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Built environment factors predictive of early rapid lung function decline in cystic fibrosis

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Abstract

Background: The extent to which environmental exposures and community characteristics of the built environment collectively predict rapid lung function decline, during adolescence and early adulthood in cystic fibrosis (CF), has not been examined.

Objective: To identify built environment characteristics predictive of rapid CF lung function decline.

Methods: We performed a retrospective, single-center, longitudinal cohort study ($n = 173$ individuals with CF aged 6–20 years, 2012–2017). We used a stochastic model to predict lung function, measured as forced expiratory volume in 1 s (FEV_1) of % predicted. Traditional demographic/clinical characteristics were evaluated as predictors. Built environmental predictors included exposure to elemental carbon attributable to traffic sources (ECAT), neighborhood material deprivation (poverty, education, housing, and healthcare access), greenspace near the home, and residential drivetime to the CF center.

Measurements and Main Results: The final model, which included ECAT, material deprivation index, and greenspace, alongside traditional demographic/clinical predictors, significantly improved fit and prediction, compared with only demographic/clinical predictors (Likelihood Ratio Test statistic: 26.78, $p < 0.0001$; the difference in Akaike Information Criterion: 15). An increase of 0.1 μg/m^3 of ECAT was associated with 0.104% predicted/yr (95% confidence interval: 0.024, 0.183) more rapid decline. Although not statistically significant, material deprivation was similarly associated (0.1-unit increase corresponded to additional decline of 0.103%

Abbreviations: BMI, body mass index; CF, cystic fibrosis; CI, confidence interval; DAG, directed acyclic graph; FEV_1pp, forced expiratory volume in 1 s of % predicted; MAE, mean absolute error; MAPE, mean absolute percentage error; RMSE, root mean-square error; SD, standard deviation; SES, socioeconomic status.

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predicted/year [−0.113, 0.319]). High-risk regional areas of rapid decline and age-related heterogeneity were identified from prediction mapping.

Conclusion: Traffic-related air pollution exposure is an important predictor of rapid pulmonary decline that, coupled with community-level material deprivation and routinely collected demographic/clinical characteristics, enhance CF prognostication and enable personalized environmental health interventions.

KEYWORDS
community material deprivation, geomarker, greenspace, medical monitoring, traffic-related air pollution

1 | INTRODUCTION

Cystic fibrosis (CF) is a life-limiting autosomal disease marked by progressive loss of lung function wherein nongenetic influences reportedly explain 50% of the variation in lung function in adolescents and young adults.[1] Rapid decline in lung function is a sustained drop relative to patient- and/or center-level norms that typically manifests from 12 to 21 years of age.[2,3] Early detection has enabled timely and effective treatment in pediatric CF clinical settings, which has corresponded to improved lung function.[4,5] A growing body of evidence has characterized how environmental exposures and community characteristics of the built environment associated with rapid lung function decline. For example, lung function, measured as forced expiratory volume in 1 s of % predicted (FEV_1pp), was lower by an average of 4.1% predicted (95% confidence interval [CI]: 3.2–5.0) when comparing children with CF living in the most versus least deprived areas in the UK.[6] Although there are few small area deprivation studies of people living with CF, individual-level characteristics like Medicaid insurance status are more frequently studied. Seminal work by Schechter et al.[7] showed that average FEV_1pp was 9.1% predicted (95% CI: 6.9–11.2) lower in Medicaid versus non-Medicaid groups. However, there is limited research on how neighborhood deprivation, in combination with individual level proxies of socioeconomic status like Medicaid insurance, relate to FEV_1pp decline. In a different aspect of environmental exposure research, Goss and colleagues linked air pollution values to the US CF Registry and showed that increased exposure to ozone and fine particulate matter (e.g., inhalable particles with aerodynamic diameters ≤ 2.5 μm, denoted $PM_{2.5}$) associated with declining lung function and more frequent pulmonary exacerbations.[8] A study in British Columbia of adults with CF found that patients who lived farthest away from their CF care center (drivetime >360 min) were at increased risk of experiencing rapid lung function decline, compared to those with the shortest commute (<45 min); respective rates of decline were 3.1% predicted/year (1.1, 5.1) versus 0.9 (0.1, 1.6).[9]

Traffic-related air pollution (TRAP), a complex mixture of particles, gasses, and other compounds emitted from traffic sources, have been consistently associated with childhood wheezing, asthma exacerbation, and the onset of asthma.[10–12] Land use characteristics, including greenspace, may also play a role in respiratory health via the mediation of other environmental exposures or directly through increased allergen exposure.[13] Greenspace can be estimated using satellite-based images and can span from forests to shrublands or grasslands to lawn grasses. Neighborhood characteristics and resources are also important determinants of health and have been captured through a transformation of related community-level measures into a neighborhood material deprivation index.[14] Despite their known roles in other respiratory diseases, these "geomarkers" have received limited attention in CF; consequently, little is known about their collective prognostic value in assessing lung function decline among CF patients.

For these reasons, we conducted a longitudinal study of a Midwestern US cohort to determine the manner and extent to which place-based characteristics of the built environment are associated with or predictive of rapid lung function decline in children and adolescents with CF. We hypothesized that including built environmental risk factors would yield more accurate lung function prediction and improved fit to the data, compared to relying only on demographic/clinical surveillance characteristics. Preliminary results were presented at the North American CF Conference.[15]

2 | MATERIALS AND METHODS

2.1 | Cohort

We performed a retrospective longitudinal cohort study of individuals with a documented CF diagnosis who received care at the Cincinnati Children's Hospital Cystic Fibrosis Center in Cincinnati, OH, USA (2012–2017). Clinical encounter data were acquired on individuals ≥6 years of age, to obtain valid lung function measurements from pulmonary function tests; maximum follow-up age was 20 years.

