. Multivariable Weibull regression with interval-censored outcomes was used to evaluate the association of $PM_{2.5}$ concentration in the year prior to birth and risk of acquisition of each organism.

Results: During follow-up 63%, 17%, 24%, and 5% of children acquired MSSA, MRSA, *S. maltophilia*, and *A. xylosoxidans*, respectively. A 10 μg/m³ increase in $PM_{2.5}$ exposure was associated with a 68% increased risk of MRSA acquisition (Hazard Ratio: 1.68; 95% Confidence Interval: 1.24, 2.27). $PM_{2.5}$ was not associated with acquisition of other respiratory pathogens.

Conclusions: Fine particulate matter is an independent risk factor for initial MRSA acquisition in young children with CF. These results support the increasing evidence that air pollution contributes to pulmonary morbidities in the CF community.

Keywords: Cystic fibrosis, *Staphylococcus aureus*, MRSA, *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, Fine particulate matter, Air pollution

Background

Cystic fibrosis (CF) lung disease is characterized by a vicious cycle of chronic pulmonary inflammation and endobronchial infection. This process can begin early in life, as inflammation and structural airway damage are often present during infancy and the preschool years [1–4]. More severe CF transmembrane conductance regulator (CFTR) mutations are associated with poorer clinical outcomes [5]; however, identification of exogenous factors that contribute to the inflammatory process and

susceptibility to infection may provide an opportunity for intervention.

Both gaseous and solid components of air pollution are associated with adverse clinical outcomes in the CF population [6–10], and fine particulate matter ($PM_{2.5}$; atmospheric particles with an aerodynamic diameter ≤ 2.5 μm), has consistently been shown to be a predictor of pulmonary morbidities [6, 8–10]. Declining lung function and increased pulmonary exacerbation rates [8] have been reported in association with long-term exposure to $PM_{2.5}$, and increased risk of pulmonary exacerbations has been described for higher short-term exposure [6, 8]. To date, few studies have examined the role of air pollution exposure in increasing susceptibility

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to respiratory pathogens in CF patients [9, 10]. We recently demonstrated that chronic $PM_{2.5}$ exposure is associated with an increased risk of initial *Pseudomonas aeruginosa* acquisition in young children with CF [10]. The purpose of this study was to evaluate early life fine particulate matter exposure and risk of initial acquisition of other CF pathogens, including methicillin-susceptible *Staphylococcus aureus* (MSSA), methicillin-resistant *Staphylococcus aureus* (MRSA), *Stenotrophomonas maltophilia*, and *Achromobacter xylosoxidans* in the same population of young children with CF.

Methods

Study population and setting

We performed a retrospective cohort study to evaluate the association between early life $PM_{2.5}$ exposure and time to initial acquisition of commonly cultured bacteria from the respiratory tract of U.S. children <6 years of age with CF, including MSSA, MRSA, *S. maltophilia*, and *A. xylosoxidans*, using the U.S. Cystic Fibrosis Foundation National Patient Registry, 2003–2009. The registry contains detailed encounter-based information on individual-level demographic and disease characteristics for all patients treated at CF Foundation-accredited care centers [11].

The study population consisted of all children residing in the lower 48 states born after December 31, 2002 and with a first encounter and respiratory culture recorded prior to 2 years of age. To evaluate incident pathogen acquisition, those children whose initial culture was positive for the pathogen of interest were excluded from that analysis. This study was approved by the Institutional Review Board of the University of Washington and the Cystic Fibrosis Foundation Registry Committee.

Particulate matter exposure

The primary exposure of interest was the mean annual concentration of $PM_{2.5}$ in the calendar year prior to birth for each child. Year prior to birth was chosen because it captured $PM_{2.5}$ exposure prior to disease onset and accounted for the known secular decline in U.S. air pollution levels that occurred during this time period.

Annual summary measures of $PM_{2.5}$ were obtained from the U.S. Environmental Protection Agency Air Quality System (https://www.epa.gov/aqs), a national network of federally and locally funded air monitoring sites located throughout the U.S. Over the course of the study, 1574 monitoring stations came on-line and went off-line; only data from those monitors in operation for an entire year with no more than a 45-day gap between measurements, which ranged from 73% of monitors in 2003 to 81% in 2002 and 2007, were utilized for analyses.

Individual-level $PM_{2.5}$ exposure for each child was assigned in the following manner. Initially, latitude and longitude coordinates for each of the monitoring stations were geocoded using ArcGIS 10.1 (ESRI, Redlands, CA). A similar procedure was then used to geocode each child's residence, taken as the centroid of the residential zip code at the time of entry into the registry. Individual-level $PM_{2.5}$ exposure was assigned using 4 common $PM_{2.5}$ exposure metrics. First, $PM_{2.5}$ exposure was determined based on a nearest monitor approach in which the closest monitoring station (based on linear distance) was identified for each of the residential zip code centroids; the corresponding $PM_{2.5}$ concentration of the monitor served as the individual-level exposure. Inverse distance weighting (IDW) procedures were then employed to estimate three $PM_{2.5}$ exposures. For the IDW approach, exposure was estimated as the weighted value (based on an exponential decay model over distance) of $PM_{2.5}$ concentrations of monitors located within 50, 30, and 10 miles of the residential zip code centroid. Individuals for whom no monitoring station was located within each of these distances were excluded from analyses. The primary $PM_{2.5}$ exposure metric was based on the IDW within 30 miles, in accordance with the previously published CF literature [8–10]; however, complete results for each metric are provided.

