The Associations Between Clinical Respiratory Outcomes and Ambient Wildfire Smoke Exposure Among Pediatric Asthma Patients at National Jewish Health, 2012–2015

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Abstract Wildfires are a growing threat in the United States. At a population level, exposure to ambient wildfire smoke is known to be associated with severe asthma outcomes such as hospitalizations. However, little work has been done on subacute clinical asthma outcomes, especially in sensitive populations. This study retrospectively investigated associations between ambient wildfire smoke exposure and measures of lung function and asthma control, Forced Expiratory Volume in 1 Second (FEV1) and the Asthma Control Test (ACT) and Children’s Asthma Control Test (CACT) test scores, during nonurgent clinic visits. The study population consisted of pediatric asthma patients (ages 4–21; n = 1,404 for FEV1 and n = 395 for ACT/CACT) at National Jewish Health, a respiratory referral hospital in Denver, Colorado, and therefore represents a more severe asthma phenotype than the general pediatric asthma population. Wildfire smoke-related PM2.5 at patients’ residential ZIP codes was characterized using satellite-derived smoke polygons from NOAA’s Hazard Mapping System combined with kriging of ground-based U.S. EPA monitors. Mixed effect models were used to estimate associations between clinical outcomes and smoke PM2.5 exposure, controlling for known risk factors and confounders. Among older children aged 12–21 we found that wildfire PM2.5 was associated with lower FEV1 the next day but higher FEV1 the day after. We found no associations between wildfire PM2.5 and FEV1 in younger children or between wildfire PM2.5 and asthma control measured by the ACT/CACT in all ages. We speculate that rescue medication usage by older children may decrease respiratory symptoms caused by wildfire smoke.

1. Introduction

Wildfire activity has increased in the United States since the mid-1980s (Dennison et al., 2014), with more large fires, longer lasting fires, and longer wildfire seasons (Westerling, 2016). Over 10 million acres burned in 2015 for the first time in the historical record. The greatest increase has occurred in the forests of the Northern Rockies and is associated with changes in regional climate (increased summer temperatures and earlier snowmelt) rather than land use (Dennison et al., 2014). Furthermore, the size and severity of wildfires are expected to increase as the U.S. climate warms in the coming century, especially in the western and south-central regions of the country, with fire season expected to average 23 days longer by 2050 compared to 2013 (Yue et al., 2013).

Wildfires emit particulate matter, carbon monoxide, ozone precursors, and other air pollutants that adversely impact human health. These impacts have been shown to include increased all-cause mortality (Johnston et al., 2012) and low birth weight (Holstius et al., 2012) as well as emergency department (B. L. Alman, 2014; Wettstein et al., 2018) and hospital admissions (B. L. Alman, 2014; Gan et al., 2017; Rappold et al., 2011) for respiratory (Henderson et al., 2011; J. C. Liu et al., 2016) and cardiovascular (Martin et al., 2013) symptoms, although overall evidence is strongest for respiratory outcomes (Gan et al., 2017; J. C. Liu, Pereira, et al., 2015; Reid et al., 2016). A survey of one fire-impacted Australian community exposed to forest fire smoke found 70% of respondents reported health effects due to the fire and 5% sought medical treatment (Henderson & Johnston, 2012).

The monetary cost of these health impacts is substantial. Butry et al. (2001) estimated that the asthma-related health care costs of a single wildfire in Florida in 1998 were between $325,000 and $700,000, while Rappold et al. (2014) estimated that a single 2008 fire in North Carolina led to a cost of $400,000 for...
Looking specifically at asthma, wildfire smoke has been linked to increases in severe asthma-related outcomes such as emergency department visits (B. L. Alman, 2014; Breanna L. Alman et al., 2016; Gan et al., 2017; Haikergwal et al., 2016; Hutchinson et al., 2018; Kolbe & Gilchrist, 2009; Prevention, 1999; Rappold et al., 2011), overall hospital visits (Churches & Corbett, 1991; Duclos et al., 1990; Gan et al., 2017; Johnston et al., 2002; Prevention, 1999; Reid, 2014), and emergency medication use (Caamano et al., 2011; Elliott et al., 2013; Tse et al., 2015). Indeed, DeFlorio-Barker et al. recently found that asthma-related hospitalizations among elderly Americans were more sensitive to ambient PM$_{2.5}$ on smoke days than on nonsmoke days (DeFlorio-Barker et al., 2019). However, there has been limited research relating wildfires to less-severe asthma outcomes.