2.2 | Outcome and predictors

The primary outcome was FEV_1pp obtained under American Thoracic Society guidelines and using standard reference equations.[16,17]

Previously identified risk factors of rapid FEV_1pp decline in CF[18] were considered potential predictors, including time-invariant variables: sex, genotype (F508del homozygous, heterozygous, or neither/unknown), and pancreatic insufficiency (defined as ever taking pancreatic enzymes), and time-varying variables: age at clinic visit (years), Medicaid insurance use, diagnosis of CF-related diabetes mellitus, culturing positive for *Pseudomonas aeruginosa* (Pa) infection and Methicillin-resistant *Staphylococcus aureus* (MRSA) infection.

Residential addresses observed at each encounter date were geocoded using DeGAUSS[19] and used to derive four key geomarkers that measure characteristics of the built environment, which were considered as predictors. Geomarkers included a surrogate of TRAP exposure known as elemental carbon attributable to traffic sources (ECAT), neighborhood deprivation index (assesses extent of poverty, vacant housing, assisted income living, educational level, median income, and health insurance coverage for a given neighborhood), percentage of greenspace near the home, and residential drivetime to the CF center. ECAT is a TRAP marker that was estimated for the 3 months before each clinical encounter using a previously validated spatiotemporal land-use model.[12] Greenspace was defined as the percentage of 30 m × 30 m pixels within 400 m of the residential address classified as green by the National Landcover Database. Access to CF care was measured using drivetime from patient residence to the CF center. Drivetime was calculated using drivetime isochrones from OpenRoute Service and defined ordinally with 11 categories for time increments of 6 min, with the last category representing drivetimes >60 min. We included drivetime as a continuous variable in the model, since an ordinal variable with five or more categories can be efficiently included as a continuous covariate in regression models.[20] Community material deprivation was derived at the census-tract level using an index comprised of American Community Survey measures related to poverty, education, housing, and access to healthcare.[14]

2.3 | Sample size and missing data

The available analysis cohort size for prediction model development was evaluated under four criteria established for prediction modeling with a continuous outcome under linear regression[21] (Section A, Supporting Information). Observed FEV_1pp after lung transplant was censored. An available case analysis strategy was undertaken, assuming that data followed the missing at random assumption.[22]

2.4 | Statistical analysis methods

Descriptive analyses were performed to evaluate data quality and ranges. Scatterplot smoothing and univariable regressions were used to examine the nature of individual relationships between the outcome and each predictor. A conceptual model of relationships between demographic, clinical, and built environment factors in relation to outcome was adapted from an established directed acyclic graph (DAG) for asthma research (Figure 1).[23] The TRIPOD reporting checklist for prediction model development studies was followed.[24] All analyses were implemented using R version 4.1.0 (R Foundation for Statistical Computing). Detailed statistical considerations, including model equations, software implementation, and additional tables and figures, are provided in Supporting Information.

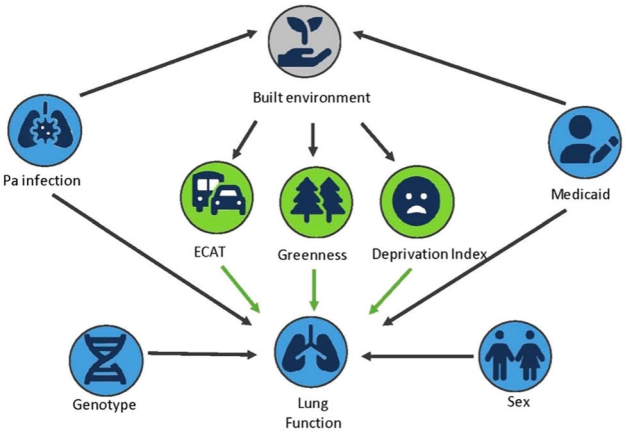

FIGURE 1 Conceptual model of relationships between demographic, clinical, and built environment factors in relation to outcome. ECAT, elemental carbon attributable to traffic exposure; Pa, *Pseudomonas aeruginosa*. [Color figure can be viewed at wileyonlinelibrary.com]

We utilized an established linear mixed effects model framework that incorporated more flexible covariance structures to model FEV_1pp decline.[25] Age at clinical encounter (in years) served as the time variable. Each model included fixed effects to estimate the association between a selected covariate and outcome, including interaction effects (covariate × time) to estimate association between a given covariate and rate of change in the outcome, a random effect to capture between-patient variation in lung function, a specialized covariance function to account for longitudinal correlation between lung function measurements taken on the same individual over time, and a residual error term.

We examined fit and predictive value individually for each covariate (Table S1). To provide context for environmental covariates, higher concentrations of ECAT are expected to result in worse health, higher levels of deprivation correspond to higher deprivation and worse health, and higher levels of greenspace correspond to better health. To obtain a final reduced model, covariates (demographic, clinical, and environmental) were jointly selected using an adaptive Bayesian lasso approach built under the aforementioned longitudinal lung function decline model.[26] Candidate covariates were further evaluated using change in Akaike information criteria (delta-AIC) and the likelihood ratio test (LRT) to check contribution to model fit to assess improvement in prediction performance. Secondary selection methods were Bayesian lasso, ridge, and elastic-net (results presented as supplemental material). Prediction performance metrics included root-mean-square error (RMSE), mean absolute error (MAE), and mean absolute percentage error (MAPE) from overall and five-fold cross-validation replicated 20 times (lower values indicate better accuracy to predict lung function).

Once we finalized the model of FEV_1pp decline, we predicted the occurrence of rapid decline using predictive probabilities based on the model, which accounts for measurement error in FEV_1pp data.[27] Specifically, we estimated the predictive probability, for a given individual at a given time, of their FEV_1pp slope falling below −1.5% predicted/year (see Supporting Information for equations). This threshold was selected based on clinical judgment, graphical inspection in previous work,[28] and has been reported in prior research.[29] A higher probability implies a greater risk of rapid decline. We examined these real-time predictive probabilities of rapid decline over time for each patient.

