**Introduction:**

Ambient particulate matter pollution from wildfire smoke is a significant issue in the United States and has grown worse in recent years. Over the past decade, wildfire smoke has accounted for roughly a quarter of PM2.5 pollution (particulate matter with a diameter smaller than 2.5 microns, as opposed to coarse particulate matter with a diameter smaller than 10 microns), and as much as half of all PM2.5 pollution in western states.1 This comes even as the US has made overall reductions in PM2.5 levels. Wildfire smoke PM2.5 is expected to continue harming these efforts, and under climate modeling projections, worsening wildfire seasons may lead to more than a doubling of current smoke PM2.5 levels, which could fully offset successes in PM2.5 reduction in certain regions.2,3 Smoke PM2.5 is not just an issue for the western US, as smoke plumes can extend far into the midwestern and eastern regions. Some projections estimate that up to three quarters of smoke-related mortality in the US is outside the west, in part due to differences in population density.4

PM2.5 pollution has been robustly linked to a wide variety of negative health effects. Due to their small size, these particles are able to travel deeper into the lungs and enter the bloodstream, at which point they can cause inflammation, affect the cardiovascular system, and even affect the central nervous system after crossing the blood-brain barrier.5 Demonstrated health impacts of ambient PM2.5 include asthma, reduced lung function, increased risk for respiratory infections, cardiovascular disease, diabetes, cancer, and premature mortality.6,7 PM2.5 associated with wildfire smoke is understudied compared to all-source PM2.5, and there is evidence that smoke-related PM2.5 may be particularly harmful, as several studies have examined the impact of both smoke and all-source PM2.5 on hospitalizations and found smoke PM2.5 to be associated with larger increases.8,9 Aguilera et al. explain that this association could be due to wildfire smoke’s higher concentration of organic compounds compared to all-source PM2.5, which increases its ability to cause oxidative stress and inflammation.8

The health impacts of wildfire smoke PM2.5 have been understudied compared to all-source PM2.5. Given the possibility that smoke PM2.5 presents a different and perhaps heighted risk profile, and is an increasingly significant problem in the US, it is important to further investigate its effects. Several studies have looked at the impact of smoke PM2.5 on mortality by analyzing the effect of acute wildfire events on daily mortality. Jegasothy et al. and Morgan et al. both studied bushfire smoke PM in Sydney, Australia, at the daily level to find mixed results, as Jegasothy et al. reported a significant positive association in adults over the age of 65, while Morgan et al. did not find an association without mortality despite a significant positive association with hospitalizations.10,11 Chen et al. and Ye et al. used similar approaches, both with daily data, to studying this association in other international contexts, and found significant, positive associations.12,13 To our knowledge, no published papers have studied this relationship at the monthly or yearly level. Compared to the daily level, this wider temporal lens captures medium- and long-term exposures, may minimize concerns around displacement (i.e. smoke days precipitating deaths that would have occurred shortly after, instead of causing deaths in individuals who would have otherwise lived), and perhaps most importantly, provide a template for further research studies that can are more accessible to run given the relative simplicity of accessing less granular data compared to daily-level statistics.

A number of papers, summarized in Table 1, have used this ecological approach to studying the effect of all-source PM2.5 on mortality. In brief, this approach involves using PM data aggregated to the geographic unit level through area- or population-weighting, using annual instead of daily outcome data, and utilizing an analytic strategy based on a Poisson regression with two-way fixed effects (TWFE) for geographic unit and year. Many other studies in this space use concentration response functions (CRFs), which are based on previous literature that directly estimate the statistical association between air pollution and health, to extrapolate from existing data and calculate the societal impact of air pollution in terms of mortality and economic cost, among other metrics.14,15,16 Those studies are not fundamentally comparable, though they rely on this type of research and are an important way this research can contribute to the field.

TWFE models are a traditionally econometric approach that have increasingly been applied in environmental and social epidemiology.17 These models compare each geographic unit to itself across multiple years (achieved by the spatial FE), adjusting for secular trends (the time FE), and therefore are hypothetically able to adjust for both observable and unobservable confounders. As a result, they are thought to produce more plausibly causal estimates than traditional models that rely on direct confounder adjustment.

