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RESEARCH SUBMISSIONS

Wildfire smoke exposure and emergency department visits for headache: A case-crossover analysis in California, 2006–2020

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Abstract

Objective: To evaluate the association of short-term exposure to overall fine particulate matter of <2.5 µm ($PM_{2.5}$) and wildfire-specific $PM_{2.5}$ with emergency department (ED) visits for headache.

Background: Studies have reported associations between $PM_{2.5}$ exposure and headache risk. As climate change drives longer and more intense wildfire seasons, wildfire $PM_{2.5}$ may contribute to more frequent headaches.

Methods: Our study included adult Californian members (aged ≥18 years) of a large de-identified commercial and Medicare Advantage claims database from 2006 to 2020. We identified ED visits for primary headache disorders (subtypes: tension-type headache, migraine headache, cluster headache, and "other" primary headache). Claims included member age, sex, and residential zip code. We linked daily overall and wildfire-specific $PM_{2.5}$ to residential zip code and conducted a time-stratified case-crossover analysis considering 7-day average $PM_{2.5}$ concentrations, first for primary headache disorders combined, and then by headache subtype.

Results: Among 9898 unique individuals we identified 13,623 ED encounters for primary headache disorders. Migraine was the most frequently diagnosed headache (N = 5534/13,623 [47.6%]) followed by "other" primary headache (N = 6489/13,623 [40.6%]). For all primary headache ED diagnoses, we observed an association of 7-day average wildfire $PM_{2.5}$ (odds ratio [OR] 1.17, 95% confidence interval [CI] 0.95–1.44 per 10 µg/m^3 increase) and by subtype we observed increased odds of ED visits associated with 7-day average wildfire $PM_{2.5}$ for tension-type headache (OR 1.42, 95% CI 0.91–2.22), "other" primary headache (OR 1.40, 95% CI 0.96–2.05), and cluster headache (OR 1.29, 95% CI 0.71–2.35), although these findings were not statistically significant under traditional null hypothesis testing. Overall $PM_{2.5}$ was associated with tension-type headache (OR 1.29, 95% CI 1.03–1.62), but not migraine, cluster, or "other" primary headaches.

Conclusions: Although imprecise, these results suggest short-term wildfire $PM_{2.5}$ exposure may be associated with ED visits for headache. Patients, healthcare providers,

Abbreviations: CI, confidence Interval; ED, emergency department; OR, odds ratio; $PM_{2.5}$, fine particulate matter of <2.5 µm.

and systems may need to respond to increased headache-related healthcare needs in the wake of wildfires and on poor air quality days.

KEYWORDS
case-crossover analysis, fine particulate matter of <2.5 µm ($PM_{2.5}$), headache, wildfires

INTRODUCTION

Anthropogenic climate change is expected to drive increasingly frequent and intense wildfires in the Western United States (US) with implications for population health.[1–3] In California, climate conditions conducive to wildfire that include high temperatures, changes in precipitation regimes, and accumulation of dried vegetation coinciding with strong downslope winds have produced historically destructive wildfire seasons.[2,4–6] The consequences of wildfires include increased carbon emissions, periods of degraded air quality due to smoke, and negative impacts on municipal budgets.[7] The total damages associated with the 2018 wildfire season alone were an estimated $149 billion.[8]

Smoke exposure from nearby wildfires is increasingly recognized as a health hazard. Fine particulate matter of <2.5 µm in diameter ($PM_{2.5}$) is the primary air pollutant of concern,[9,10] with wildfire-specific $PM_{2.5}$ (hereafter "wildfire $PM_{2.5}$") potentially more health harmful than $PM_{2.5}$ from fossil fuel combustion (e.g., traffic). Wildfire $PM_{2.5}$ may result in worse health outcomes because the chemical compositions tend to have higher concentrations of oxidative and pro-inflammatory compounds.[10–13] Exposure to wildfire $PM_{2.5}$ has previously been associated with wide-ranging health outcomes including all-cause mortality[14–16]; respiratory events[17]; risk of hospitalization among those with cardiovascular disease[18–20]; and increased risk of low birth weight and preterm birth.[21,22] Although short-term exposure to high levels of $PM_{2.5}$ (from all sources) has previously been associated with increased risk of emergency department (ED) visits for headache including migraine,[23–27] we know of no studies that consider whether wildfire $PM_{2.5}$ exposure is associated with any headache-related outcomes. Primary headache disorders are extremely prevalent[28] and associated with an estimated annual cost of up to $16.6 billion in lost productivity, work and school absences, and short-term disability for migraine alone.[29–32] Identification of potential triggers or exacerbating factors for headache such as wildfire $PM_{2.5}$ could therefore have implications for both patients and clinical practice.