2.5 | Prediction maps

Interactive and static maps were developed to investigate relative and combined contributions of geomarkers in predicting rapid lung function decline in CF across the geographic region of the study cohort. Each HTML file in the supplement is designed for a user to search a specific place of interest along with additional lookup functions. Additional static maps are provided in Figures S2 and S3.

2.6 | Ethical statement

This study was approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board (Protocol ID: 2018-5936).

3 | RESULTS

3.1 | Cohort and built environment characteristics

The analysis cohort consisted of 173 CF patients (52.6% male) aged 6–20 years old with more than half who were F508del homozygotes (characteristics summarized in Table 1). There was

TABLE 1 Clinical and built environment characteristics*.

Clinical		Built environment	
F508del mutation		ECAT, μg/m^3 (in prior 3 months before PFT)	
Homozygous	98 (56.65%)	At baseline	0.391 (0.143)
Heterozygous	67 (38.73%)	During follow-up	0.359 (0.128)
None	8 (4.62%)	Deprivation index	
Male gender	82 (47.40%)	At baseline	0.307 (0.088)
Age at baseline, years	10.60 (4.25)	During follow-up	0.308 (0.096)
FEV_1pp at baseline	93.55 (19.43)	Greenspace, %	
BMI percentile at baseline	54.91 (25.03)	At baseline	86.53 (14.62)
Medicaid insurance use	70 (40.46%)	During follow-up	88.59 (13.01)
Microbiology		Drivetime to center (min)	
Pa		At baseline	
At baseline	26 (15.03%)	0–6	2 (1.15%)
Ever during follow-up	112 (64.74%)	7–12	4 (2.31%)
MRSA		13–18	14 (8.09%)
At baseline	30 (17.34%)	19–24	31 (17.91%)
Ever during follow-up	78 (45.08%)	25–30	36 (20.80%)
CF-related diabetes mellitus	34 (19.65%)	31–36	31 (17.91%)
Duration of follow-up, years	4.48 (2.95)	37–42	15 (8.67%)
Number of PFTs	25.69 (22.9)	43–48	23 (13.29%)
		49–54	9 (5.20%)
		55–60	5 (2.89%)
		> 60	3 (1.73%)

Abbreviations: CF, cystic fibrosis; ECAT, elemental carbon attributable to traffic exposure; FEV_1pp, forced expiratory volume in 1 s of % predicted; MRSA, methicillin-resistant *Staphylococcus aureus*; Pa, *Pseudomonas aeruginosa*; PFT, pulmonary function test; SD, standard deviation.

*Expressed as mean (SD) for continuous variables and *n* (%) for categorical variables.

an available sample size of 248 individuals over follow-up, but we restricted primary analysis to 173 patients due to missingness in select variables (Figure S4). The majority of patients in the analysis cohort went on to develop Pa over follow-up and nearly half were diagnosed with MRSA. ECAT exposure and deprivation index at baseline averaged 0.307 μg/m^3 and 0.307, respectively, and were similar during follow-up, while extent of greenspace was high overall (86.53%). Most patients (57%) had drivetime from 19 to 36 min. Patients contributed 4445 lung function measurements (FEV_1) over the follow-up timeframe. The median number of observations per patient was 20 and ranged from 1 to 145. Patients with missing data on one or more predictors (demographic, clinical, or built environment) were excluded from the analysis cohort. Data from those patients who resided in locations without available ECAT exposure estimates ($n = 68$) or did not have an address that could be geocoded ($n = 5$) were excluded. Two patients were excluded due to missing BMI data.

3.2 | Prediction modeling results

Deprivation index, drivetime to health center, extent of greenspace, and ECAT were associated with FEV_1pp in individual regressions (Table S1). After adjusting for demographic/clinical characteristics including sex, Medicaid insurance use, CF-related diabetes, BMI, infections with Pa and MRSA, and performing covariate selection, we found that including deprivation index, greenspace, and ECAT exposures as a main effect and their interaction with age yielded a significantly better fit and improved prediction of FEV_1, compared with a model with only clinical/demographic characteristics (Table 2). Based on the final model from lasso selection, exposure to ECAT was associated with a more rapid decline; specifically, an increase of 0.1 μg/m^3 of ECAT was associated with a 0.104% predicted/yr (95% CI: 0.024, 0.183) more rapid decline when adjusted for other environmental exposures and routinely collected demographic/clinical covariates. Similarly, a 0.1-unit increase in the socioeconomic deprivation index associated with 0.103% predicted/yr (95% CI: −0.113, 0.319) more rapid decline, however this association was not statistically significant. Greenspace was retained as a covariate in the final model, but its association with rapid FEV_1pp decline was not statistically significant. Associations between demographic/clinical characteristics and rate of decline, as well as SD estimates for the variance components (between- and within-patient and residual error), were similar between the final model and the model excluding geomarkers, except for the estimated intercept of lung function and effect of age. However, 95% CIs for the corresponding estimates overlapped.

We randomly evaluated multiple subjects' predicted lung function trajectories with 95% CIs and estimated real-time risk of rapid decline of lung function for the models with and without geomarkers, and we present three subjects as cases (Figure 2). The graphs on the left panel show the observed (black dots) and the estimated lung function trajectories (blue dashed line stands for the model without geomarkers; red-solid line stands for the model with geomarkers) with their 95% CIs from the proposed prediction model. The graphs on the right panel present the predicted real-time risk of rapid decline for each individual over time. The predicted trajectories from the final model and the model without geomarkers appeared similar, however, the model with geomarkers had smaller RMSE, MAE, and MAPE, compared to the model without geomarkers (Table S2). Although the difference in the predicted trajectories from these two models have similar patterns, the difference in the predicted real-time risk is higher for two of the three cases shown. Observed ECAT exposure, deprivation index, and greenspace for these subjects are plotted over age (Figure S1).

