PUBLIC HEALTH

Exploring spatial heterogeneity in synergistic effects of compound climate hazards: Extreme heat and wildfire smoke on cardiorespiratory hospitalizations in California

Chen Chen[1]*, Lara Schwarz[2,3], Noam Rosenthal[4], Miriam E. Marlier[4], Tarik Benmarhnia[1]

Extreme heat and wildfire smoke events are increasingly co-occurring in the context of climate change, especially in California. Extreme heat and wildfire smoke may have synergistic effects on population health that vary over space. We leveraged high-resolution satellite and monitoring data to quantify spatially varying compound exposures to extreme heat and wildfire smoke in California (2006–2019) at ZIP Code Tabulation Area (ZCTA) level. We found synergistic effects between extreme heat and wildfire smoke on daily cardiorespiratory hospitalizations at the state level. We also found spatial heterogeneity in such synergistic effects across ZCTAs. Communities with lower education attainment, lower health insurance coverage, lower income, lower proportion of automobile ownership, lower tree canopy coverage, higher population density, and higher proportions of racial/ethnic minorities experienced higher synergistic effects. This study highlights the need to incorporate compound hazards and environmental justice considerations into evidence-based policy development to protect populations from increasingly prevalent compound hazards.

INTRODUCTION

Global exposure to extreme heat and wildfires has grown in recent years and is expected to continue intensifying in the context of climate change (*1*–*7*). A small increase in global temperature can result in extreme local temperature (*8*, *9*). Hotter temperatures from a warming climate coupled with lower moisture from changes in precipitation regimes also produce drier conditions, intensifying the risk for larger wildfires (*9*, *10*). Wildfires and heat waves have increased in length, intensity, and size under climate change, particularly on the United States West Coast (*11*–*15*), with record-breaking events occurring frequently in recent years (*2*). As a result, populations have been increasingly exposed to co-occurring extreme heat and wildfire smoke (*16*).

Aside from increases in co-occurrence due to climate change, exposure to extreme heat and wildfire smoke both increase the risk of adverse health outcomes, including cardiovascular and respiratory complications. Extreme heat can lead to dehydration and vasodilation of blood vessels, which can produce heat stress and pressure the thermoregulatory process, increasing pulmonary and cardiac strain (*17*). It has been estimated that 0.36 million deaths globally were attributed to high temperatures (i.e., temperature higher than the local temperature associated with the lowest mortality rate) in 2019 (*18*). The inhalation of particulate matter from wildfire smoke can also produce oxidative stress and inflammation, which triggers cellular damage and increases the risk of cardiopulmonary disease (*19*). Global deaths attributable to fine particulate matter ($PM_{2.5}$) from smoke are estimated to be 340,000 to 680,000 per year (*20*, *21*). Because of the regularity of these concurrent exposures and their similar physiological impacts, these events may act synergistically to further aggravate health effects. Communities may be overburdened by these concomitant events, and developing adaptation strategies based on exposure information from both extreme heat and wildfire smoke can protect against these dual risks. However, most efforts to mitigate the adverse health impacts of extreme heat and wildfire smoke did not consider this potential synergistic effect. For example, existing early warning systems for wildfire smoke and extreme heat are issued separately by different government agencies in California. The local National Weather Service offices issue heat advisories in advance of forecast periods of high heat, while the local air quality management district sends out air quality warnings to promote behavior changes based on Air Quality Index created by the U.S. Environmental Protection Agency (EPA). If a synergistic effect existed between wildfire smoke and extreme heat, issuing a joint warning earlier considering the compound hazards would be beneficial. Besides, existing evaluation of climate-related health impacts generally estimates the influence of each climate hazard separately and ignores potential synergistic effects between climate hazards (*22*), which might underestimate the actual health burden and jeopardize the effectiveness of climate change adaptation plans.