Motivated by recent intensification of wildfires in the Western US and the profound societal burden associated with headache, we examined, for the first time, the association between short-term exposure to wildfire $PM_{2.5}$ and ED visits for primary headache disorder in California. Our case-crossover analysis leverages a unique administrative database comprised of healthcare claims for privately insured Californians followed from 2006 to 2020 and separately considers exposure to wildfire and overall $PM_{2.5}$ levels estimated using ensemble machine learning models. We hypothesized a priori that exposure to wildfire $PM_{2.5}$ would be associated with increased risk of ED visits for primary headache disorders, and that the association would be stronger for wildfire versus overall $PM_{2.5}$.

METHODS

The Optum Clinformatics® Data Mart Database is a large, de-identified commercial and Medicare Advantage claims database. Patient-level commercial claims data linked to patient residential zip code are available from January 1, 2006, through December 31, 2020. Member enrollment data; diagnostic codes from outpatient, ED, and inpatient visits; and pharmacy claims are deterministically linked across file types with a unique patient identifier.

Using these data, we conducted a case-crossover analysis[33–35] to examine the association of wildfire and overall $PM_{2.5}$ concentration with ED visits for primary headache (i.e., headaches not caused by another disease or injury) in California. Because individuals serve as their own controls in case-crossover analysis, this approach eliminates confounding by time-invariant individual- and area-level confounders and is therefore well-suited to the study of short-term effects of environmental exposures.[36–38] Individuals eligible for the present study were aged ≥18 years at the time of their ED visit, resided in California, and had at least one headache-related healthcare encounter within the study period. The sample size for this analysis was determined based on the available data, and thus no power calculation was conducted. There were no missing data. This study was approved by the Institutional Review Boards at Stanford University (Protocol #40974) and the University of Pennsylvania (Protocol #850741). Requirement for written informed consent was waived for this study.

Emergency department visits for primary headache

The primary outcome of interest for this analysis was an ED visit for primary headache identified using diagnostic codes from the *International Classification of Diseases*, *Ninth Revision* (ICD-9) and the *Tenth Revision* (ICD-10). We limited our analysis to ED visits with headache-associated diagnoses in the first, second, or third diagnostic position. Visits for primary headache were a priori further subclassified as related to tension-type headache, migraine headache, cluster headache, and "other" primary headache (Table S1) given differences in clinical severity, treatment, and risk factors.

Fine particulate matter concentrations

First, daily average concentrations of overall $PM_{2.5}$ were estimated for each California zip code with ensemble models that integrated multiple machine learning algorithms (including random forest, gradient boosting, and deep learning) and predictor variables including outdoor $PM_{2.5}$ measurements from the Environmental Protection Agency Air Quality System (AQS), aerosol optical depth, plume height, and meteorological variables (precipitation, minimum and maximum temperature, surface shortwave radiation, specific humidity, wind speed and direction) extracted from the high-resolution Gridded Surface Meteorological dataset (gridMET).[39]

Second, daily measures of wildfire $PM_{2.5}$ for each zip code were estimated using a spatio-temporal multiple imputation approach. Briefly, $PM_{2.5}$ concentrations attributable to wildfire smoke were estimated for zip-code-days identified by comparing the observed $PM_{2.5}$ values to estimated counterfactual values in the absence of wildfire smoke. The wildfire $PM_{2.5}$ ensemble model achieved high accuracy ($R^2 = 0.86$, root mean square error [RMSE] = 3.48); for additional details, see Aguilera et al. 2021.[40] Using daily, zip code-level estimates of exposure, we calculated the average concentrations of wildfire $PM_{2.5}$ and overall $PM_{2.5}$ in the 7-day window prior to each case and control date based on participant residential zip code.

Covariates

Additional patient-level demographic characteristics derived from insurance eligibility files included sex (female or male), age category (18–34; 34–54; 55–64; ≥65 years), and calendar year of ED visit. We additionally assigned season for all headache-related visits (winter: December–February; spring: March–May; summer: June–August; fall: September–November).

Statistical analysis

We first calculated the number and percentage of all ED visits for primary headache disorders that occurred by sex, age category, and across headache subtypes. We conducted a time-stratified case-crossover analysis to estimate the association of 7-day average $PM_{2.5}$ concentrations with ED visits for primary headache. For each ED visit, we selected up to four control dates matched on day of week, month, and calendar year to account for secular trends and seasonality. We used conditional logistic regression analysis in which the unit of analysis is the matched set of ED visits and control dates.