3.3 | Prediction mapping

Using the final model, we mapped the marginal and total impacts of selected geomarkers on rate of lung function decline (% predicted/year) for the city and surrounding suburban areas (Figure 3). As the shaded area changes from green to red, the rate of decline increases. The gray areas on the maps are census tracts with unavailable community material deprivation index values due to suppressed American Community Survey data in census tracts with small populations. Figure 3 illustrates the spatial distribution of the distinct contributions, moving clockwise from the upper left, of ECAT (Figure 3A), deprivation index (Figure 3B), and greenspace (Figure 3C) on the rate of change in CF lung function. Figure 3D illustrates the combined additive impact, by highlighting geographic regions in the urban core of Cincinnati, OH, that are close to truck traffic and are highly deprived. These maps not only reinforce our findings that patients living in areas with high ECAT and high deprivation experience a greater decline in lung function, but importantly, highlight that patients experiencing high ECAT are often living in highly deprived communities. The bottom right panel of Figure 3 illustrates this additive impact, by highlighting geographic regions in the urban core of Cincinnati, OH that are close to truck traffic and are highly deprived. There was a variable association between individual and cumulative geomarkers and overall level of lung function (% predicted) (Figure S2)

Total contributions of ECAT, socioeconomic deprivation and greenspace on rate of FEV_1pp decline were mapped specifically for Hamilton County (OH) in Figure 4, to add granularity to the primary results. For this particular county, the largest estimated impacts were observed in three areas that included pink-shaded regions, corresponding to elevated ECAT and deprivation index values and lower greenness: i) the majority of the riverfront, which encompasses a higher density of truck/bus routes and in lower elevation, compared to non-riverfront areas; ii) concentrations around the CF center location (blue dot) and northward; iii) a

TABLE 2 Model parameter estimates, fit, and performance, according to clinical and built environmental predictors*.

	Final model	Excluding geomarkers
Parameter		
Intercept	83.16 (49.68, 116.64)*	99.67 (77.77, 121.57)*
Female	11.82 (3.12, 20.52)*	11.46 (2.78, 20.14)*
Heterozygous	6.72 (−15.92, 29.36)	6.53 (−16.05, 29.10)
Homozygous	4.78 (−17.52, 27.09)	4.64 (−17.51, 26.79)
Pa	0.58 (−2.70, 3.86)	0.47 (−2.82, 3.76)
Medicaid	−9.47 (−18.62, -0.31)*	−11.08 (−19.97, −2.19)*
ECAT	13.23 (2.02, 24.45)*	
Deprivation index	−2.38 (−32.84, 28.09)	
Greenspace	0.13 (−0.06, 0.33)	
Age	1.30 (−1.90, 4.49)	−0.69 (−3.27, 1.90)
Female × age	−1.07 (−2.14, −0.01)*	−1.05 (−2.12, 0.02)
Heterozygous × age	0.13 (−2.52, 2.78)	0.17 (−2.48, 2.81)
Homozygous × age	0.01 (−2.61, 2.62)	0.06 (−2.54, 2.67)
Pa × age	−0.16 (−0.38, 0.06)	−0.15 (−0.37, 0.07)
Medicaid × age	0.49 (−0.62, 1.61)	0.59 (−0.51, 1.70)
ECAT × age	−1.04 (−1.83, -0.24)*	
Deprivation index × age	−1.03 (−3.19, 1.13)	
Greenspace × age	−0.01 (−0.03, 0.01)	
SD		
Between patient	10.94 (7.65, 13.44)	10.88 (7.58, 13.38)
Within patient	0.94 (0.83, 1.05)	0.94 (0.83, 1.05)
Residual	7.95 (7.77, 8.12)	7.97 (7.80, 8.14)
Fit		
-2LL	32211.03	32237.8
BIC	32362.22	32338.6
AIC	32253.03	32267.8
LRT	Chi-squared, *df*, *p*-value	26.8, 6, 0.00016
Predictive performance		
RMSE, % predicted	11.10 (8.87, 13.33)	11.30 (9.07, 13.53)
MAPE, %	10.80 (7.68, 13.92)	11.50 (8.29, 14.71)
MAE, % predicted	8.65 (7.02, 10.28)	8.85 (6.94, 10.76)

Abbreviations: −2LL, negative two times the log-likelihood for the model; AIC, Akaike Information Criterion (smaller is better); BIC, Bayesian Information Criterion (smaller is better); df, degrees of freedom; LRT, Likelihood Ratio Test (comparing a selected model with and without built environment geomarkers); MAE, mean absolute error (smaller is better); MAPE, mean absolute percentage error (smaller is better); RMSE, root-mean-square error (smaller is better); SD, standard deviation (square root) of variance component estimate from model.

*Parameter estimates and metrics for predictive accuracy reported with 95% CI. The CIs are useful to quantify the uncertainty around the estimated mean error in our prediction. 95% CI is a range of values that one can be 95% confident contains the true mean error in our prediction for the corresponding error type. Symbol "×" refers to interaction effects, representing association between a given covariate and rate of change in lung function decline. Geomarker terms include ECAT, deprivation index, and greenspace.