Outcomes

The primary outcomes were time to first positive culture for MSSA, MRSA, *S. maltophilia*, and *A. xylosoxidans* recorded in the registry. CF Foundation guidelines of care recommend quarterly (i.e., four times annually) respiratory cultures [12], typically obtained from oropharyngeal swabs in this young, non-expectorating population. Because the exact date of acquisition is not known with this surveillance approach, pathogen acquisition was defined as occurring in the interval between the date of previous negative culture (left hand endpoint) and the date of first positive respiratory culture (right hand endpoint).

Statistical analysis

Demographic and clinical characteristics were compared between children acquiring each pathogen and those that remained pathogen-free during follow-up using Student t tests with unequal variances for continuous variables and Chi square tests for categorical variables.

Multivariable Weibull regression with interval censored outcomes [13] was used to evaluate the association between mean annual $PM_{2.5}$ concentration in the year prior to birth and time to first recorded positive culture for each pathogen. For each analysis, children entered

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the study upon first clinical encounter recorded in the registry. Subjects were right censored on the date of the last encounter prior to December 31, 2009 if they remained pathogen-free during follow-up. All analyses were adjusted a priori for the following potential confounders: sex, race (white vs. non-white), ethnicity (Hispanic vs. non-Hispanic), insurance status (any private insurance vs. no private insurance), urban/rural status using the Rural Urban Commuting Area coding Version 2.0 [14] (defined as urban, large rural, small rural, or isolated), age at diagnosis of CF, diagnosis by newborn screening, and CFTR functional class, defined as follows: Severe, both CFTR mutations result in minimal CFTR function (class 1, 2, or 3), including F508 del; Residual, at least one allele with a mutation resulting in partial CFTR function (class 4 or 5); Unclassified, both alleles with unknown functional class, or one allele with minimal CFTR function and the second with unknown functional class. Results of multivariable models are presented as hazard ratios (HR) and corresponding 95% confidence intervals (CI) for each 10 µg/m^3 increase in PM$_{2.5}$ exposure. A two-sided *P* value <0.05 was considered statistically significant. All analyses were performed using R (Version 3.0.2) [15].

Results

A total of 4522 children in the CFF Registry were born after December 31, 2002 and had a first registry encounter and respiratory culture recorded prior to 2 years of age. Of these 3463 (77%) had PM$_{2.5}$ data from the year prior to birth available from a monitoring station within 30 miles of the residence location and comprised the study population. The cohorts for each of the pathogens investigated varied slightly due to the inclusion of only incident cases (Fig. 1). A total of 1885 of 3012 (63%) children acquired MSSA, 706 out of 4111 (17%) acquired MRSA; 992 of 4136 (24%) acquired *S. maltophilia*; and 201 of 4255 (5%) acquired *A. xyloxidans* while under study. The median time to initial acquisition amongst those who acquired these pathogens was 20 months (25th–75th percentiles: 13, 32 months), 30 months (25th–75th percentiles: 17, 46 months), 23 months (15, 37 months), and 34 months (20, 49 months), respectively.

Table 1 compares the demographic and clinical characteristics of those children acquiring and remaining free of each organism during follow-up. Children acquiring each pathogen were more likely to have severe CFTR mutations and less likely to be diagnosed by newborn screening than those remaining pathogen-free. Children with any private insurance were less likely to acquire MRSA, *S. maltophilia*, and *A. xylosoxidans* compared to children with no private insurance. Males were more likely than females to acquire MSSA and *A. xylosoxidans*, while