Our understanding of the potential synergistic effects of wildfire smoke and extreme heat is limited. Previous studies have focused on compounded effects of extreme heat and ambient air pollution, while none directly explored compounded effects of extreme heat and wildfire smoke. Systematic reviews found evidence of synergistic effects for heat with $PM_{2.5}$ on all-cause mortality and respiratory and cardiovascular morbidity (*22*) and weak evidence of effect modification by $PM_{2.5}$ on heat-mortality association (*23*). However, compared to ambient $PM_{2.5}$ from other sources, $PM_{2.5}$ during wildfire events were more intense—often an order of magnitude larger than ambient $PM_{2.5}$ levels from other sources—and could produce distinct physiological responses and adaptive behaviors with or without concurrent extreme heat event (*24*). Previous epidemiological study also found higher impact on respiratory hospitalizations from exposure to wildfire $PM_{2.5}$ than exposure to ambient $PM_{2.5}$ from other

[1]Scripps Institution of Oceanography, University of California San Diego, La Jolla, CA, USA. [2]Herbert Wertheim School of Public Health and Longevity Science, University of California San Diego, La Jolla, CA, USA. [3]School of Public Health, San Diego State University, San Diego, CA, USA. [4]Department of Environmental Health Sciences, University of California Los Angeles, Los Angeles, CA, USA.
*Corresponding author. Email: chc048@ucsd.edu

sources (*25*). These differences warrant independent study of the synergistic effects between wildfire smoke and extreme heat.

Such compounded impacts may also have important environmental justice implications since community factors may modulate the synergistic effect of co-occurring climate hazards. Previous studies found spatial heterogeneity in health impacts associated with extreme heat events (*26*–*28*), wildfire smoke events (*29*, *30*), and effect modification of air pollution on health effects of extreme heat (*31*). Underprivileged communities have increased vulnerability to wildfire smoke (*32*, *33*) and extreme heat (*23*). We use the term vulnerability as defined by the National Institute of Environmental Health Sciences report, and such vulnerability could originate from a combination of socioeconomic, environmental and personal factors (*34*). In other words, the vulnerability could be driven by both exposure disparity and differential response. For example, communities with lower socioeconomic status might have lower financial capacity to guard themselves against climate hazards like wildfire smoke and extreme heat and thus experience higher exposures (*33*). Neighborhood-level risk factors such as crime, noise, and traffic can also lead to acute and chronic changes in the functioning of body systems and increase the effect of environmental exposures such as air pollution and heat in communities with lower socioeconomic status (*35*–*38*). Because of historical discriminative practices and structural racism, racially marginalized communities also have less adaptive capacity (e.g., lower housing quality and worse baseline health status) toward climate hazards, experiencing a 50% higher vulnerability to wildfires (*32*) and greater impacts from extreme heat (*23*, *39*). A recent review found strong evidence suggesting that climate change will likely disproportionately affect communities of color and exacerbate racial disparities in health (*39*). However, existing studies on synergistic health effects of air pollution and extreme heat usually estimate an overall measure at a regional or country level using time-series analysis or case-crossover design (*22*, *23*, *31*). No study has evaluated fine-scale spatial variability in the synergistic effects or explored what community-level sociodemographic characteristics are important to explain the differential synergistic effects. Identifying the local effects of these compounded climate hazards can be used to inform appropriate measures that account for the specific vulnerability of the community to reduce related health burdens. By exploring what community-level sociodemographics are important in explaining spatial differences in synergistic effects of two key climate hazards, we can highlight the need to incorporate environmental justice considerations into adaptation efforts toward climate change and promote health equity and provide evidence to aid decisions like siting clean air and cooling centers and targeted educational campaign.