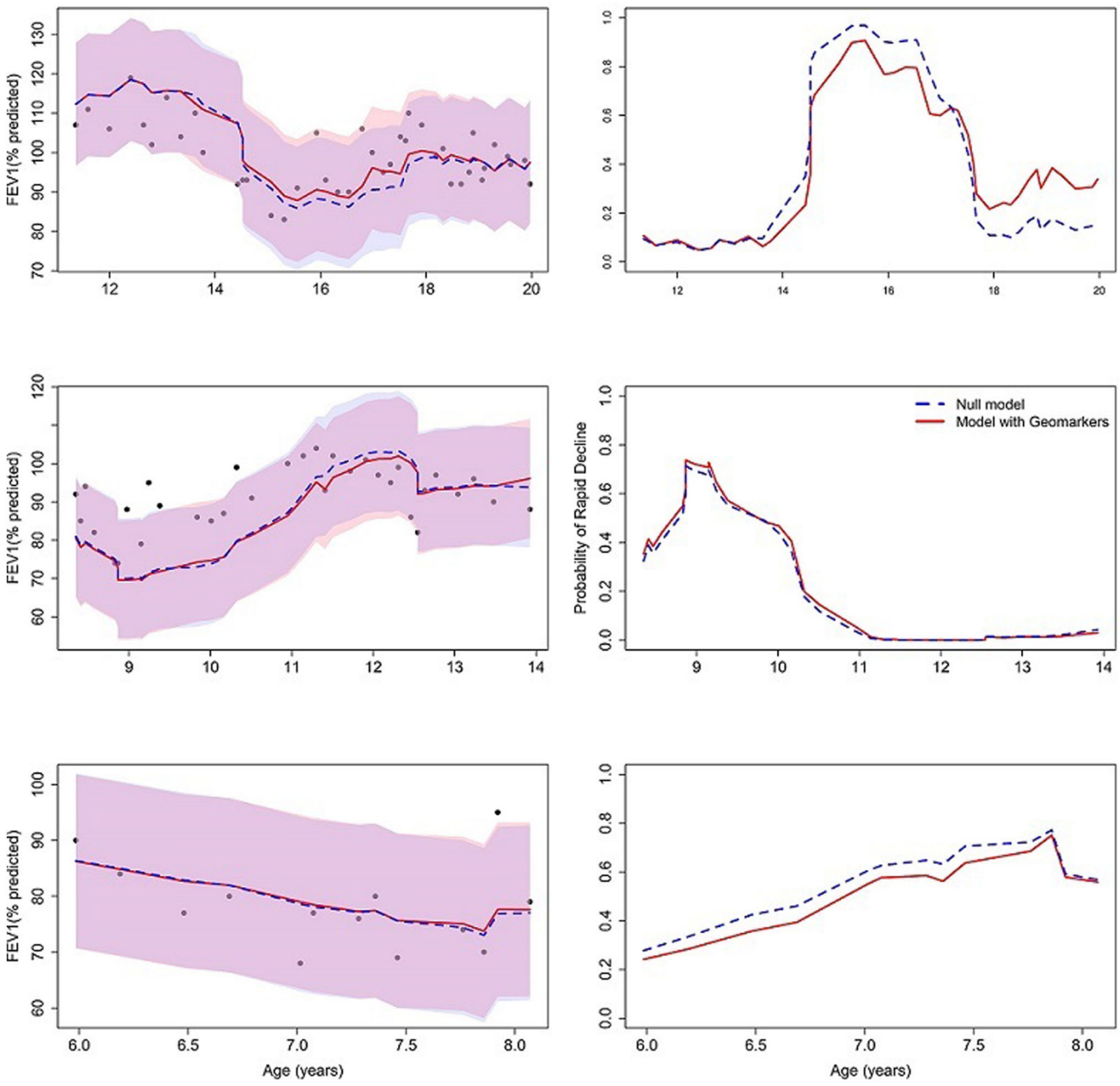

FIGURE 2 Left panel: Observed FEV1pp (black dots) against age are shown with dynamic predictions from both the null model (model without geomarkers, blue dashed line) and model with geomarkers (red solid line) and 95% CIs (blue and red bands for null model and model with geomarkers, respectively); Right panel: real-time risk for rapid lung function decline (blue dashed line is the probability of rapid decline with null model; red solid line is the probability of rapid decline for the model with geomarkers). Each row corresponds to an individual patient. The first patient (top row) was a male F508del homozygote who was first diagnosed with Pa infection at age 13 and used Medicaid insurance. Over the follow-up period, his median (range) ECAT exposure, deprivation index, and greenspace percentage were 0.279 (0.176–0.429) $\mu g/m^3$, 0.418 (0.279–0.795), and 92.9% (60.8%–100%), respectively. His median ECAT exposure was lower than the study population median, while his median deprivation index was above the study population median and his median percentage of greenspace was similar to the study population median. His risk of rapid decline peaked around 16 years old. The middle row shows another patient who was a male F508del heterozygote, never diagnosed with Pa and used Medicaid insurance. His median (range) ECAT exposure, deprivation index, and greenspace percentage were 0.311 (0.232–0.528) $\mu g/m^3$, 0.393 (0.187, 0.408), and 94.5% (81.4%–95.5%), respectively. His median ECAT exposure was slightly lower than the study population median, while his median deprivation index and greenspace percentage exceeded the study population median. The patient was at high risk early in follow-up, but the risk diminished into adolescence. The last row includes a patient who was a male F508del heterozygote, never diagnosed with Pa, and had Medicaid. His median (range) ECAT exposure, deprivation index, and greenspace percentage are 0.267 (0.176–0.386) $\mu g/m^3$, 0.462 (0.462–0.462), and 94.5% (81.4%–95.5%), respectively. His median ECAT exposure and greenspace percentage were lower than the study population median, while his median deprivation index was well above the study population median. He experienced steady decline, and, in turn, the real-time risk of rapid decline elevated over the 2 years of follow-up but downturned towards the last observation. [Color figure can be viewed at wileyonlinelibrary.com]