Our work seeks to estimate the associations between ambient wildfire smoke exposure to such less-severe outcomes during subacute clinic visits (in-patient nonurgent care visits scheduled at least 14 days in advance) among patients with asthma. In particular, we focus on retrospective analyses of two outcomes: Forced Expiratory Volume in 1 second (FEV1), a measure of airway obstruction, and self-reported asthma control over the prior four weeks as measured by the Asthma Control Test (ACTTM; Nathan et al., 2004; National Asthma & Prevention, 2007; Schatz et al., 2006), or Childhood Asthma Control Test (CACTTM; Bime et al., 2016; A. H. Liu et al., 2007; A. H. Liu et al., 2010). We hypothesize that increased wildfire PM$_{2.5}$ exposure at the home address will be associated with decreased FEV1 and increased risk of poor asthma control. To address this hypothesis we concentrate on a highly susceptible population: pediatric (age ≤ 21) patients in the National Jewish Health (NJH) Research Database who have an active problem of asthma.

### 2. Materials and Methods

#### 2.1. Geographic Region

This study includes patients residing throughout the western United States. However, because NJH is located in Denver, most patients in the study lived in Colorado (Figure 1) at the time of their clinic visits. Wyoming is the second-most represented state in our outcome cohorts, while a small number of patients traveled to NJH from California, Oregon, Washington, Idaho, Wyoming, North and South Dakota, Nebraska, Kansas, Oklahoma, Texas, New Mexico, and Arizona.

#### 2.2. Exposure and Health Outcome Data

##### 2.2.1. Smoke and Nonsmoke PM$_{2.5}$

To determine if each patient’s residential ZIP code was impacted by smoke on a given day, we used a smoke product from the National Oceanic and Atmospheric Administration’s Hazard Mapping System (HMS) (Ruminski et al., 2006). The HMS product uses visible satellite imagery to estimate the spatial extent of smoke (Rolph et al., 2009; Ruminski et al., 2006). The primary source of the visible imagery used by the HMS is from geostationary satellites, which over the period of this study have a refresh interval of about 15 min (Brey et al., 2017). Intermittently, imagery from the Polar-orbiting Operational Environmental Satellite (POES), Advanced Very High Resolution Radiometer (AVHRR), and Moderate resolution Imaging Spectroradiometer (MODIS) satellites are also used, which have a 1-km resolution in the 3.9-mm band. The combination of visible and infrared imagery allows some discrimination between smoke and cloud (clouds and fire hot spots are visible under infrared but smoke plumes are not), although human judgment is sometimes required when both are present (Rolph et al., 2009). Trained satellite analysts assess the visible imagery and evaluate smoke-plume extent. The HMS product is not able to determine whether a given plume is at ground level or higher in the atmosphere. The HMS smoke product also does not discriminate between wildfires, prescribed fires, agricultural burning, or any other source of smoke when performing the smoke plume analysis (Ruminski et al., 2006). However, Brey et al. (Brey et al., 2017) show that the
majority of smoke plumes analyzed by the HMS are the result of fires located on forested lands, particularly in the western United States. The HMS smoke products are stored as shape files that contain daily information on the spatial extent of smoke plumes. These data were downloaded from ftp://satepsanone.nesdis.noaa.gov/volcano/FIRE/HMS_ARCHIVE/. The number and extent of smoke plumes within this archive represents a conservative estimate due to the limitations of visible satellite data (e.g., daytime only, optimal viewing angle just after sunrise and just before sunset, distinguishing between smoke, clouds, and anthropogenic haze) (Brey et al., 2017). However, HMS smoke plumes remain a common binary metric used to determine if smoke is in the atmospheric column (Brey & Fischer, 2016; Brey et al., 2017; Gan et al., 2017; Larsen et al., 2017).

Ambient daily PM$_{2.5}$ monitoring data were downloaded from the U.S. EPA Air Quality System (AQS). AQS archives ambient monitoring data collected by the EPA, state, tribal, and local environmental agencies. We used both the Federal Reference Method (FRM) daily PM$_{2.5}$ monitoring sites (EPA parameter code 88101) and sites that reasonably agree with FRM sites (EPA parameter code 88502). The daily-average PM$_{2.5}$ observations were interpolated to a 15 × 15-km grid over the contiguous United States using ordinary kriging (Isaaks & Srivastava, 1989; Janssen et al., 2008; Jerrett et al., 2005) following the assumptions described in Lassman et al. (2017). This kriging technique creates a continuous PM$_{2.5}$ map with approximately 15 × 15-km horizontal grid spacing for each day across the United States.