As a highly diverse state that is heavily affected by extreme heat and wildfire smoke, California is a unique context to investigate this potential synergistic effect and explore whether the synergistic effect varies by community characteristics. The racial/ethnic composition of California is highly diverse—according to the 2020 census, Hispanics make up the largest racial/ethnic group (39%), which is followed by white (35%), Asian American (15%), and Black (5%) (*40*). Income inequality is a major concern, and California has one of the largest income gaps in the country; 20% of the state's net worth is concentrated in ZIP Code Tabulation Areas (ZCTAs) that are home to only 2% of the population (*41*). Furthermore, projections show that California will be one of the most climatologically risk-prone areas in the country in the next decades (*42*). Wildfires already account for 50% of total primary fine particulate matter emissions in California, and this percentage will only increase under climate change (*1*, *43*). Extreme heat exposure is also expected to increase, and projections show that the frequency of extreme temperatures will increase by 10-fold in many California regions (*44*). Approximately 68% of the state of California was exposed to both extreme heat and wildfire smoke particulate matter concurrently during the 2020 wildfire season, and these co-exposures are expected to continue increasing under climate change (*45*, *46*).

Here, we leveraged highly resolved satellite and monitoring environmental data to estimate compound exposures to extreme heat and wildfire smoke $PM_{2.5}$ from 2006 to 2019 in California. We estimated the individual and joint effect of these hazards on cardiorespiratory hospitalizations and evaluated whether synergistic effects exist in such compounded climate hazards. We estimated these effects for California overall and then used a spatiotemporal approach to explore heterogeneity in such synergistic effects at the ZCTA level. Last, we investigated the effect modification of the synergistic effects by community characteristics to highlight the environmental justice implications of these compounded impacts, which could support evidence-based mitigation and adaptation policy development.

RESULTS

We analyzed cardiorespiratory hospitalizations in the general population among 995 California ZCTAs (66.8% of California population) with populations larger than 1000 that experienced at least 1 day of extreme heat alone, wildfire smoke alone, or compound exposure to both hazards. For our main analyses, we choose the 85th percentile of historical summer daily maximum heat index as the threshold for extreme heat day and $\geq$15 μg/m^3 wildfire-specific $PM_{2.5}$ concentration as the threshold for wildfire smoke day a priori. These threshold values were adopted from health-based guidelines for daily $PM_{2.5}$ used by the World Health Organization (WHO) and heat wave definition used by the U.S. EPA (*47*, *48*).

From 2006 to 2019, we observed 206,302 (4.06% among all ZCTA-days) extreme heat alone ZCTA-days, 32,089 (0.63%) wildfire smoke alone ZCTA-days, and 5423 (0.11%) compound exposure ZCTA-days (Table 1). Although we included data for the entire year, most compound exposure days occurred between June and November (99.9% of all compound exposure days) (fig. S1A and table S1). Years with >1 day of compound exposure per ZCTA are 2008 (2.14 days) and 2017 (1.68 days) (fig. S1B and table S2). ZCTAs with higher numbers of compound exposure days were in the northern mountains and central valley, likely driven by the higher occurrence of wildfires in surrounding mountains (Fig. 1A). The northern mountain and central valley areas had more days with wildfire smoke alone during the study period than other regions (Fig. 1C). Since we defined extreme heat days using percentiles of historical summer daily maximum heat index from the year 1980 to the year 2005, the total number of days with extreme heat alone was different across ZCTAs and more days occurred in the coastal region and the southern desert (Fig. 1B). This could be a result of rapidly increasing temperatures during recent decades and consistently high temperatures coupled with a minimum cutoff value of 80°F and a maximum cutoff value of 105°F for the extreme heat definition. The ZCTA-specific threshold values for extreme heat were higher in the central valley and the southern desert (fig. S2A). Across all years and ZCTAs in the study, we observed 18,143,419 cardiorespiratory hospitalizations.

Table 1. List of climate hazard definitions explored in state-level estimates and the corresponding number of exposed ZCTA-days among 995 ZCTAs in California, 2006–2019. The extreme heat threshold is based on the percentile of the historical summer (July and August, 1980–2005) daily maximum heat index value. The wildfire smoke threshold is based on wildfire-specific $PM_{2.5}$ ($\mu g/m^3$).