a greater proportion of Hispanic children acquired MRSA and *A. xylosoxidans* than did non-Hispanics.
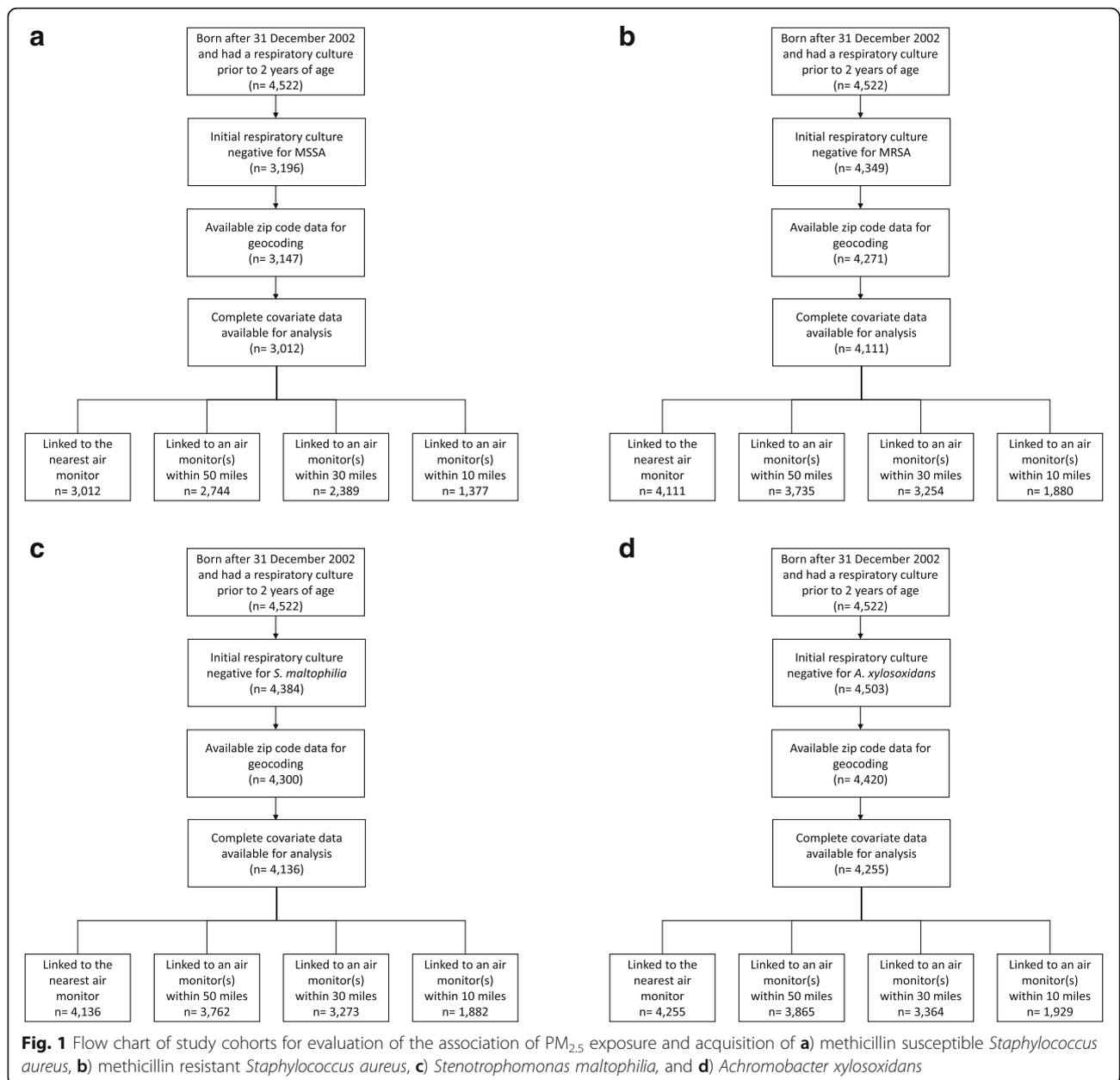
Mean annual PM$_{2.5}$ concentrations for the study population in the year prior to birth by acquisition status of each pathogen are presented in Table 2. For all metrics of PM$_{2.5}$ exposure and for each pathogen, children who had a positive culture during follow-up had a higher mean PM$_{2.5}$ exposure in the year prior to birth compared to those that remained pathogen-free.

Results of the Weibull regression evaluating the association of PM$_{2.5}$ exposure and risk of acquisition of respiratory pathogens are presented in Table 3. For each 10 µg/m^3 increase in PM$_{2.5}$ exposure, there was a statistically significantly increased risk of MRSA acquisition (HR = 1.56; 95% CI: 1:13, 2.14). PM$_{2.5}$ exposure was not associated with increased risk of MSSA (HR = 0.97; 95% CI: 0.80, 1.17), *S. maltophilia* (HR = 1.28; 95% CI: 0.99, 1.66) or *A. xylosoxidans* (HR = 1.42; 95% CI: 0.78, 2.58) acquisition. Similar results were obtained in the analysis of the nearest monitor and IDW 50- and 10-mile PM$_{2.5}$ metrics; however, in the nearest monitor PM$_{2.5}$ exposure analysis, PM$_{2.5}$ was associated with an increased risk of *S. maltophilia* acquisition (HR = 1.34; 95% CI: 1.07, 1.68).