Included in Table 1 is Wang et al., who applied a modified differences-in-differences design to studying the effect of annual PM2.5 on mortality at the census tract level in New Jersey, and clearly explained this analytic approach.18 Many other studies in Table 1 are explicitly modeled after Wang et al., with similar methodology. Though the vocabulary used is different, their approach is functionally identical to the Poisson regression with TWFE. Differences in terminology may have arisen due to the relative newness of TWFE models in epidemiology. Many of the papers in Table 1 source their methodology to Armstrong et al., which demonstrated how conditional Poisson models run using the `gnm’ package in R can be used to analyze panel data in epidemiologic contexts.19 As confirmed by our analyses, this approach is functionally identical to running a quasi-Poisson regression with TWFE using the `fixest` package in R, which is a newer package designed specifically for this approach and is more computationally efficient, though `fixest` is for now more commonly used in econometric studies. A major drawback of the `gnm` package is the lack of transparency around which standard errors (SEs) are used, unlike `fixest.` SE choice has an enormous impact on the statistical significance of model results, and the implications of this will be discussed later in this paper.

The studies in Table 1 are fundamentally quite similar, but they do frequently make different design choices at several stages. Aggregating environmental data to the chosen spatial level of analysis can be done through different methods, typically either weighted by area or by population, which can create potentially nontrivial differences. TWFE models minimize the number of covariates that should be included, but they cannot control for variables that vary across time and space, such as temperature, which is frequently included as a covariate in these models. Temperature can be modeled in a few different ways and is most commonly modeled linearly or using natural splines with different degrees of freedom. Other common covariates include precipitation and economic output. Other modeling choices include FE specifications, weighting the regression by population, and SE choice, among other possibilities. All these choices can be reasonably made a priori, though they may still have a nontrivial impact on the researchers’ findings. In this manner, different reasonable specifications may lead to important differences in findings even with scrupulous researcher behavior.20

This paper analyzes the effect of wildfire smoke PM2.5 on all-cause mortality in the contiguous US at the county-month level. We use a quasi-Poisson regression with FEs as has been previously done, though we use the `fixest` package, which is newer and more flexible for these analyses than the `gnm` package. Given the variety of different model specifications that have been used in similar analyses, we systematically vary these choices to determine the range of estimates that can be obtained through a priori reasonable modeling approaches. We then recommend a set of specifications and several best practices for future studies in this area.

**Methods:**

**Estimating wildfire smoke PM2.5 exposure:**

Wildfire smoke PM2.5 data come from Childs et al. 2022, which produced 10km2 gridded estimates for the entire US for all days, 2006-2020.1 In brief, their methods involved determining which days had wildfire smoke plumes overhead based on satellite imagery. For such “smoke days,” PM2.5 anomalies from EPA ground stations were attributed to wildfire smoke PM2.5, and the smoke-attributable PM2.5 value was calculated as the difference between the anomalous value and the 3-year non-smoke day median. A machine learning model was used to predict ground station values, including data on meteorological measures, aerosol optical depth predictions, HYSPLIT trajectory points, and topological data, among other sources. After training, this ML model was used to generate gridded, smoke-attributable PM2.5 predictions for the entire country. These data have already been used to measure exposure in environmental epidemiology studies such as Wen & Burke 2022.2

Population-weighted aggregation was used to take the daily, 10km2 gridded smoke PM2.5 estimates from Childs et al. to the county-month level. Population data came from WorldPop’s 2013 estimates, which provide values of population density at the 10km2 level. The proportion of each county that overlapped with a grid cell was calculated, population densities were combined with these areas to determine the total population of each county-grid cell overlap, and then the mean smoke PM2.5 estimate across all overlapping grid cells was calculated, weighted by grid cell population. Population weighting was used because counties often cover large tracts of land and do not have an evenly distributed population, so area-weighting estimates may misrepresent the population’s true exposure to smoke PM2.5 or other environmental variables.

**Mortality and population data:**

Mortality data were obtained from the CDC’s Wide-ranging Online Data for Epidemiologic Research (WONDER) site’s 1999-2000 multiple cause of death data.3 WONDER mortality data is based on death certificates of US residents, with information on primary cause of death, additional non-primary causes, and demographic data. Aggregated versions of these data are publicly available without a DUA, but a DUA is necessary to access the granular counts, including cells with fewer than 10 events.

The primary outcome in this study is all-cause mortality, as reported in the CDC WONDER database, which captures all death certificates from US residents. All-cause mortality was assessed using ICD10 codes A00-Z99. Cause-specific mortality was determined using ICD10 codes I00-I99 for cardiovascular mortality; H62-H67 and J00-J99 were used for respiratory mortality.