The case-crossover design has five major assumptions for exchangeability between case and control periods: (i) variation in exposure over time; (ii) no selection bias; (iii) exchangeability of risk of exposure; (iv) exposure assessment accuracy is independent of case status; and (v) transient effect.[41] Our study satisfies nearly all these assumptions. First, we observed variation of $PM_{2.5}$ concentrations over time. Second, patient data was derived from ED encounters and inclusion was not predicated on air pollution levels. Third, area-level wildfire and overall $PM_{2.5}$ concentrations are not impacted by individual headache cases and our time-stratified control selection process has been shown to maximize exchangeability for air pollution and weather exposures.[42] Similarly, we estimated $PM_{2.5}$ concentrations using a validated approach that is independent of any case status. Finally, although research on the effects of wildfire $PM_{2.5}$ and headache remain limited, previous assessments suggest most health effects occur within the week following the exposure.[43,44]

We estimated odds ratios (ORs) for the associations of wildfire $PM_{2.5}$ and overall $PM_{2.5}$ by comparing concentrations in the 7-day period preceding ED visit dates versus control dates.

Our interpretation of study results extends beyond consideration of statistical significance alone to include the width of the 95% confidence intervals (CIs) and the range of values included therein, the magnitude of estimated ORs, and occurs within the context of previously published scientific research on headache and the environment. Main exposure variables re-scaled such that ORs corresponded to a $10\,\mu g/m^3$ increase in the concentration of $PM_{2.5}$. For context, the United States Environmental Protection Agency (EPA) has established a 24-h national air quality standard for fine particle of $35\,\mu g/m^3$[45] and a $10\,\mu g/m^3$ increase in daily total $PM_{2.5}$ has been associated with ~1% increase in all-cause mortality.[46] We first estimated the association with all primary headache diagnoses combined, and then separately for tension-type headache, migraine headache, cluster headache, and "other" primary headache. We fitted conditional logistic regression models to plot the predicted odds of ED visits for all primary headaches as a function of $PM_{2.5}$ concentrations.

Secondary analyses

As headache risk and severity differs within populations by age and sex, we additionally conducted analyses within these subgroups.[47–50] For subgroup analyses, we conducted Cochran's *Q* test for heterogeneity to ascertain whether subgroup results differed from overall estimates.[51] Cochran's *Q* is a two-sided pairwise multiple comparison test with threshold for significance of $p < 0.05$. Finally, because wildfire activity in California is concentrated in the fall, we estimated the associations of wildfire $PM_{2.5}$ and overall $PM_{2.5}$ with ED visits for primary headache restricted to visits that occurred in September, October, and November.

Sensitivity analyses

We considered alternative windows for $PM_{2.5}$ exposure and repeated our analysis to average 7-day $PM_{2.5}$ concentration of $\leq 50\,\mu g/m^3$ to examine whether the dose–response and overall findings persisted after excluding the highest concentrations of $PM_{2.5}$. In additional sensitivity analyses, we further identified outpatient visits and inpatient hospitalizations for primary headache disorders.

As outpatient visits are often scheduled in advance and because inpatient hospitalizations for primary headache are rare, we did not expect them to be associated with $PM_{2.5}$ concentrations. We therefore conducted a negative outcome control analysis in which we examined the association of wildfire $PM_{2.5}$ and overall $PM_{2.5}$ concentrations with outpatient visits and inpatient hospitalizations for primary headache.[52,53]

All statistical analyses were conducted using R statistical software version 3.5.6 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Among 9898 unique individuals in California aged ≥18 years, we identified 13,623 unique ED encounters for primary headache disorders for which we selected 48,017 control dates matched on weekday, month, and calendar year. Most ED visits occurred among patients who were male (76.3%) and 40.5% were aged between 35 and 54 years. Migraine was the most frequently diagnosed headache (47.6%) followed by "other" primary headache (40.6%), whereas tension-type headache (10.4%) and cluster headache (1.3%) comprised the minority of diagnoses (Table 1). The average concentrations of wildfire $PM_{2.5}$ and overall $PM_{2.5}$ by zip code are depicted in Figure 1.

In our analysis of wildfire $PM_{2.5}$ and all primary headache, we estimated that odds of an ED visit increased by 17% for every 10 $\mu g/m^3$ increase in the 7-day average concentration (OR 1.17, 95% CI 0.95–1.44) (Figure 2, Table S2). By subtype, we observed positive associations between wildfire $PM_{2.5}$ and ED encounters for tension-type headache (OR 1.42, 95% CI 0.91–2.22), "other" primary headache (OR 1.40, 95% CI 0.96–2.05), and cluster headache (OR 1.29, 95% CI 0.71–2.35), although the estimated association for cluster headache was imprecise due to its relatively rare nature (~1% of all headache cases). We did not observe clear evidence for migraine headache (OR 1.07, 95% CI 0.83–1.37). In our analysis of overall $PM_{2.5}$ and ED encounters for all primary headache, we observed no clear evidence of an association. In our analysis of headache subtypes, we did not observe any evidence of an association with ED encounters for migraine headache or cluster headache, but we did observe a weak, positive association with "other" primary headache (OR 1.09, 95% CI 0.96–1.24) and a stronger association with tension-type headache (OR 1.29, 95% CI 1.03–1.62) (Figure 2, Table S2). Many of the associations estimated were imprecise, as evidenced by wide CIs.