Discussion

In this large, national cohort of U.S. CF patients <6 years of age, PM$_{2.5}$ exposure was associated with an increased risk of initial acquisition of MRSA (but not of the other organisms we examined), with a 56% (95% CI: 13%, 114%) increased risk of MRSA acquisition for each 10 µg/m^3 increase in PM$_{2.5}$. We recently reported a similar association between PM$_{2.5}$ exposure and risk of initial *P. aeruginosa* acquisition in the same cohort, with a 24% (95% CI: 1–51%) increased risk of *P. aeruginosa* acquisition for each 10 µg/m^3 increase of PM$_{2.5}$ in the year prior to birth, after adjustment for covariates [10]. Similarly, Collaco et al. [9] reported increased odds of *P. aeruginosa* prevalence (Odds Ratio [OR] for each 10 µg/m^3 increase in PM$_{2.5}$ = 1.12; 95% CI: 1.01, 1.23) among 677 patients in the U.S. CF Registry, employing the average PM$_{2.5}$ exposure in 2006 based on the nearest monitor within 30 miles of residential zip code. Our findings suggest that air pollution is an independent risk factor for and may play a previously unrecognized role in respiratory colonization by MRSA and *P. aeruginosa* in the CF population.

Chronic infection with MRSA is associated with poorer clinical outcomes and survival in CF patients [16–18]. Of concern, MRSA prevalence among U.S. CF patients has increased steadily from 9% in 2002 to 27% in 2012 [19]. About 70% of MRSA isolates among children with CF in the US are "health care–associated" (SCCmec II) versus "community-associated" (SCCmec

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Fig. 1 Flow chart of study cohorts for evaluation of the association of PM$_{2.5}$ exposure and acquisition of **a**) methicillin susceptible *Staphylococcus aureus*, **b**) methicillin resistant *Staphylococcus aureus*, **c**) *Stenotrophomonas maltophilia,* and **d**) *Achromobacter xylosoxidans*

IV) strains [20], though the prevalence of SCCmecIV relative to SCCmecII strains has increased over the last decade. Known risk factors for MRSA acquisition in CF patients include colonization with *P. aeruginosa* [20], more frequent clinic visits [20] and higher mean ambient temperature [21]. To our knowledge, the association of air pollution exposure and risk of MRSA acquisition has not previously been evaluated.

The mechanism by which exposure to PM$_{2.5}$ may increase the risk of MRSA acquisition among young CF patients deserves further exploration. As there are no data to suggest that components of air pollution directly increase exposure to MRSA or other pathogens, it seems

more likely that adverse effects of PM$_{2.5}$ exposure on the CF airway increases susceptibility to MRSA infection. Limited in vitro studies exist regarding the biologic mechanisms by which exposure to fine particulate matter adversely affects the CF airway. Kamdar and colleagues demonstrated that PM$_{2.5}$ increases oxidative stress and mitochondrial signaling-mediated apoptosis in CF human bronchial epithelial cells [22] which in turn could increase airway inflammation. Further, Geiser et al. demonstrated higher uptake of inhaled nanoparticles by alveolar epithelial cells and increased inflammatory response of CFTR mutant mice compared to wild type [23]. The effects of gaseous air pollutants on the CF

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Table 1 Demographic and clinical characteristics of young children with cystic fibrosis by pathogen acquisition status, 2003–2009

Respiratory Pathogen	MSSA			MRSA			S. maltophilia			A. xylosoxidans		
	Acquired (n = 1885)	Negative (n = 1127)	P value	Acquired (n = 706)	Negative (n = 3405)	P value	Acquired (n = 992)	Negative (n = 3144)	P value	Acquired (n = 201)	Negative (n = 4054)	P value
Male (%)	909 (48)	589 (52)	0.04	347 (49)	1731 (51)	0.44	502 (51)	1581 (50)	0.89	86 (43)	2061 (51)	0.03
White (%)	1750 (93)	1019 (90)	0.02	636 (90)	3134 (92)	0.10	913 (92)	2887 (92)	0.88	179 (89)	3726 (92)	0.19
Hispanic (%)	201 (11)	121 (11)	0.99	50 (7)	403 (12)	<0.01	124 (13)	327 (10)	0.07	35 (17)	430 (11)	<0.01
Any Private Insurance (%)	984 (52)	591 (52)	0.93	301 (43)	1903 (56)	<0.01	471 (47)	1721 (55)	<0.01	79 (39)	2174 (54)	<0.01
Age at diagnosis, months, mean (SD)	2.5 (4.3)	2.2 (4.3)	0.12	2.7 (4.3)	2.3 (4.2)	0.66	2.5 (4.2)	2.4 (4.3)	0.26	3.2 (4.8)	2.4 (4.2)	0.03
Identified by newborn screening (%)	663 (35)	611 (54)	<0.01	213 (30)	1555 (46)	<0.01	358 (36)	1414 (45)	<0.01	68 (34)	1756 (43)	<0.01
CFTR functional class[a] (%)												
Severe	1275 (68)	714 (63)	0.04	514 (73)	2148 (63)	<0.01	695 (70)	1991 (63)	<0.01	134 (67)	2638 (65)	0.03
Residual	156 (8)	116 (10)		45 (6)	328 (10)		60 (6)	315 (10)		8 (4)	373 (9)	
Unclassified	454 (24)	297 (26)		147 (21)	929 (27)		237 (24)	838 (27)		59 (29)	1043 (26)	

Data given as No. (%) unless otherwise indicated, *MSSA* methicillin susceptible *Staphylococcus aureus*, *MRSA* methicillin resistant *Staphylococcus aureus*, *S maltophilia*, *Stenotrophomonas maltophilia*, *A. xylosoxidans*, *Achromobacter xylosoxidans*