We used the following method to segregate wildfire smoke PM$_{2.5}$ from other, nonwildfire-related PM$_{2.5}$. First, daily nonsmoke PM$_{2.5}$ was provisionally estimated by kriging PM$_{2.5}$ ambient monitor data from only those monitor sites with no overlapping HMS smoke plume for that day. Then the seasonal nonsmoke background was calculated as the median of these nonsmoke PM$_{2.5}$ estimates for each season and grid cell. The seasons were defined as follows: winter: December, January, and February; spring: March, April, and May; summer: June, July, and August; and fall: September, October, and November. We took the median of the nonsmoke values instead of the mean to reduce the effect of smoke-impacted grid cells missed by HMS smoke plumes that misclassify smoke-impacted PM$_{2.5}$ concentrations as nonsmoke and skew the seasonal distribution. We then kriged the full set of daily PM$_{2.5}$ monitor observations to the same grid to get a daily estimate of total PM$_{2.5}$. Then we subtracted off the seasonal background level from each full daily PM$_{2.5}$ concentration (setting negative differences to zero) to compute our final estimate of the daily component of PM$_{2.5}$ derived from wildfire smoke. The remaining component of daily PM$_{2.5}$ (equal to the seasonal background unless the background was higher than the full daily PM$_{2.5}$ concentration) was then defined to be the daily nonsmoke PM$_{2.5}$ concentration.

From the resulting daily concentration grids for smoke PM$_{2.5}$ and nonsmoke PM$_{2.5}$ covering the contiguous United States, we used population-weighted (CIESIN, 2017) means to estimate the pollutant concentrations at each ZIP code represented in our FEV1 and ACT/CACT patient cohorts. Specifically, we took the mean of the PM$_{2.5}$ concentration in the grid cells overlapping that ZIP code, weighted by both the population of each grid cell and the amount of areal overlap between the grid cell and the ZIP code. Figure 1 displays the locations of wildfires in the western United States during the years 2012–2015 overlaid with locations and shapes of these ZIP codes. For easier visualization we did not include grid lines in this figure. Figure 2 shows, for FEV1 and ACT/CACT patient cohorts, the average daily total PM$_{2.5}$ (yellow) and wildfire PM$_{2.5}$ (red) concentrations over all the ZIP codes weighted by the overall number of patient clinic visits associated with each ZIP code. The temporal pattern of wildfire smoke PM$_{2.5}$ exhibits seasonality, with the bulk of nonzero wildfire PM$_{2.5}$ days occurring during June–August of each year. Figure 2 also shows, on an inverted scale, the number of patient clinic visits by day (black). The increase in clinic visits apparent during periods of high wildfire PM$_{2.5}$ is an artifact of the study design and does not necessarily imply that more asthma clinic visits occurred during those periods.

Figure 1. Map of western U.S. wildfires between 2012 and 2015 overlaid with ZIP codes appearing in our two asthma outcome cohorts. All-agency wildfire location and size data for this figure were downloaded from https://wildfire.cr.usgs.gov/firehistory/data.html. Wildfires smaller than 10 acres were excluded. Data do not include false alarms, assist fires, or prescribed fires. Wildfire event data shown here are distinct from the Hazard Mapping System (HMS) smoke plume data described in the main text.
2.2.2. Ozone

Ozone is a known respiratory irritant. Ambient ozone mixing ratios from ground-based monitors were downloaded from the U.S. EPA AQS. Daily average mixing ratios were calculated at each ZIP code by taking the median mixing ratio from monitors located either within the ZIP code boundary or within a 20-km buffer around the ZIP code centroid. ZIP codes that did not contain and were not within 20 km of an ozone monitor were assigned a missing value, and patients living in those ZIP codes were dropped from the analysis.

2.2.3. Meteorology

Meteorological variables such as temperature and precipitation have been shown to correlate with asthma symptoms (Dabrera et al., 2013; Xu et al., 2017; Yue et al., 2013). Meteorological monitor data were downloaded from the NOAA National Climate Data Center (ftp://ftp.ncdc.noaa.gov/pub/data/). These data included, for each monitor on each day, mean temperature and precipitation. The daily value of each of these variables was calculated at each ZIP code by taking the median of values from monitors located within the ZIP code boundary or within a 20-km buffer around the ZIP code centroid. ZIP codes that did not contain and were not within 20 km of a monitor for a given meteorological variable were assigned a missing value, and patients living in those ZIP codes were dropped from the analysis.

2.3. Asthma Outcomes

2.3.1. FEV1

Forced Expiratory Volume in 1 second (FEV1) measures the maximum amount of air a person can push out of their lungs in the first second of an exhalation. It is used to evaluate airway obstruction, where lower values are a manifestation of bronchoconstriction in asthma and COPD. FEV1 depends on physical attributes such as height and sex, though within each patient respiratory symptoms and exacerbations are linked to decrements in FEV1. We also explored several other pulmonary function test outcomes in our sensitivity analyses. These outcomes include FEV1 % Predicted, Forced Vital Capacity (FVC), FVC % Predicted, the ratio of FEV1 to FVC (FEV1/FVC), and FEV1/FVC % Predicted. FVC measures the patient’s total lung capacity. The % Predicted outcomes relate the patient’s measurement to their expected value giving their age, gender, and height.