Figure 3 depicts the predicted odds of an ED visit for primary headache as a function of wildfire and overall $PM_{2.5}$ concentration. For both wildfire and overall $PM_{2.5}$, the odds of an ED visit increase with rising 7-day average concentrations with consistently higher predicted odds for wildfire $PM_{2.5}$ versus overall $PM_{2.5}$, but with wider CIs.

TABLE 1 Emergency department encounters for primary headache disorders in California.

Variable	*N* (%)
Total	13,623 (100.0)
Sex	
Male	10,395 (76.3)
Female	3228 (23.7)
Age category, years	
18–34	3272 (24.0)
35–54	5522 (40.5)
55–64	1648 (12.1)
≥65	3181 (23.4)
Headache type	
Tension type headache	1418 (10.4)
Migraine headache	5534 (47.6)
Cluster headache	182 (1.3)
"Other" primary headache	6489 (40.6)

Secondary analyses

In subgroup analyses, we did not observe meaningful differences between men and women (Cochrane's $Q = 0.86$, $p = 0.36$) (Table S3). By age category, we observed the strongest association between wildfire $PM_{2.5}$ and headache among patients aged 18–34 years (OR 1.13, 95% CI 0.80–1.58) and the strongest association between overall $PM_{2.5}$ and headache among those aged ≥65 years (OR 1.18, 95% CI 0.99–1.40; Cochran's $Q = 354.69$, $p < 0.01$) (Table S4). In analysis restricted to ED visits that occurred in the fall, associations were generally increased in magnitude for all primary headache and subtype groups in our analysis of both wildfire $PM_{2.5}$ and overall $PM_{2.5}$. (Table S5).

Sensitivity analyses

In sensitivity analysis of alternative exposure windows ranging from same-day to 7-day average, we observed increasing strength of association with increased length of exposure window (Table S6). Analysis with values of $PM_{2.5}$ restricted to concentrations of ≤50 $\mu g/m^3$ were consistent with those of our main analysis (Table S7). Finally, in our negative outcome control analysis we observed reduced odds of inpatient hospitalizations for primary headache associated with a 10 $\mu g/m^3$ increase in 7-day average wildfire $PM_{2.5}$ (OR 0.97, 95% CI 0.96–0.98) and no relation with outpatient visits (OR 0.98, 95% CI 0.90–1.08). For overall $PM_{2.5}$ we observed no evidence of an association with inpatient hospitalizations but reduced odds of outpatient visits (OR 0.98, 95% CI 0.97–0.99) for primary headache (Table S8).

DISCUSSION

In this case-crossover study, we present a novel analysis of the association between short-term exposure to wildfire $PM_{2.5}$ and