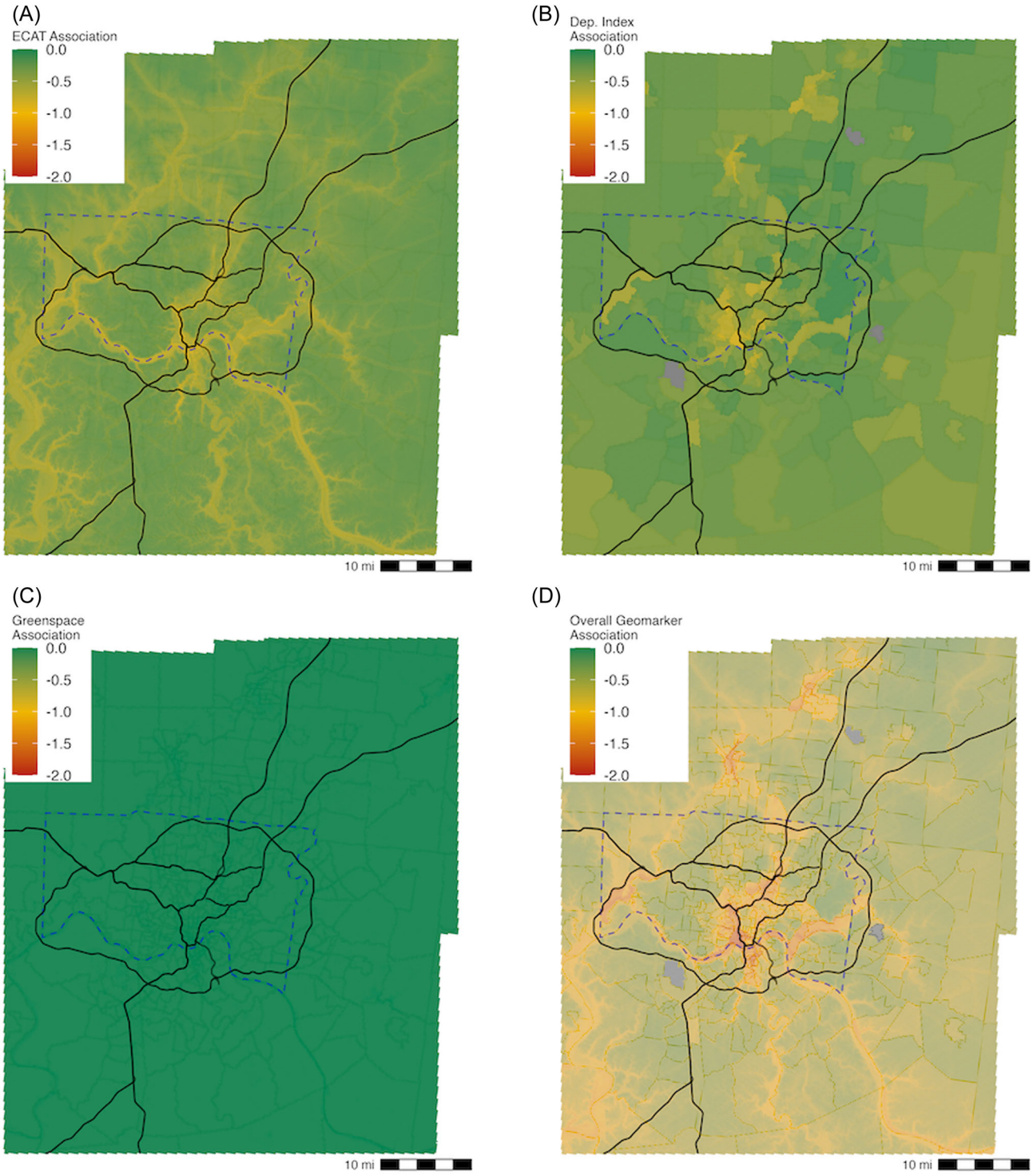

FIGURE 3 Distinct (individual relative) contributions of ECAT, deprivation index and greenspace (A–C, respectively) and the combined contribution of all three geomarkers (D) on rate of change on CF lung function (FEV1pp). As the color changes from green to red, the rate of decline increases in severity. Area within dashed lines represents Hamilton County, while the larger area shows the entire region. ECAT, elemental carbon attributable to traffic sources; FEV1pp, forced expiratory volume in 1 s of % predicted. [Color figure can be viewed at wileyonlinelibrary.com]

crescent-shaped area in the southeastern portion. The interactive version of this map, which is provided as supplemental material, presents each geomarker's marginal impact on rate of FEV_1pp decline.

3.4 | Sensitivity analyses

Patients excluded from the primary analysis cohort due to missing covariates, particularly ECAT, had longer drivetimes, increased