2.3.2. ACT/CACT

The Asthma Control Test (ACT) and the Childhood Asthma Control Test (CACT) are self- or caregiver-administered questionnaires that are validated for assessing asthma control over the prior month. For
pediatric patients aged 12–21, the ACT is a five-item questionnaire with scores ranging from 5 (poor control of asthma) to 25 (complete control of asthma) with four-week recall on symptoms and daily functioning. For children aged 4–11, the CACT is a seven-item questionnaire composed of three caregiver-reported and four child-reported items. The four child-reported items are scored on a four-point scale from 0 to 3, and three caregiver-reported items are scored on a six-point scale from 0 to 5. The final score is a sum and ranges from 0 to 27, where higher scores indicate better asthma control (Bime et al., 2016).

For the purposes of the present study, ACT scores of 20–25 were categorized as Well Controlled (WC), 16–19 as Not Well Controlled (NWC), and 5–15 as Very Poorly Controlled (VPC) (National Asthma & Prevention, 2007). Similarly, CACT scores of 20–27 were categorized as WC, 13–19 as NWC, and 0–12 as VPC (A. H. Liu et al., 2010). Due to the small number of VPC test scores our analyses pooled the NWC and VPC scores into a single category.

2.4. Patient Population

This study included pediatric (age ≤ 21 years) patients who visited an NJH clinic between 2012 and 2015 and who were listed in the NJH Research Database (which pulls information directly from the NJH electronic health record) as having an active problem of asthma. Only patients living in ZIP codes with nonmissing ozone, mean temperature, and precipitation values were included in our study population. Thus, 85% of patients lived in metropolitan areas with a population greater than 50,000 and 75% lived in metropolitan areas with a population greater than 250,000. Nearly 80% lived in metropolitan areas along the Front Range. Patients aged 18–21 years (4.2% of our study population) were included as pediatric patients following the recommendations of the U.S. Department of Health and Human Services (U.S. Department of Health and Human Services, 2003) and the American Academy of Pediatrics (American Academy of Pediatrics, 1988; Pediatrics, 2008).

NJH is a referral hospital, so our study population likely reflects a more severe phenotype of pediatric asthma compared with the general asthma population. As our purpose was to investigate less-severe respiratory endpoints rather than acute or exacerbation-related endpoints, we eliminated from our cohort all patient clinic visits scheduled less than 14 days in advance. NJH is primarily an outpatient hospital and does not have its own critical care facilities, but patients may make short-notice appointments for acute respiratory symptoms not requiring emergency department admission. A short time interval between scheduling a clinic visit and the visit itself was thought by NJH clinicians to be an indicator of an acute episode, and therefore, such visits were dropped from our main analysis. However, because socioeconomic factors may play into the willingness or ability of a family to schedule appointments far in advance, and dropping such visits might limit the generalizability of our results to disadvantaged patients, the impact of including these visits is investigated in a sensitivity analysis.

For the FEV1 cohort we extracted those patients with at least one FEV1 test result, at least one of which occurred within the first three days after a nonzero smoke PM$_{2.5}$ concentration was estimated at the patient's ZIP code. The three-day window is used to allow investigation of lagged wildfire smoke impacts. The mean, median, and range for the number of FEV1 measurements per patient are 7.05, 5, and 1–114, respectively, with 86% of patients having two or more FEV1 measurements.

For the ACT/CACT cohort we extracted those patients with at least one ACT/CACT score, at least one of which occurred within 33 days after a nonzero smoke PM$_{2.5}$ concentration was estimated at the patient's ZIP code. The larger lag day window compared with FEV1 was used because the ACT/CACT instrument asks about asthma control over the prior four weeks. We padded this 28-day interval to 33 days to be sensitive to lagged smoke effects at the beginning of the four-week period. However, unlike with FEV1, our ACT/CACT models are not sensitive to when the symptoms recorded on the ACT/CACT took place relative to the smoke impact at the patient's residence; in some cases symptom may precede exposure. The mean, median, and range for the number of ACT/CACT scores per patient are 1.90, 1, and 1–16, respectively, with 44% of patients having two or more ACT/CACT test results. The two cohorts share 328 patients and 875 clinic visits.

The study protocol was approved by the National Jewish Health Institutional Review Board (HS-3007). The requirement of informed consent was waived because the study presented no more than minimal risk to patients, the rights and welfare of patients were not adversely affected, the study could not be practically
be carried out without a waiver due to its retrospective design, and patients will be able to access study results. Full merged, de-identified data sets are publically available through the Open Science Framework website (Crooks, 2019).