[a] CFTR Mutation class is defined as follows: Severe, includes children in which both CFTR allele mutations result in minimal CFTR function (class 1, 2, or 3), including F508 del; Residual, children for which at least one allele with a mutation resulting in partial CFTR function is present (class 4 or 5); Unclassified, both alleles with unknown functional class, or one allele with minimal CFTR function and the second with unknown functional class

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Table 2 Mean and standard deviations of $PM_{2.5}$ concentrations ($\mu g/m^3$) in year prior to birth for young children with cystic fibrosis from 2003 to 2009, overall and by methicillin susceptible *Staphylococcus aureus*, methicillin resistant *Staphylococcus aureus*, *Stenotrophomonas maltophilia*, and *Achromobacter xylosoxidans* acquisition status

| | Respiratory Pathogen | | | | | | | | | | | |
| | MSSA | | | MRSA | | | S. maltophilia | | | A. xylosoxidans | | |
	Overall	Acquired	Negative	Overall	Acquired	Negative	Overall	Acquired	Negative	Overall	Acquired	Negative
PM2.5 Metric												
Nearest monitor[a]	12.04 (2.75)	12.20 (2.77)	11.77 (2.71)	12.06 (2.79)	12.55 (2.62)	11.95 (2.81)	12.06 (2.78)	12.46 (2.67)	11.94 (2.81)	12.06 (2.78)	12.65 (2.48)	12.03 (2.79)
IDW: 50 miles[b]	12.27 (2.58)	12.45 (2.60)	11.99 (2.52)	12.27 (2.60)	12.83 (2.39)	12.15 (2.63)	12.27 (2.60)	12.65 (2.48)	12.16 (2.63)	12.28 (2.60)	12.86 (2.30)	12.25 (2.61)
IDW: 30 miles[c]	12.29 (2.66)	12.46 (2.68)	12.01 (2.59)	12.31 (2.68)	12.85 (2.50)	12.21 (2.70)	12.31 (2.68)	12.69 (2.55)	12.19 (2.71)	12.32 (2.67)	12.95 (2.40)	12.29 (2.40)
IDW: 10 miles[d]	12.26 (2.76)	12.40 (2.79)	12.04 (2.69)	12.31 (2.81)	12.96 (2.73)	12.19 (2.80)	12.30 (2.80)	12.64 (2.71)	12.20 (2.82)	12.32 (2.80)	13.08 (2.50)	12.29 (2.81)

MSSA methicillin susceptible *Staphylococcus aureus*, *MRSA* methicillin resistant *Staphylococcus aureus*, *S maltophilia*, *Stenotrophomonas maltophilia*, *A xylosoxidans*, *Achromobacter xylosoxidans*, $PM_{2.5}$ particulate matter ≤2.5 μm in aerodynamic diameter, *IDW* inverse distance weighted

[a] Subjects with available $PM_{2.5}$ data (nearest monitor), by respiratory pathogen: MSSA (*n* = 3012), MRSA (*n* = 2744), S. *maltophilia* (*n* = 4111), S. *maltophilia* (*n* = 4136) and A. *xylosoxidans* (*n* = 4255)

[b] Subjects with available $PM_{2.5}$ data (IDW: 50 miles), by respiratory pathogen: MSSA (*n* = 2744), MRSA (*n* = 3735), S. *maltophilia* (*n* = 3762) and A. *xylosoxidans* (*n* = 3865)

[c] Subjects with available $PM_{2.5}$ data (IDW: 30 miles), by respiratory pathogen: MSSA (*n* = 2389), MRSA (*n* = 3254), S. *maltophilia* (*n* = 3273) and A. *xylosoxidans* (*n* = 3364)

[d] Subjects with available $PM_{2.5}$ data (IDW: 10 miles), by respiratory pathogen: MSSA (*n* = 1377), MRSA (*n* = 1880), S. *maltophilia* (*n* = 1882) and A. *xylosoxidans* (*n* = 1929)

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Table 3 Results of multivariable Weibull regression with interval censored outcomes[1] evaluating the association of $PM_{2.5}$ exposure and time to methicillin susceptible *Staphylococcus aureus*, methicillin resistant *Staphylococcus aureus*, *Stenotrophomonas maltophilia*, and *Achromobacter xylosoxidans* acquisition for young children with cystic fibrosis, 2003–2009

$PM_{2.5}$ metric	Nearest monitor	IDW: 50 miles	IDW: 30 miles	IDW: 10 miles
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
MSSA	0.91 (0.77, 1.08)	0.93 (0.77, 1.13)	0.97 (0.80, 1.17)	0.90 (0.71, 1.15)
MRSA	*1.48 (1.14, 1.93)*	*1.68 (1.24, 2.27)*	*1.56 (1.13, 2.14)*	*1.78 (1.17, 2.69)*
S. maltophilia	1.34 (1.07, 1.68)	1.30 (1.00, 1.65)	1.28 (0.99, 1.66)	1.10 (0.79, 1.53)
A. xylosoxidans	1.48 (0.91, 2.41)	1.44 (0.83, 2.53)	1.42 (0.78, 2.58)	1.51 (0.68, 3.34)