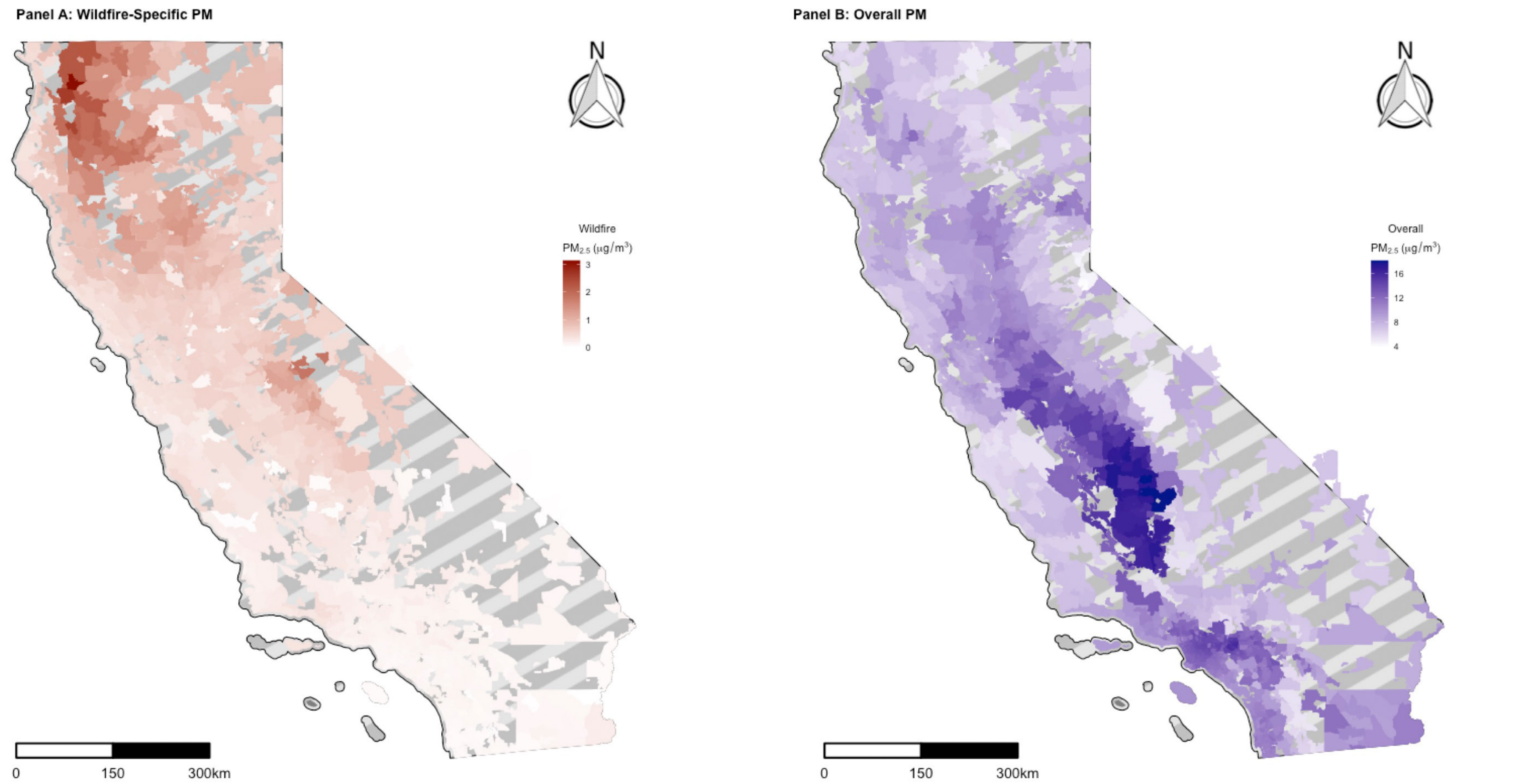

FIGURE 1 Average concentrations of wildfire-specific fine particulate matter of <2.5 μm ($PM_{2.5}$) (A) and overall $PM_{2.5}$ (B) in California by zip code from January 1, 2006, to December 31, 2020.

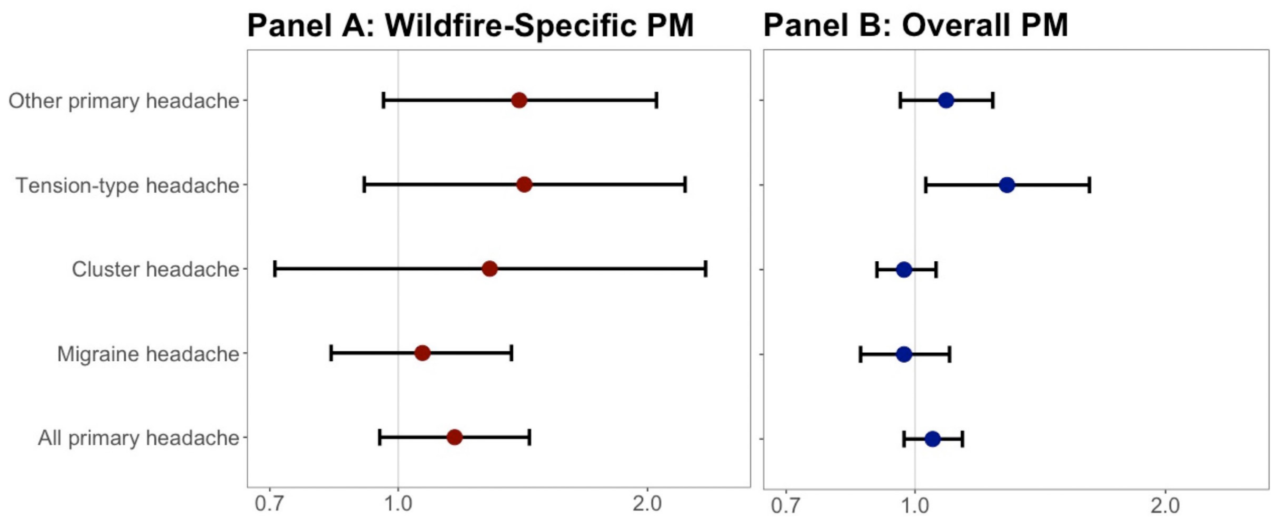

FIGURE 2 Association of wildfire-specific $PM_{2.5}$ and overall $PM_{2.5}$ with emergency department (ED) visits for primary headache. We used conditional logistic regression to estimate the association of 7-day average wildfire-specific fine particulate matter of <2.5 µm ($PM_{2.5}$) concentration (A) and overall $PM_{2.5}$ concentration with whether an individual had an ED encounter for any primary headache disorder. We additionally considered associations for headache subtypes classified as migraine headache, cluster headache, tension-type headache, and "other" primary headache disorders. Odds ratios (ORs) were estimated using conditional logistic regression models, where the OR reflects the association for a 10 µg/m^3 increase in the 7-day average $PM_{2.5}$ concentration.