2.5. Statistical Methods

We used mixed effect models with a random intercept by subject to analyze both FEV1 and ACT/CACT. We used the random intercept model because we have repeated measurement data for each subject in our data set. All models included indicators for calendar month (January, February, etc.) to control for known time-of-year variation in symptoms among asthmatic patients, as well as nonlinear terms for subject age (natural spline with three degrees of freedom) because lung function and asthma control naturally improve through childhood. Subject race and gender were available but were highly collinear with the subject-specific random intercept and thus were not included in our primary models. For FEV1, our models included mean daily temperature at lags 0 and 1 (each represented by natural spline with three degrees of freedom), precipitation at lags 0 and 1, and ozone and nonsmoke PM2.5 at lags 0–3. For ACT/CACT, we included these same meteorological and air pollution variables but averaged over lags 0–33 rather than using the FEV1 distributed lag form. FEV1 models assumed a Gaussian response, while ACT/CACT models assumed a binary response contrasting between asthma control categories. Analysis of data was performed using R version 3.3.2 (R Core Team, 2017). Random effect models were run using the lme function package “nlme” (Pinheiro et al., 2016) for FEV1 and the glmmPQL function in the “MASS” package (Venables & Ripley, 2002) for ACT/CACT. Statistical significance was assessed by comparing the 95% confidence interval to the expected value under the null hypothesis; in all analyses herein this expected null value was 0.0.

It is plausible that demographic factors may affect patient’s exposure or biological response to wildfire smoke. We therefore investigated effect modification by self-reported gender, age group (4–11 versus 12–21 years, corresponding to the recommended ages for the CACT and ACT, respectively), and race (three categories: white, black/African-American, and missing/declined).

For ACT/CACT, the time interval between the test date and the wildfire smoke exposure may modify our main results. Specifically, if wildfire smoke exposure reduces asthma control over many days, any observed association may be attenuated when smoke exposure occurs proximal to the test date. This is because the ACT/CACT asks about the number of times a symptom occurred or a medication was used over the prior 28 days, so a patient coming to clinic soon after smoke exposure may not have had time to fully experience a health impact spanning many days. Such a patient may therefore have scored higher on the test (i.e., more controlled) than they would have a few days later. Because of this, in addition to our main model we also investigated splitting the 0–33-day lag mean exposure into two exposures, a 0–7-day lag mean exposure, and an 8–33-day lag mean exposure to determine whether the coefficients of the former are attenuated compared to those of the latter.

2.6. Sensitivity Analyses

Five separate sensitivity analyses were performed. First, we varied the buffer distance that was used to define which ozone and meteorological monitors contribute to the ZIP code’s median values. Changing the buffer size can thus change the proportion of missing values as well as the median values themselves. Alternative buffer distances included 10 and 50 km from the ZIP code centroid.

Second, to determine to what extent our main results were driven by large but rare wildfire PM2.5 concentrations, we replaced our wildfire and nonwildfire PM2.5 exposure variables with an overall PM2.5 concentration variable and a daily indicator for the presence of wildfire smoke. For FEV1 models, this indicator variable took the value 1 when wildfire PM2.5 concentrations were above 10 μg/m³ and the value 0 otherwise (at each lag). For the ACT/CACT model, the indicator also took the values 0 or 1 at each lag, but these were then averaged over the 0–33-day window, yielding an exposure metric proportional to the number of wildfire smoke days falling in that time window.

Third, we studied the influence of meteorological and nonwildfire air pollution variables on our main results. We first removed all nonwildfire air pollution variables from our models, and then removed these as well as all meteorological variables, leaving only wildfire PM2.5 itself, calendar month, and age.
Fourth, we tested whether the results for FEV1 were consistent with other closely related pulmonary function test measures: FEV1 % Predicted, FVC (Forced Vital Capacity), FVC % Predicted, FEV1/FVC, and FEV1/FVC % Predicted. When testing the % Predicted end points we dropped age, race, and gender from our models as these factors are accounted for in the prediction.

Fifth, to investigate the impact of including clinic visits scheduled less than 14 days in advance we re-ran our analyses including all visits without reference to the scheduling date but still meeting our other selection criteria.

3. Results

3.1. Descriptive Analyses

Our data set included 395 pediatric asthmatic patients who completed the ACT/CACT survey and 1,404 patients with recorded FEV1 test results. There were a total of 475 patient clinic visits in the ACT data set and 2,022 clinic visits in the FEV1 data set. Three-hundred-twenty-eight patients and 875 unique clinic visits appeared in both cohorts. The descriptive statistics of our study population are summarized in Table 1. Among patients whose race and gender were given, the most common were male and white, although the largest race group was missing/declined. The average age was between 10 and 11 years. Mean FEV1 was 2.10 L. A large majority (80.0%) of ACT test scores fell into the WC category, while only 20.0% fell into the NWC and VPC categories together.

Summary statistics of ZIP code-level air pollution and meteorological values associated with our patient visits are described in Table S1. The distribution of wildfire PM$_{2.5}$ was highly skewed, with a maximum...
concentration over 30 times the mean in the FEV1 cohort. For nonsmoke PM$_{2.5}$ this ratio was below 10. Maximum and minimum values were closer together in the ACT/CACT cohort than in the FEV1 cohort due to the 0–33-day averaging time, which moderated extremes. For example, the maximum value of smoke PM$_{2.5}$ in the ACT/CACT cohort was only 5.99 µg/m$^3$.