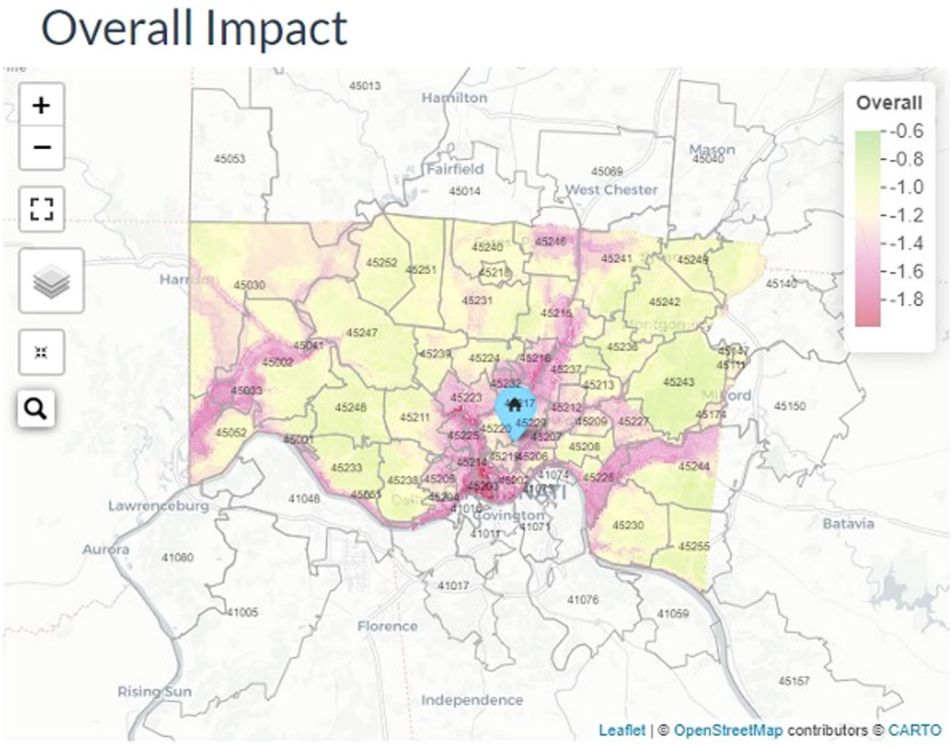

FIGURE 4 Hamilton county-specific impact of the three predictive geomarkers (ECAT, socioeconomic deprivation index, and greenspace) on rate of change in CF lung function (FEV1pp). As the color changes from green to red, the rate of decline increases in severity. Geocoding was used for geomarker values. Zip codes are provided here for reference. The smaller area shown here is depicted within dashed lines of the entire region shown in Figure 3. ECAT, elemental carbon attributable to traffic sources; FEV1pp, forced expiratory volume in 1 s of % predicted. [Color figure can be viewed at wileyonlinelibrary.com]

greenspace, and higher rates of Medicaid insurance use; other observed characteristics were similar (Table S3). These differences were expected because ECAT exposure estimates were only available for areas around the urban core of Cincinnati; however, other geomarkers were available in the broader areas. When fitting models that included this cohort with the data from individuals used for primary analysis ($n = 248$), the intercept estimate of FEV_1pp was higher, but 95% CIs overlapped (Table S4). There was a higher magnitude of association between Pa and rate of FEV_1pp decline. Including socioeconomic deprivation index and greenspace yielded improved model fit and predictive performance (LRT: 14.4, $p = 0.006$).

We implemented the final prediction model without accounting for Medicaid insurance use and observed its effect on impact of deprivation index. Excluding Medicaid insurance use from the model increased the main effect of the deprivation index in magnitude (from −2.37 to −9.26) and decreased the interaction effect of deprivation index by age in magnitude (from −1.03 to −0.597). However, both main and interaction effects of deprivation index remained insignificant. Excluding Medicaid insurance use from our model did not alter the effects of ECAT and greenspace.

In another sensitivity analysis of the final model, we substituted the time-varying measurements of Pa infection with an indicator of chronic Pa, which was defined as a history of at least four cultures positive for Pa.[30] Associations between geomarkers and rate of lung function decline did not substantively change, compared to the final model. The main effect of chronic Pa was larger (and statistically significant), compared to that of time-varying Pa (which was statistically insignificant).

4 | DISCUSSION

Environmental exposures and community characteristics, including air pollution and community material deprivation, are powerful predictors of many diseases. We examined these factors in the context of rapid lung function decline among people living with CF and their capacity as novel targets in personalized CF clinical management (e.g., secondary environmental health interventions) during late adolescence and early adulthood—when rapid lung function decline most often occurs. In our study, individuals with CF who resided in areas with higher levels of ECAT and increased community material deprivation were at highest risk of rapid FEV_1pp decline, even after accounting for routinely collected demographic/clinical characteristics.

Findings were drawn from rigorous covariate selection processes that we undertook using a recently published approach motivated by evaluating markers of pediatric CF lung disease progression.[26] Including sex, genotype, Medicaid insurance use,

infections with Pa, and environmental exposures measuring deprivation index, ECAT, and greenspace as main effects and their interactions with age yielded a parsimonious model with the highest predictive performance (Table 2). ECAT and deprivation index variables showed similar prediction power and were more predictive than greenspace, but including all three as predictors exhibited the best fit and performance of all models examined. While this final model has explanatory value, not all three of these variables were statistically significant based on their individual coefficients. We selected this final model based primarily on predictive performance, which does not necessarily mean that explanatory value will be optimized.[31] Little is known about ECAT exposure and CF lung function decline, but increased area deprivation index has been associated with lower lung function in children (aged 6-18 years) with CF, which was adjusted for demographic/clinical covariates.[32] Our findings corroborated this association, which was still observed after adjusting for Medicaid insurance use; however, it is worth noting that insurance status does not necessarily coincide with low income, given expansion of Medicaid and choosing to enroll to gain more comprehensive coverage. While Medicaid insurance use has been used in past CF research as a proxy for socioeconomic status,[33] more recent research, including this study, suggests that community material deprivation can provide additional information and predictive value for monitoring lung function decline.

Individualized predictions highlight the changing nature of disease progression within the individual patient (Figure 2) and how these predictions can be made more accurate by integrating built environment characteristics (Table S2). Prediction maps identified areas of greatest potential risk for rapid lung function decline throughout the region studied (Figure 3). More precise, interactive mapping reflected areas of elevated ECAT exposure and socioeconomic deprivation (Figure 4). Taken together, these graphics and interactive applications can facilitate point-of-care identification of periods in which an individual patient may be at high risk of rapid lung function decline. Findings from this study along with the approach and mapping application could serve as a clinical prognostic aid for localized monitoring and development of novel decision support tools to treat rapid CF disease progression.

Exposure to TRAP and the neighborhoods in which patients reside are important predictors of pulmonary decline in CF that may be used to enhance clinician assessments of prognosis and enable personalized environmental health interventions. Researchers and physicians may consider strategies to avoid or reduce air pollution exposures, including in-home air filters to improve or reduce lung function decline in CF patients. A recent meta-analysis of 6 intervention studies (five in adults; one in pediatrics) on particulate matter exposure in asthmatics confirmed past findings that air filters showed no statistically significant association between air filter use and FEV_1.[34] Despite similar challenges with intervention delivery/effective use (e.g., having a sufficient number and maintenance costs of home air filters within a household) the difference in asthma and CF manifestations (including within disease) warrant intervention studies to examine CF-specific efficacy and estimate heterogeneous intervention effects. Combined strategies, which have also been considered in pediatric asthma, include indoor home cleaning and tobacco smoke reduction.[35] Additional investigation should be conducted to understand how pharmacologic interventions and antioxidant supplementation may benefit CF patients at elevated risk for air pollution exposures and/or living in communities with high deprivation.[36,37] Our model identified Pa infection as a predictor of rapid decline alongside these geomarkers. Lung infections like Pa or MRSA may moderate the relationship between socioeconomic deprivation and lung function decline. A previous study shows that neighborhood deprivation doubled the odds of MRSA infection in children with CF.[38] Future studies employing appropriate causal inference methods are needed to evaluate these effects. Furthermore, based on prior association analyses, predictive modeling of these influences would likely differ between regions and be subject to seasonality.[39,40]