$PM_{2.5}$ particulate matter ≤2.5 μm in aerodynamic diameter, *IDW* inverse distance weighted, *HR* hazard ratio, *CI* confidence interval, *MSSA* methicillin susceptible *Staphylococcus aureus*, *MRSA* methicillin resistant *Staphylococcus aureus*, *S maltophilia* *Stenotrophomonas maltophilia*, *A xylosoxidans*, *Achromobacter xylosoxidans*
[1]All regression models were adjusted for: sex, race, ethnicity, insurance status, rural urban commuting area, diagnosis by newborn screening, age at diagnosis of CF, and CFTR mutation class. Results of regression models reflect the hazard ratio associated with a 10 μg/m³ increase in $PM_{2.5}$ exposure. Hazard ratios that are significantly different from 1.00 ($P < 0.05$) are in italics

airway are less well understood; however, increased ozone levels have been shown to downregulate CFTR function in human bronchial epithelial cells [24].

Similarly, epidemiological studies have demonstrated adverse clinical outcomes associated with short and long-term air pollution exposure among CF patients, as well as for specific constituents of air pollution. In the first such investigation, utilizing the U.S. CF Registry, Goss, et al. [8] reported increased pulmonary exacerbations associated with the long term exposure to PM_{10}, $PM_{2.5}$ and ozone, with declining lung function and FEV_1 associated with increased $PM_{2.5}$ exposure. Subsequently, Goeminne, et al. [6] conducted a case-crossover study in a cohort of Belgium CF patients and reported that short-term exposure to PM_{10} (OR = 1.04; 95% CI: 1.00–1.08), ozone (OR = 1.11; 95% CI: 1.05–1.17) and NO_2 (OR = 1.03; 95% CI: 1.00–1.07) were associated with increased risk of pulmonary exacerbations. Farhat, et al. reported an increased risk of pulmonary exacerbation with a two-day lagged ozone exposure (Relative Risk = 1.86; 95% CI, 1.14–3.02) in a longitudinal analysis of Brazilian CF patients in a metropolitan city [7]. However, Jassel, et al. reported no association of $PM_{2.5}$, ozone or proximity to major road ways and frequency of pulmonary exacerbations in a cohort of 145 children with CF [25].

In the general population, prenatal exposure to air pollution is a risk factor for low birth weight [26, 27], which in turn is a risk factor for adverse respiratory outcomes in early childhood [28]. In addition, post-natal air pollution exposure has been associated with an increased risk of bronchiolitis and recurrent wheeze in infants and young children [29, 30]. Our findings of increased risk of MRSA acquisition in CF patients may be in part mediated by these same risk factors, particularly since $PM_{2.5}$ exposure was measured in the year prior to birth.

Environmental factors are associated with approximately 50% of the population variability in lung function [31] and *P. aeruginosa* acquisition [32] in CF patients. Many of the CF-related pathogens are naturally

occurring in the environment, although few studies have investigated specific environmental factors that may contribute to pathogen acquisition [33]. *P. aeruginosa* is the most widely studied CF-related bacterium with seasonal variations in acquisition [34] and differential geographic residual relative risk [13] reported. These same factors may contribute to MRSA acquisition in CF patients.

Strengths of the present investigation include the large, national cohort with regular respiratory culture results. There are also several limitations. First, available $PM_{2.5}$ data was limited to outdoor exposure. Therefore, evaluation of cumulative exposure to $PM_{2.5}$ including indoor air pollution was not possible. Similarly, the gaseous components of air pollution (e.g. ozone and nitrous oxides) as well as coarse particulate matter ($PM_{2.5-10}$), were not considered. Second, $PM_{2.5}$ exposure was based upon a nearest monitor approach rather than monitoring at the patient's residence, which may have resulted in misclassification of $PM_{2.5}$ exposure. Furthermore, as air pollution exposure was determined in the calendar year prior to birth, change in zip code of residence during follow-up may not accurately represent long-term $PM_{2.5}$ exposure. Third, information on environmental tobacco smoke exposure, preterm birth/low birth weight, or maternal occupational exposures, potentially important variables, were not available. Fourth, information on MRSA strains (SCCmec type or Panton Valentine Leukocidin status) was unavailable so we were not able to distinguish community vs. healthcare associated strains. It is possible that the risk of MRSA acquisition associated with $PM_{2.5}$ exposure may differ by subtypes. Finally, respiratory cultures were performed primarily on oropharyngeal swabs in the non-expectorating young cohort. The specificity and, even more, the sensitivity of oropharyngeal cultures in comparison to lower respiratory samples is limited [35]; results of this study may not be generalizable to lower airway colonization. Nonetheless, oropharyngeal swabs are standard of care for assessment of respiratory cultures in pre-expectorating patients in

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the U.S., and acquisition of pathogens in the upper airway is generally considered an important clinical outcome.