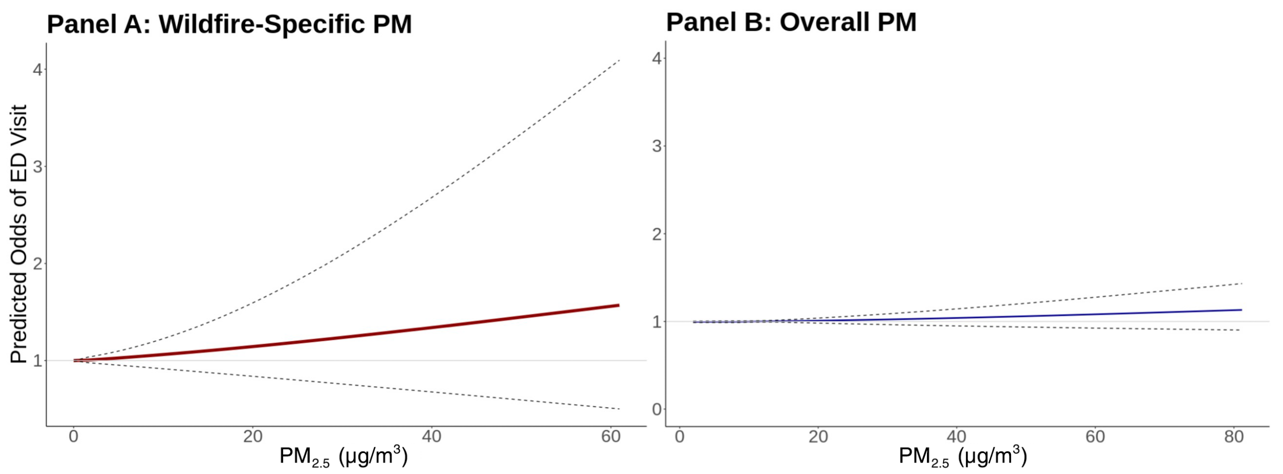

FIGURE 3 Predicted odds of emergency department (ED) visit as a function of the concentration of fine particulate matter of <2.5 µm ($PM_{2.5}$). The associations of 7-day average wildfire-specific $PM_{2.5}$ and overall $PM_{2.5}$ with ED visits for primary headache disorders were estimated separately using conditional logistic regression. Fitted conditional logistic regression models were then used to plot the predicted odds of ED visits for primary headaches a function of continuous wildfire-specific $PM_{2.5}$ (A) and overall $PM_{2.5}$ (B) in µg/m^3 with fitted values restricted below the 95th percentile of observed $PM_{2.5}$.

ED visits for headache in California. Many of the estimated associations we present do not reach the threshold for statistical significance as the 95% CI includes the null value. Our results may nevertheless provide evidence for an underlying relation between wildfire smoke exposure and ED visits for primary headache disorders. First, the estimated ORs deviate meaningfully from the null value,[54] particularly in the context of prior studies population health effects of environmental exposure in which associations are often modest in magnitude.[55–57] Second, we interpret our results in the context of some prior research that suggests common pollutants may trigger headache. Finally, we consider our results in the context of accumulating evidence that wildfire smoke exposure negatively affects a wide range of health outcomes.[58] Our findings thus provide preliminary evidence that short-term exposure to wildfire $PM_{2.5}$ may be associated with ED visits for primary headache disorders and points to the need for public health action to mitigate these exposures.

In our analysis, associations were stronger in magnitude for wildfire $PM_{2.5}$ versus overall $PM_{2.5}$ for primary headache disorders overall and generally across headache subtypes. Whereas background urban particulate matter is produced by fossil fuel combustion (e.g., traffic emissions), wildfire produces $PM_{2.5}$ through combustion of organic materials at substantially higher temperatures.[59] Particulate matter from wildfires has been previously demonstrated to contain more pro-inflammatory and oxidative compounds[10] and on average has smaller particle size.[60] These features may collectively increase the likelihood of headache exacerbation.[61] The composition of wildfire $PM_{2.5}$ also differs by ecoregion, and smoke from several wildfires can combine to produce distinct mixtures with possibly varying health impacts.[62–64]

We found an association between wildfire $PM_{2.5}$ and all primary headache, estimating that odds of an ED visit increased by 17% for every 10 μg/m^3 increase in the 7-day average concentration. Prior studies that examine the association between particulate matter generally and primary headache have showed mixed results. A study by Mukamal et al.[65] did not find clear association between ED encounter for headache and $PM_{2.5}$ levels in the days (0–2 days) prior. Vodonos et al.[66] found a slightly increased risk of ED headache visits with increased levels of PM_{10} on the same day in autumn (fall). A study by Özsaraç et al.[67] found an association between increased cumulative monthly number of ED visits for migraine and "other" primary headache disorders as the chief complaint and increased monthly mean levels of PM_{10}. Chiu et al.[68] found an association between short-term, average levels on the same and previous 2 days, exposure to air pollution including PM_{10} and clinic visits for headache.