Table S2 shows the associations between nonwildfire variables and same day (or same lag period) wildfire smoke PM$_{2.5}$ estimated using simple linear regression. In both outcome cohorts each 1-µg/m$^3$ increase in wildfire PM$_{2.5}$ was positively associated with ozone and temperature but negatively associated with precipitation. Nonsmoke PM$_{2.5}$ was positively associated with smoke PM$_{2.5}$ in the ACT/CACT cohort, but negatively associated in the FEV1 cohort.

### 3.2. Wildfire Smoke Exposure and Lung Function

Figure 3 displays our main results. For FEV1 we observed no associations at lag 0 (0.011 (95% CI: −0.056, 0.080; $p = 0.728$) liters per 10-µg/m$^3$ increase in smoke PM$_{2.5}$), lag 1 (−0.055 (95% CI: −0.123, 0.012; $p = 0.109$)), lag 2 (0.050 (95% CI: −0.010, 0.110; $p = 0.102$)), or lag 3 (−0.025 (95% CI: −0.089, 0.040; $p = 0.431$)) (Figure 3a). Likewise, for ACT/CACT, we did not find associations between wildfire PM$_{2.5}$ and asthma control (Figure 3b); the logarithm of the odds ratio was 0.505 (95% CI: −1.96, 2.97; $p = 0.688$) per 10 µg/m$^3$ for WC versus NWC and VPC.

### 3.3. Effect Modification

We investigated possible effect modification by age, gender, race, and, for ACT/CACT, time interval between exposure and clinic visit. In the FEV1 cohort, when stratifying by age, we found an alternating pattern of significant lagged associations (−0.190 (95% CI: −0.298, −0.081; $p = 0.0007$) at lag 1, 0.106 (95% CI: 0.003, 0.208; $p = 0.043$) at lag 2) among children age 12 to 21, but not among ages 4–11 (Figure 4a). An association at lag 2 was also observed among white children but not among black/African American children (Figure 4c). No significant associations were found in either gender group (Figure 4b).

Our main ACT/CACT result of no association with wildfire PM$_{2.5}$ continued to hold when we stratified by age (Figure S1a) and gender (Figure S1b). While this null result also held for white children and children with other/missing race (Figure S1c) the association for black/African-American was significant and in the direction of poorer asthma control, with a log odds ratio of 5.06 (95% CI: 0.972, 9.16; $p = 0.019$) per 10-µg/m$^3$ increase in wildfire PM$_{2.5}$. Splitting our wildfire PM$_{2.5}$ coefficient into a 0–7-day lag coefficient and an 8–33-day lag coefficient yielded null results (Figure S2).

### 3.4. Sensitivity Analyses

As stated above, we investigated the sensitivity of our results by modifying our analysis pipeline in five ways. First, we investigated changing the buffer distance used to characterize exposure to temperature and non-smoke PM$_{2.5}$ air pollutants. As shown in Figure S3, the positive but nonsignificant lag 2 association with FEV1 was observed under all three buffer distances and reached significance under the 50-km buffer. No significant associations were observed under the 10-km buffer for either endpoint, although the ACT/CACT did not converge under that buffer due to low sample size (Figure S4).

Second, we replaced the continuous exposure variable with a discrete exposure variable. Doing so also yielded null results for both FEV1 and ACT/CACT (Figure S5).

Third, we varied the covariate model. For FEV1, when excluding meteorological and air pollution variables other than wildfire PM$_{2.5}$ from the model, the lag pattern of associations (in particular the negative point estimate at lag 1 and positive point estimate at lag 2) remained but did not reach statistical significance (Figure S6). For ACT/CACT, our main results remained null under all three confounder models (Figure S7).

Fourth, we ran models on five alternative pulmonary function test outcomes. None had statistically significant associations at any lag (Figure S8). However, underlying these null results were noticeable differences between age groups (Figure S9). As with our main FEV1 results, older children had an alternating pattern of negative and positive associations at lags 1 and 2, respectively, for FVC, while FEV1 % Predicted yielded a negative association at lag 1.
Figure 3. Main results. (a) Associations between daily wildfire PM$_{2.5}$ exposure and change in FEV1 by lag day under a distributed lag model. (b) Associations between 0–33-day mean wildfire PM$_{2.5}$ exposure and asthma control category extracted from ACT/CACT scores, by asthma control category pairs. Vertical bars indicate 95% confidence intervals. Asthma control categories are defined as WC = Well Controlled, NWC = Not Well Controlled, and VPC = Very Poorly Controlled. Positive coefficients in (b) indicate higher odds of better asthma control.