Conclusions

In conclusion, increasing levels of exposure to fine particulate matter was found to be a risk factor for initial MRSA acquisition in young children with CF. These results further strengthen the growing evidence that increased levels of air pollution are associated with adverse outcomes in the CF population. Additional studies that investigate the impact of air pollution on other CF-related outcomes in young children are recommended. Given the morbidity associated with CF chronic respiratory infections and lack of strategies available to patients to prevent them, future studies that can elucidate other risk factors for these infections are needed.

Abbreviations
A. xylosoxidans: *Achromobacter xylosoxidans*; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; CI: confidence interval; FEV_1: forced expiratory volume in one second; HR: hazard ratio; IDW: inverse distance weighted; MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-susceptible *Staphylococcus aureus*; NO_2: nitrogen dioxide; OR: odds ratio; *P. aeruginosa*: *Pseudomonas aeruginosa*; PM_{10}: particulate matter ≤10 μm in aerodynamic diameter; $PM_{2.5}$: particulate matter ≤2.5 μm in aerodynamic diameter; *S. maltophilia*: *Stenotrophomonas maltophilia*; SD: standard deviation

Availability of data and materials
The data that support the findings of this study are available from the Cystic Fibrosis Foundation but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

Authors' contributions
All of the authors had access to the full dataset (including the statistical reports and tables) and take responsibility for the integrity of the data and the accuracy of the data analysis. KJP, AJD, JW, JDM, MR conceived and designed the study. KJP and MR collected the data and KJP analyzed the data. KJP, AJD, JW, JDM, MR interpreted the data. KJP and MR wrote the first draft of the paper. KJP, AJD, JW, JDM, MR reviewed and approved the final report.

Ethics approval and consent to participate
This study was approved by the institutional review board at the University of Washington and the Cystic Fibrosis Foundation Registry Committee. Informed consent is provided to participate in the registry by participants and/or their legal guardians.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

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References
1. Long FR, Williams RS, Adler BH, Castile RG. Comparison of quiet breathing and controlled ventilation in the high-resolution CT assessment of airway disease in infants with cystic fibrosis. Pediatr Radiol. 2005;35:1075–80.
2. Long FR, Williams RS, Castile RG. Structural airway abnormalities in infants and young children with cystic fibrosis. J Pediatr. 2004;144:154–61.
3. Martinez TM, Llapur CJ, Williams TH, Coates C, Gunderman R, Cohen MD, et al. High-resolution computed tomography imaging of airway disease in infants with cystic fibrosis. Am J Respir Crit Care Med. 2005;172:1133–8.
4. Hoo AF, Thia LP, Nguyen TT, Bush A, Chudleigh J, Lum S, et al. Lung function is abnormal in 3-month-old infants with cystic fibrosis diagnosed by newborn screening. Thorax. 2012;67:874–81.
5. Mott LS, Park J, Murray CP, Gangell CL, de Klerk NH, Robinson PJ, et al. Progression of early structural lung disease in young children with cystic fibrosis assessed using CT. Thorax. 2012;67:509–16.
6. Goeminne PC, Kicinski M, Vermeulen F, Fierens F, De Boeck K, Nemery B, et al. Impact of air pollution on cystic fibrosis pulmonary exacerbations: a case-crossover analysis. Chest. 2013;143:946–54.
7. Farhat SC, Almeida MB, Silva-Filho LV, Farhat J, Rodrigues JC, Braga AL. Ozone is associated with an increased risk of respiratory exacerbations in patients with cystic fibrosis. Chest. 2013;144:1186–92.
8. Goss CH, Newsom SA, Schildcrout JS, Sheppard L, Kaufman JD. Effect of ambient air pollution on pulmonary exacerbations and lung function in cystic fibrosis. Am J Respir Crit Care Med. 2004;169:816–21.
9. Collaco JM, McGready J, Green DM, Naughton KM, Watson CP, Shields T, et al. Effect of temperature on cystic fibrosis lung disease and infections: a replicated cohort study. PLoS One. 2011;6:e27784.
10. Psoter KJ, De Roos AJ, Mayer JD, Kaufman JD, Wakefield J, Rosenfeld M. Fine particulate matter exposure and initial Pseudomonas Aeruginosa acquisition in cystic fibrosis. Ann Am Thorac Soc. 2015;12:385–91.
11. Knapp EA, Fink AK, Goss CH, Sewall A, Ostrenga J, Dowd C, et al. The Cystic Fibrosis Foundation patient registry. Design and methods of a National Observational Disease Registry. Ann Am Thorac Soc. 2016;13:1173–9.
12. Cystic Fibrosis Foundation, Borowitz D, Robinson KA, Rosenfeld M, Davis SD, Sabadosa KA, et al. Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. J Pediatr. 2009;155:S73–93.
13. Psoter KJ, Rosenfeld M, De Roos AJ, Mayer JD, Wakefield J. Differential geographical risk of initial Pseudomonas Aeruginosa acquisition in young US children with cystic fibrosis. Am J Epidemiol. 2014;179:1503–13.
14. WWAeMI Rural Health Research Center. http://depts.washington.edu/uwruca/ruca-data.php. Accessed 14 May 2017.
15. R Development Core Team. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2017. p. 16.
16. Goss CH, Muhlebach MS. Review: Staphylococcus Aureus and MRSA in cystic fibrosis. J Cyst Fibros. 2011;10:298–306.
17. Dasenbrook EC, Checkley W, Merlo CA, Konstan MW, Lechtzin N, Boyle MP. Association between respiratory tract methicillin-resistant Staphylococcus Aureus and survival in cystic fibrosis. JAMA. 2010;303:2386–92.
18. Dasenbrook EC, Merlo CA, Diener-West M, Lechtzin N, Boyle MP. Persistent methicillin-resistant Staphylococcus Aureus and rate of FEV1 decline in cystic fibrosis. Am J Respir Crit Care Med. 2008;178:814–21.