Another study by Dales et al.[69] found an increased risk of headache hospitalizations from acute increases (24-h mean concentrations) in air pollution including $PM_{2.5}$ and PM_{10} in Santiago Province of Chile using optimal lags of 1 day for all relative risks. Chang et al.[70] found an increased risk of outpatient headache visits associated with days with higher $PM_{2.5}$ levels in Taipei, Taiwan. Using data from Edmonton, Canada ED visits from 1992 to 2002, Szyszkowicz et al.[24] found increased frequency of visits for general headache, as well as migraine, associated with exposure to increased concentrations of $PM_{2.5}$ lagged by 0, 1, and 2 days only among female patients during the cold season (October–March). A study by Szyszkowicz and Kousha[71] from April 2004 to 2011 in nine cities in Ontario, Canada found an association between air pollutant levels, including $PM_{2.5}$, lagged by 0–8 days and the number of ED visits for headache, in addition to migraine, among females.

Prior studies of short-term $PM_{2.5}$ exposure have focused primarily on migraine. A second study by Szyszkowicz et al.[23] found an association between SO_2 and $PM_{2.5}$ levels, lagged by 2 days, and ED visits in a time-series analysis of ED visits across five cities in Canada. In their case-crossover analysis of data from Taipei, Taiwan from 2006 to 2011, Chen et al.[26] found that outpatient clinic visits for migraine were only associated with increased concentrations of $PM_{2.5}$ on warm days (i.e., mean daily temperature ≥23°C). Among 18,921 patients in Seoul who visited the ED with migraine as the primary complaint, Lee et al.[25] found each interquartile range increase in short-term $PM_{2.5}$ concentrations was associated with a 3% increase in ED visits for migraine. Finally, Elser et al.[72] found that annual average $PM_{2.5}$ concentrations were linearly associated with measures of migraine severity including outpatient neurology visits and migraine-specific urgent care visits among Sutter Health patients in Northern California from 2014 to 2018. Although notably Li et al.[73] did not find an association between particulate matter exposure and headache among 98 individuals in the Greater Boston area assessed via electronic survey from 2016 to 2017.

In contrast with some of this prior research, we found no clear evidence of an association between wildfire $PM_{2.5}$ and ED visits for migraine. One possible explanation is that wildfire $PM_{2.5}$ exposure does not precipitate migraine headache, although this is less likely given prior research that links pollution with migraine onset. Another potential explanation is that individuals with known migraine headache disorder can avoid being treated in the ED by taking prophylactic medications or at-home abortive therapies (i.e., non-steroidal anti-inflammatory drugs and triptans)[74] or by changing their behaviors such as by wearing an N95 mask or using air filtration systems. Finally, it is possible that migraine headache is frequently misclassified as "other" primary headache disorder.

Beyond migraine, our analysis considers multiple subtypes of primary headache. We observed an association between wildfire $PM_{2.5}$ exposure and ED encounter for tension-type and "other" primary headache. We also find an association between wildfire $PM_{2.5}$ exposure and ED visits for cluster headache. Cluster headache is typified by recurrent, unilateral pain that involves the orbital or periorbital region with associated lacrimation, rhinorrhea, conjunctival injection, ptosis or miosis, and periorbital edema.[75] Individual attacks are rapid in onset characterized by excruciating pain that typically last 15–180 min and tend to "cluster" together occurring as frequently as every other day for several weeks separated by periods of remission.[76,77]

Because of the severe nature of these headaches, management is focused primarily on pharmacological prevention, e.g., with calcium channel blocking agents (e.g., verapamil).[78] To our knowledge, no prior studies have assessed the association of short-term wildfire $PM_{2.5}$, or any air pollutant, with cluster headache. Although imprecise, our finding is potentially important given the severe and highly morbid nature of cluster headaches. While studying this outcome is complicated due to the long time-period over which the attacks can occur, if wildfire smoke is indeed associated with cluster headache, these individuals may therefore take extra care to mitigate their exposure to avoid subsequent attacks. More broadly, examination of the role of various environmental exposures in the onset of cluster headache including $PM_{2.5}$ may be an important area for future research.