Data from WONDER were available with county-level population estimates stratified by age, sex, and race/ethnicity, but lacked data on marital status. The American Community Survey 5-year data (ACS-5) begins in 2009 and includes data on marital status, and therefore was used on conjunction with the WONDER data. The “B12002” table of the ACS-5 was used to gather data on marital status across age categories. Mortality and marital status data were aggregated at the county-month level with stratifications by age, sex, race/ethnicity, and marital status for the years 2009-2020, excluding the months after February in 2020 to avoid disruptions due to the COVID-19 pandemic. This roughly decade-long period included many major wildfire events and captured the trend of increasing wildfire smoke exposure in the US, which is expected to continue in the coming decade.

**Environmental control data:**

Monthly mean temperature and precipitation were used as important covariates that would not otherwise be accounted for in the TWFE model. Monthly mean temperature and precipitation data at the 4km2 level were obtained from Oregon State’s PRISM Climate group and aggregated to the county level by both population- and area-weighting. Other potential confounders do not need to be controlled for due to the nature of the analytic approach, and the relative infrequency with which existing studies directly control for additional covariates.

**Estimating the effect of wildfire smoke PM2.5 on mortality:**

Our models utilized a quasi-Poisson regression with two-way fixed effects. Quasi-Poisson regression was chosen because our total mortality is a count variable, though the model results can be interpreted as an effect on the mortality rate due to the offset term. We did not choose negative binomial regression because, although both models are capable of handling overdispersed data, negative binomial regression gives outsized weight to smaller counties, while quasi-Poisson regression weights counties by size more evenly.4 Our analyses involved running many regressions with slight variations in specification, so it would be impractical to enumerate them all. Equations 1-3 show the three sets of FEs we studied, along with our recommended approach to modeling covariates, though the covariate selection is varied in our main analysis.

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All three equations model the natural logarithm of mortality counts for each county *c*, month *m*, and year *y*. Equation 1 uses a county-calendar month FE, ˙˙ƒ

*ηc-m*,and a year FE, *ƛy*. The county-calendar month FE creates dummy variables for each county-calendar month in our sample (in other words, 3,083 counties \* 12 calendar months = 36,996 intercepts). The potential value of this FE instead of the more common county-only FE is that different counties may have different seasonal effects for variables unmeasured in our regression. Like with other FEs that incorporate county, this FE means the model compares each county’s mortality counts to themselves over time, theoretically eliminating the need to control for both measured and unmeasured year-invariant county-month-level confounders such as socioeconomic status, urbanicity, and so forth. The year FE *ƛt* creates dummies for each year of our sample (11 dummies total for years 2009-2020), controlling for nationwide secular trends.

Equation 2 is substantially similar to Equation 1 but uses a county FE, *ηc* (creating 3,083 intercepts, one for each county), and a year-month FE, *ƛy-m* (creating 12 calendar months \* 15 years = 180 intercepts). This set of FEs compares each county to itself across all months in all years, adjusting for secular trends by each month of each year. This approach does not adjust for seasonality.

Equation 3 uses a county FE, *ηc* (creating 3,083 intercepts, one for each county), and a year FE, *ƛy-m* (creating 15 intercepts, one for each year). It is conceptually the simplest, comparing each county to itself across all months in all years, adjusting for secular trends at the yearly level.

Other parameters in Equations 1-3 vary slightly across the regressions we ran in our analysis, but they are substantially similar, so they are explained here. *SmokePMc, m, y* represents the mean daily wildfire smoke-attributable PM2.5 pollution in county *c* during month *m* of year *y*, and is our main variable of interest. We used no lag terms, so this regression models the effect of same-month smoke PM2.5 on mortality. *Tempc,m,y*represents the mean monthly temperature of each county, and a natural cubic spline with 3 degrees of freedom is applied to account for nonlinear effects of temperature on mortality. Similarly, *Precipc,m,y* represents the mean precipitation for each county, modeled linearly. The offset term *ln(Popc,y)* represents the total population of each county *c*  in each year *y*, and it is included so that the model results can be interpreted as an effect on mortality rates instead of on raw mortality counts. εc,m,y represents the error term. β*1* represents the average effect of an additional µg/m3 of average monthly smoke PM2.5, though it must be exponentiated to be interpretable as a risk ratio. The model was weighted by county population size. Robust standard errors were used, and they were clustered at the county level to account for within-unit correlation. Modeling was done using the fixest package in R 4.2.0. Tests for significance were two-tailed.

This model’s county-month and year fixed effects cannot control for confounders that vary across both time and county. We chose to directly adjust for temperature and precipitation because they clearly vary across both county and time, and are known to be associated with wildfire risk, ambient PM2.5, and mortality.5–8 Other potential confounders are not directly measured, and represent a possible source of bias.