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19. Cystic Fibrosis Foundation. Patient registry 2008 annual report. Bethesda: Cystic Fibrosis Foundation; 2009.
20. Muhlebach MS, Heltshe SL, Popowitch EB, Miller MB, Thompson V, Kloster M, et al. Multicenter observational study on factors and outcomes associated with various Methicillin-resistant Staphylococcus Aureus types in children with cystic fibrosis. Ann Am Thorac Soc. 2015;12:864–71.
21. Collaco JM, Raraigh KS, Appel LJ, Cutting GR. Respiratory pathogens mediate the association between lung function and temperature in cystic fibrosis. J Cyst Fibros. 2016;15:794–801.
22. Kamdar O, Le W, Zhang J, Ghio AJ, Rosen GD, Upadhyay D. Air pollution induces enhanced mitochondrial oxidative stress in cystic fibrosis airway epithelium. FEBS Lett. 2008;582:3601–6.
23. Geiser M, Stoeger T, Casaulta M, Chen SZ, Semmler-Behnke M, Bolle I, et al. Biokinetics of nanoparticles and susceptibility to particulate exposure in a murine model of cystic fibrosis. Particle and Fibre Toxicology. 2014;11:19.
24. Qu F, Qin XQ, Cui YR, Xiang Y, Tan YR, Liu HJ, et al. Ozone stress down-regulates the expression of cystic fibrosis transmembrane conductance regulator in human bronchial epithelial cells. Chem Biol Interact. 2009;179:219–26.
25. Jassal MS, Yu AM, Bhatia R, Keens TG, Davidson Ward SL. Effect of residential proximity to major roadways on cystic fibrosis exacerbations. Int J Environ Health Res. 2013;23:119–31.
26. Dadvand P, Parker J, Bell ML, Bonzini M, Brauer M, Darrow LA, et al. Maternal exposure to particulate air pollution and term birth weight: a multi-country evaluation of effect and heterogeneity. Environ Health Perspect. 2013;121:267–373.
27. Stieb DM, Chen L, Eshoul M, Judek S. Ambient air pollution, birth weight and preterm birth: a systematic review and meta-analysis. Environ Res. 2012;117:100–11.
28. Kwinta P, Pietrzyk JJ. Preterm birth and respiratory disease in later life. Expert Rev Respir Med. 2010;4:593–604.
29. Pino P, Walter T, Oyarzun M, Villegas R, Romieu I. Fine particulate matter and wheezing illnesses in the first year of life. Epidemiology. 2004;15:702–8.
30. Karr CJ, Demers PA, Koehoorn MW, Lencar CC, Tamburic L, Brauer M. Influence of ambient air pollutant sources on clinical encounters for infant bronchiolitis. Am J Respir Crit Care Med. 2009;180:995–1001. 17
31. Collaco JM, Blackman SM, McGready J, Naughton KM, Cutting GR. Quantification of the relative contribution of environmental and genetic factors to variation in cystic fibrosis lung function. J Pediatr. 2010;157:802–7.
32. Green DM, Collaco JM, McDougal KE, Naughton KM, Blackman SM, Cutting GR. Heritability of respiratory infection with Pseudomonas Aeruginosa in cystic fibrosis. J Pediatr. 2012;161:290–5.
33. Ramsay KA, Stockwell RE, Bell SC, Kidd TJ. Infection in cystic fibrosis: impact of the environment and climate. Ex Rev Resp Med. 2016;10:505–19.
34. Psoter KJ, De Roos AJ, Wakefield J, Mayer J, Rosenfeld M. Season is associated with Pseudomonas Aeruginosa acquisition in young children with cystic fibrosis. Clin Microbiol Infect. 2013;19:E483–9.
35. Rosenfeld M, Emerson J, Accurso F, Armstrong D, Castile R, Grimwood K, et al. Diagnostic accuracy of oropharyngeal cultures in infants and young children with cystic fibrosis. Pediatr Pulmonol. 1999;28:321–8.