Given the recent, broad uptake of highly effective CFTR modulators,[41–43] more sensitive methods are necessary to detect changes in FEV_1pp decline. Our analysis reflects estimated lung function decline during the pre-CFTR modulator period with ranges of 1.3% to 1.7% predicted/year.[18] Assessments of modulator-initiated trends in FEV_1pp have emerged and are ongoing, and it is likely that lung function monitoring will proceed through remote collection as evidenced by the COVID-19 pandemic. The novel modeling application and tools developed in the current study could be adapted for post-CFTR modulation of lung function over time as more data are accrued, and modalities change. Examples include the evolution of the CF care model from quarterly to less frequent clinical visits, which may not significantly impact estimated rate of lung function decline if using mixed-effects models and certain assumptions are met.[44] External cohort studies are needed to ascertain generalizability of these findings and further inform prospective interventional studies of secondary environmental health interventions to mitigate effects of ECAT exposure. Using historical patient demographic data, the individualized predictive data and maps from the current study could be adapted for integration with an electronic health record and downstream clinical informatics applications. These point-of-care technologies require prospective validation and clinician coproduction/testing and system implementation (e.g., electronic health record system integration). Real-time predictive probabilities from this study could be used for these point-of-care risk assessments.

This study has several potential limitations. Geomarkers were limited to residential ECAT, deprivation index, greenspace, and drivetime to the CF center. A wider list of geomarkers may identify additional predictors of lung function decline. Although the CF center studied had provided care for a sample size of 248 individuals over follow-up, we restricted primary analysis to 173 patients due to missingness in ECAT and BMI variables. Our

sensitivity analyses suggested inherent differences according to living in suburban versus urban regions, which may limit generalizability of the primary analysis cohort utilized in this study. The considered ECAT measure was estimated for 3 months before each clinical encounter rather than using daily or weekly estimated values. Temporally scaled ECAT is based on EPA sampling conducted approximately every 6 days. Monthly estimates are sometimes only based on one or two measurements; therefore, a 3-month average was chosen for greater stability. Because ECAT is more spatially variable than temporally variable,[45] predictive gains with incorporating daily or weekly values are unlikely. Furthermore, observing drops in FEV_1pp requires longer follow-up and would not correspond to daily/weekly values. We did not examine other covariance structures to account for between- and within-subject FEV_1pp heterogeneity, but a prior empirical study suggests that the model utilized in the current study outperforms structures previously applied to CF FEV_1pp data.[46] Our study of built environment factors did not include tobacco smoke exposure, given limited reliability and potential underreporting of these data during the study period. Underestimated smoke exposure prevalence has been nationally noted in the CFFPR Annual Report,[47] and efforts are underway to improve reporting and gather objective measures, especially for secondhand smoke exposure.[48]

This study identifies the combined and actual effects of stressors and multiple pollutants inherent in the built environment of children living with CF. The individualized predictive mapping from this study highlights how clinicians can utilize these characteristics of a single CF patient alongside routinely collected demographic and clinical care data to monitor lung function and risk of rapid decline.

AUTHOR CONTRIBUTIONS

Conceptualization: Emrah Gecili, Cole Brokamp, Eleni-Rosalina Andrinopoulou, John P. Clancy, Yizhao Ni, Patrick Ryan, and Rhonda D. Szczesniak. *Data curation*: Emrah Gecili, Cole Brokamp, Erika Rasnick, Anushka Palipana, Teresa Pestian, Andrew Vancil, and Rhonda D. Szczesniak. *Formal analysis*: Emrah Gecili, Weiji Su, Andrew Vancil, Grace Chen Zhou, Ruth H. Keogh, Pedro M. Afonso, and Rhonda D. Szczesniak. *Funding acquisition*: Emrah Gecili and Rhonda D. Szczesniak. *Investigation*: Emrah Gecili, Rhonda D. Szczesniak, Christopher Siracusa, Cole Brokamp, Erika Rasnick, and Patrick Ryan. *Methodology*: Cole Brokamp, Erika Rasnick, Andrew Vancil, Emrah Gecili, Rhonda D. Szczesniak, Anushka Palipana, Judith W. Dexheimer, Yizhao Ni, Pedro M. Afonso, Eleni-Rosalina Andrinopoulou, and Ruth H. Keogh. *Project administration*: Emrah Gecili and Rhonda D. Szczesniak. *Resources*: Christopher Siracusa and Rhonda D. Szczesniak. *Software*: Cole Brokamp, Andrew Vancil, Emrah Gecili, and Erika Rasnick. *Supervision*: Rhonda D. Szczesniak and Emrah Gecili. *Validation*: Emrah Gecili and Anushka Palipana. *Visualization*: Emrah Gecili, Andrew Vancil, and Cole Brokamp. *Writing–original draft*: Emrah Gecili, Cole Brokamp, Patrick Ryan, and Rhonda D. Szczesniak. *Review & editing*: All authors. Authors Emrah Gecili and Rhonda D. Szczesniak had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICTS OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest to report.

DATA AVAILABILITY STATEMENT

Built environment data that support the findings of this study are available by geocoding information from the following websites in the public domain: https://geomarker.io and https://degauss.org. The corresponding author does not have permission to provide demographic and clinical data, but an empirically simulated version of these data will be made available upon reasonable request pending institutional approval. The actual data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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