While the offset term does allow the model coefficients to be interpreted as affecting the mortality rate instead of the raw death counts, and this effect on the mortality rate is not age-adjusted, strictly speaking. However, the county-month fixed effect accounts for county-level population age structures, and the year fixed effect accounts for nationwide trends in aging. These combined effects minimize the concern of confounding by population age structure, because in order for it to be a confounder, county age structure would have to vary year-to-year in a way that is correlated with changes in smoke PM2.5 and is not captured in national trends, which is not highly plausible.

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| **Table 1: Ecological research studies using Poisson regression with TWFE to study particulate matter pollution’s effect on health** | | | | | | | | |
| **Article** | **Journal** | **Exposure** | **Outcome** | **Spatial & temporal levels** | **Modeling approach** | **FEs** | **Covariates** | **Main findings** |
| Wang et al. 2016 | Environmental Health Perspectives | Area-weighted PM2.5 from 1km2 initial grid | AC mortality | Census tract – year level, 2004-2009 | **Poisson regression with overdispersion** | Census tract and year | linear spline (df=1) | 3% (.2, 5.9%) increase in mortality per 2µg/m3 annual increase |
| Renzi et al. 201921 | Environmental Health Perspectives | Area-weighted PM10 from 1km2 initial grid | AC mortality for ages 35+ | 378 municipalities in Latium (IT) at the year level, 2006-2012 | **Conditional Poisson regression (based on Wang et al. 2016)** | District and year | Mean summer temp, mean winter temp, std. dev of summer temp, std. dev of winter temp | .8% (.2, 1.3%) increase in mortality per 1 µg/m3 annual increase |
| Yu et al. 202222 | PLOS Medicine | Wildfire smoke PM2.5 from .25 degree^2 initial grid | Cancer mortality (1,332,526 total deaths) | Municipality-level in Brazil at the year level, 2010-2016 | Quasi-Poisson regression | Municipality and year | Temperature, GDP | RR = 1.02 (1.01, 1.03) for all-cancer mortality per 1 µg/m3 annual increase |
| Fan et al. 202323 | Environmental Research | Pop-weighted PM2.5 from .01 degree^2 initial grid | Cancer mortality (947,337 total deaths) | 53 districts in Jiangsu Province at the year level, 1998-2013 | **Conditional Poisson regression (based on Wang et al. 2016)** | District and year | Air temp, relative humidity | 2.7% (2.0, 3.4%) increase in cancer mortality per 1 µg/m3 annual increase |
| Yu et al. 202024 | PLOS Medicine | Population-weighted PM2.5 from 1km2 initial grid | AC mortality (217,510 total deaths) | Postcode region (449 total) at the year level, 1990-2013 | **Conditional Poisson regression (based on Wang et al. 2016)** | Postcode and year | Mean summer and winter temp, sd of summer and winter temp; economic development | 2.02% (1.41, 2.63%) per 1µg/m3 annual PM2.5 increase |
| Leogrande et al. 201925 | Environmental International | Population-weighted exposure to industrial PM10 | Mortality in 11 areas in Taranto (IT) | Cohort-level, n=262,375 individuals | **Conditional Poisson regression (based on Wang et al. 2016)** | Year, area, age group | -- | 1.86% (-0.06, 3.83%) increase per 1µg/m3 industrial PM10 |
| Yu et al. 202227 | Environmental International | Population-weighted PM2.5 from initial .05 degree^2 grid | Loss of life expectancy | Municipalities in Brazil (5,565 total) at the year level, 2010-2018 | Conditional Poisson regression (based on Yu et al. 2020) | Municipality, year | mean summer and winter temps, and their SDs; GDP per capita | RR=1.18 (1.15, 1.21) for all-mortality for each 10µg/m3 increase in annual PM2.5 |
| Han et al. 202136 | Environmental International | Population-weighted PM2.5 from 11km2 grid | AC mortality | 2,869 counties in China, data from 2000 and 2010 censuses | **Conditional Poisson regression (based on Wang et al. 2016)** | Municipality, year | mean summer and winter temps, and their SDs (population weighted) | 3.8% (3.0-5.0) increase in ACM per 10µg/m3 annual PM2.5 increase |
| Nyadanu et al. 202228 | Atmospheric Pollution Research | Zonal statistics aggregation from .01 degree2 initial grid | Stillbirths (81,611 stillbirths out of 5,229,338 total births) | District level (260 districts in Ghana) at the year level, 2012-2019 | **Conditional Poisson regression (based on Wang et al. 2016)** | District and year | Temperature (same aggregation as PM2.5)--season-specific mean and SD values | RR = 1.03 (.97, 1.09) per 10µg/m3 annual avg all-source PM2.5 |