LIMITATIONS

Data for this study were derived from a database of private and Medicare Advantage claims. Our results therefore do not reflect the experiences of the poorest Californians. Yet, headache follows a social gradient and is less common among wealthier individuals.[79,80] Similarly, wildfires may disproportionally affect vulnerable populations including indigenous and migrant populations, older and low-income individuals.[3,81,82] Further examination of the implications of wildfires for headache that specifically considers potential modifications by individual, and community-level social class and material resources is needed. Although such individual- and area-level covariates were not available in these data, we control for any confounding by time-invariant characteristics with the case-crossover design because individuals serve as their own controls.

In the setting of wildfires, $PM_{2.5}$ co-occurs with several other toxicants. Additionally, major wildfire events may stoke significant anxiety and fear among residents.[83,84] It is therefore possible that the associations presented here reflect some combination of these factors rather than the effects of $PM_{2.5}$ alone. These data did not include measures of factors such as time spent indoors, housing quality and infiltration of smoke, or whether the individual commuted to work outside of their residential zip code, all of which could confound the association between wildfire smoke exposure and headache. In the present study, confounding by these factors should be minimized by the case-crossover design in which control periods are matched to dates of ED visits on weekday, month, and calendar year within an individual. Further, we assigned $PM_{2.5}$ exposure metrics at the patient residential zip code level based on data availability. This method assumes constant $PM_{2.5}$ concentrations within zip codes, while heterogeneity may in fact exist. Future studies could improve on our design by using address-level healthcare and patient-level mobility data to reduce exposure misclassification. Our study lacked sufficient statistical power to examine heterogeneity in the association between wildfire $PM_{2.5}$ and headache-related ED visits by sex and age group. As previously mentioned, the estimated association between wildfire $PM_{2.5}$ and ED visits for cluster headache was also imprecise, likely due to the relatively rare nature of this headache disorder. Because most outpatient visits are scheduled in advance, we considered outpatient visits for primary headache disorders as a negative outcome control. However, some percentage of outpatient visits are comprised of urgent care and same-day appointments, which could plausibly be expected to occur more frequently among symptomatic individuals in response to wildfire smoke exposure.

Finally, we know of no studies that have validated ED claims for primary headache disorders, and thus the outcome measure is potentially subject to misclassification particularly across subtypes of primary headache disorders. However, we have no reason to suspect this misclassification varies systematically based on levels of $PM_{2.5}$. Moreover, ED visits capture only the subset of individuals experiencing headache severe enough that it prompts treatment seeking in the acute care setting. Our outcome measure is meaningful insofar as it reflects the immediate headache-related burden imposed on local healthcare systems by wildfire $PM_{2.5}$. However, there is an important role for future research that considers implication of wildfire for headache wherever more sensitive measures of headache, such as self-report, are available.

CONCLUSION

This case-crossover study presents a novel analysis of the association between exposure to wildfire $PM_{2.5}$ exposure and ED visits for primary headache disorders in California, where anthropogenic climate change, fire management practices, and population shifts have produced historically devastating wildfires in the recent past. Our findings provide the first preliminary evidence that short-term exposure to wildfire $PM_{2.5}$ may be associated with ED visits for primary headache disorders. Providers and healthcare systems may need to respond to increased headache-related healthcare needs. Individuals with headache may need to avoid going outdoors in the wake of wildfires and on poor air quality days.

AUTHOR CONTRIBUTIONS

Study concept and design: Holly Elser, Sebastian T. Rowland, Joan A. Casey, Maksym S. Marek, Andrea L. C. Schneider. *Acquisition of data*: Holly Elser, Mathew V. Kiang, Tarik Benmarhnia. *Analysis and interpretation of data*: Holly Elser, Sebastian T. Rowland, Joan A. Casey. *Drafting of the manuscript*: Holly Elser, Sebastian T. Rowland, Joan A. Casey, Brittany Shea, Vivian Do. *Revising it for intellectual content*: Holly Elser, Sebastian T. Rowland, Maksym S. Marek, Mathew V. Kiang, Brittany Shea, Vivian Do, Tarik Benmarhnia, Andrea L. C. Schneider, Joan A. Casey. *Final approval of the completed manuscript*: Holly Elser, Sebastian T. Rowland, Maksym S. Marek, Mathew V. Kiang, Brittany Shea, Vivian Do, Tarik Benmarhnia, Andrea L. C. Schneider, Joan A. Casey.

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CONFLICTS OF INTEREST

Holly Elser, Sebastian T. Rowland, Maksym S. Marek, Mathew V. Kiang, Brittany Shea, Vivian Do, Tarik Benmarhnia, Andrea L.C. Schneider, and **Joan A. Casey** declare no conflicts of interest.

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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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