Figure 4. Lagged associations between ambient wildfire PM$_{2.5}$ exposure and FEV1 stratified by (a) age group, (b) gender, and (c) race. Vertical bars indicate 95% confidence intervals. The $p$ values for the contrasts between age categories at each lag: ages 4–11 versus 12–21 at lag 0 = 0.741, ages 4–11 versus 12–21 at lag 1 = 0.0017, ages 4–11 versus 12–21 at lag 2 = 0.0504, ages 4–11 versus 12–21 at lag 3 = 0.622.
Fifth, we expanded our data set to include clinic visits scheduled on any date, not just those scheduled at least 14 days in advance. Doing so yielded 1,694 patients and 8,988 visits for pulmonary function testing and 459 patients and 1,275 visits for ACT/CACT. The additional patients were demographically similar to our main study population except that blacks/African-Americans were underrepresented among the additional ACT/CACT subjects. The FEV1 results, while displaying the same lag pattern as in our main population, remained null under this larger population (Figure S10). However, our original finding of a negative association at lag 1 among older children was still observed (Figure S11), as was our finding of a positive lag 2 association among white children. Furthermore, the results for white children also displayed a negative association at lag 1, yielding a lag pattern similar to that found in older children in our original population. However, for ACT/CACT, our finding of a positive association among black/African-American children was no longer evident (Figure S12). Across all six pulmonary function test outcomes, lagged associations remained null except for the lag 1 association with FVC % Predicted, which became negative (Figure S13). When broken down by age group, though, older children again had negative FEV1 and FVC associations at lag 1, while FVC still had a positive association at lag 2 (Figure S14). However, younger children had positive lag 1 associations with FEV1/FVC and FEV1/FVC % Predicted.

4. Conclusions

Our FEV1 cohort results show no change in lung function following ambient wildfire smoke PM$_{2.5}$ exposure, in contradiction to our hypothesis. However, when broken out by age group, more detailed inference becomes possible. Younger patients aged 4–11 years did not exhibit associations with wildfire PM$_{2.5}$ at any lag, but older patients aged 12–21 experienced below-normal lung function on the day after wildfire smoke exposure, then above-normal lung function the following day, and finally a return to baseline on the third day (Figure S1a). To explain the result among older children we speculate that patients took rescue medication one to two days postexposure to relieve respiratory symptoms caused by smoke exposure. Future studies using GPS- and Wi-Fi-enabled rescue inhalers will be well-positioned to confirm or refute this interpretation. If this speculation is correct, our results suggest that rescue medication may adequately protect older children against short-term respiratory impacts caused by wildfire smoke exposure, and, furthermore, that providers and public health officials should encourage access to and proper use of rescue medication during high-smoke days.

Decrement in lung function associated with wildfire smoke have previously been observed in nonasthmatic children (Jacobson Lda et al., 2014; Reid et al., 2016), but not in the general pediatric asthmatic population (Jacobson et al., 2012; Jalaludin et al., 2000; Vora et al., 2011; Wiwatanadate & Liwsrisakun, 2011), although an increase in medication use has been observed (Vora et al., 2011), as has a decrease in peak expiratory flow rate specifically among those asthmatic patients without bronchial hyperreactivity (Jalaludin et al., 2000). Our results using all-age pediatric asthmatic patients are consistent with the bulk of these findings. However, our result of a negative association at lag 1 followed by a positive association at lag 2 among older children has not been described previously.

The differences between age groups that we observed in our FEV1 results suggest that behavioral or age-related vulnerability factors play a substantial role in mediating the impact of wildfire smoke exposure on lung function in asthmatic children. Specifically, we speculate that either our null results for younger children are due to “harvesting,” whereby more vulnerable subjects are more likely to suffer acute symptoms and thus be removed from this study's risk pool at a higher rate, or that younger children with severe asthma are more likely to be confined indoors by caregivers and thus receive lower personal air pollution exposures. Future panel studies incorporating wearable air pollution monitoring devices could clarify these issues.

Overall, our FEV1 results appear to be driven by associations observed in white children and male children, although this finding may simply be attributable to the larger sample sizes of these categories. We do not believe that the null result at lag 0 among all demographic groups is necessarily indicative of a true lack of same-day effect because our 24-hr average exposure measure at lag 0 includes exposures occurring during hours after the clinic visit.

Our ACT/CACT results are largely consistent with the null hypothesis of no association between wildfire PM$_{2.5}$ and asthma control, indicating that the ability of children and caregivers to control children's
asthma over a four-week time scale was unaffected by ambient wildfire smoke. A positive association (indicating higher odds of poorer asthma control with greater wildfire PM$_{2.5}$ exposure) was observed in African-American children, which is consistent with the literature on socioeconomic vulnerability, although this result was not robust to changes in our analysis pipeline (Figure S12).

Our study has a number of strengths. To our knowledge, it is the first epidemiologic study of wildfire smoke to focus on less-severe clinical asthma outcomes. Other studies have focused on the acute effects of wildfire smoke and air pollution on adult and children's health (Jacobson Lda et al., 2014; Kunzli et al., 2006; Reid et al., 2016; Wiwatanadate & Liwrisakun, 2011). The study populations here are also relatively large compared to other studies of clinical asthma outcomes.

The study also has a number of limitations. First, the clinical definition of asthma is not precise, and clinicians differ (even within NJH) on how to apply various criteria. This study did not attempt to validate asthma diagnoses listed in the NJH Research Database. Second, our method of characterizing exposure to wildfire PM$_{2.5}$ may not be accurate or representative of individual wildfire PM$_{2.5}$ exposure; in addition to the uncertainty inherent in kriging and in using ambient concentrations as a proxy for personal exposures, some of the smoke PM$_{2.5}$ may be misclassified as nonsmoke PM$_{2.5}$ and vice versa. Third, the two-week interval we used to distinguish acute versus nonacute clinic visits may be too strict and leave out some nonacute visits, or too permissive in that a patient may happen to be having an acute event when they come to a regularly scheduled visit. However, without text mining or physician review of medical records this was the most efficient method of distinguishing acute from nonacute clinic visits. That being said, our results for FEV1 among older children were similar even when relaxing the two-week constraint.

Fourth, medication use has a large impact on asthma symptoms, and we have no information regarding when or which medications were used. Fifth, for ACT/CACT, the time order of exposures and symptoms is not known so associations with this end point should be interpreted with care. Lastly, since NJH is a tertiary treatment center, our patient population likely reflects more severe asthma phenotypes and may not be representative of the general asthmatic population, especially since patients with more severe asthma may be more likely to use rescue medication when under environmental stress than patients with less severe asthma, either because they are more symptomatic or because they are better informed about exposures.

However, our results underscore the need for a better understanding of the toxicological effects of wildfire smoke, in particular of cellular and molecular responses, and how these responses are modified by medications. The literature on this topic is limited but growing. Roscioli et al. (2017) found that wildfire smoke caused autophagic dysregulation of the epithelium in an air-liquid interface experiment, indicating possible mechanism whereby wildfire smoke could exacerbate lung disease. Studies of a population of adolescent rhesus monkeys exposure to wildfire smoke prenatally found decreased pulmonary function compared to unexposed control animals (Black et al., 2014; Black et al., 2017), and this difference was associated with modulation of multiple genes related to the toll-like receptor pathway. Furthermore, Bassein et al. (2017) found that exposure was associated with reduced IL-8 synthesis in response to lipopolysaccharide challenge. These results indicate that immune dysregulation can persist for years after exposure.

While wildfire PM$_{2.5}$ is far from the only air pollutant known to negatively impact respiratory and other diseases (Thurston et al., 2017; U.S. Environmental Protection Agency, 2009, 2013), it is one of the few whose associated health burden is expected to increase over the coming century as the Earth's climate changes and now-forested areas become drier. Focusing in on the Colorado Front Range, where most of the population in our study resides, Liu et al. (Z. Liu, Wimberly, et al., 2015) combined climate modeling and spatial demographic modeling to estimate the change in wildfire risk as the climate changes and the wildland-urban interface expands. They found that both of these factors individually increased risk (with climate change being the stronger driver), and, when modeled together, operated synergistically to increase the area of the wildland-urban interface predicted to burn annually by 456% between 2010 and 2050. Looking nationally, Liu et al. (J. C. Liu et al., 2016) calculated the change in respiratory hospitalizations among elderly Americans by midcentury expected due to climate change-related wildfire smoke. They found an increase of 4,990 high-smoke days and an additional 179 respiratory hospital admissions by 2046–2051 under the A1B climate change scenario, with the Front Range region of Colorado set to experience one of the largest percentage increases in the country.
In addition, much of the smoke that impacts Colorado is from fires that are located in other regions. Val Martin et al. (2013) showed that over the period 2000–2012, which overlaps the first half of our study period, the long-range transport of smoke was frequent. Val Martin et al. also pointed out that 2012 was an extreme fire year in Colorado; smoke from the High Park Fire drove unhealthy levels of PM2.5 (>100 μg/m³) in the Front Range. While there were several periods of elevated smoke in summer 2015 in the Front Range, much of this smoke was from fires located in the U.S. Pacific Northwest and British Columbia (Lindaa et al., 2017). Brey et al. (Brey et al., 2017) provide a comprehensive analysis of which fires contribute to the HIMS smoke plumes used in the present analysis. They show that a large fraction of the plumes over the Rocky Mountain region during summer are from large wildfires in the U.S. Pacific Northwest and the Southwest. Taken alongside the Liu et al. (Z. Liu, Wimberly, et al., 2015) results, it is reasonable to infer that population health impacts due to wildfire smoke exposure will increase if wildfire activity continues to grow throughout the U.S. west and southern Canada.

Conflict of Interest

The authors report no competing interests or financial conflicts of interest.

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