Definition	Extreme heat threshold	Wildfire smoke threshold	# of ZCTA-days with exposure (%)		
			Extreme heat alone	Wildfire smoke alone	Compound
EH85_WF0	85th	>0	150,310 (2.95)	448,190 (8.81)	61,415 (1.21)
EH85_WF5	85th	5	194,161 (3.82)	116,128 (2.28)	17,564 (0.35)
EH85_WF15	85th	15	206,302 (4.06)	32,089 (0.63)	5,423 (0.11)
EH85_WF35	85th	35	210,174 (4.13)	11,266 (0.22)	1,551 (0.03)
EH95_WF0	95th	>0	68,675 (1.35)	482,235 (9.48)	27,372 (0.54)
EH95_WF5	95th	5	88,258 (1.73)	125,903 (2.47)	7,789 (0.15)
EH95_WF15	95th	15	93,408 (1.84)	34,873 (0.69)	2,639 (0.05)
EH95_WF35	95th	35	95,272 (1.87)	12,042 (0.24)	775 (0.02)

We used relative excess risk due to interaction (RERI) to quantify the relative difference between the joint effect of two co-occurring hazards (extreme heat and wildfire smoke) and the sum of individual effects of the two hazards (*49*). When estimating statewide effect estimates using a time-stratified case-crossover design that did not consider spatial heterogeneity, we observed a RERI of 0.04 (95% CI, 0.01 to 0.06) for same-day exposure and hospitalization, suggesting a positive synergistic effect on the additive scale (Fig. 2A and table S3). In other words, we found a higher health impact due to interactions of wildfire smoke and extreme heat than the sum of health impacts from the individual hazards separately. As more stringent definitions were used for either hazard, there were fewer exposed ZCTA-days for each exposed category (Table 1), and RERI point estimates became higher with wider confidence intervals (CIs) (Fig. 2A and table S3). RERIs for previous-day exposure and hospitalization (lag 1) were similar (Fig. 2A and table S3). Although the synergistic effect on the additive scale (difference in effect estimates) is more relevant to public health than the synergistic effect on the multiplicative scale (ratio in effect estimates), we estimated the latter as a sensitivity analysis and found a similar pattern (fig. S3 and table S3). Besides, we observed odds ratios (ORs) of 1.01 (95% CI, 1.00 to 1.01), 1.03 (95% CI, 1.02 to 1.03), and 1.07 (95% CI, 1.05 to 1.09) for individual effects of extreme heat and wildfire smoke alone, and joint effect of combined exposure to both hazards, respectively (Fig. 2B and table S3). Similarly, ORs of individual and joint effects increased with definition stringency for both same-day and lag-1 metrics (Fig. 2B and table S3). ORs of previous-day exposure and hospitalization (lag 1) were similar for wildfire smoke and combined exposure but lower for extreme heat.

To allow the synergistic effect to vary across space, we used a within-community matched design (see details in Materials and Methods) to calculate ZCTA-specific rate ratios for individual and joint effects of extreme heat and wildfire smoke, as well as the corresponding ZCTA-specific RERIs. The ORs estimated by case-crossover design are equivalent to incidence rate ratios estimated by within-community matched design assuming appropriate control for confounders like seasonality, and the corresponding RERIs are also comparable. We failed to estimate RERI in four ZCTAs because no hospitalization was observed in selected control days of these ZCTAs, which is expected given the small population (<3500). To account for spatial autocorrelation, we leveraged spatial information across the remaining 991 ZCTAs with a spatial Bayesian hierarchical model (BHM) and calculated the post-pooling ZCTA-specific RERIs and noise-to-signal ratios (Fig. 3), which were of similar patterns as the pre-pooling estimates (fig. S4A). The median ZCTA-specific RERIs after incorporating the spatial information were 0.11 [interquartile range (IQR), −0.14 to 0.35], indicating positive synergistic effects between wildfire smoke and extreme heat among most ZCTAs in our study. We also observed strong spatial heterogeneity in ZCTA-specific RERIs, with positive synergistic effects in the northern mountain, central valley, and large coastal metropolitan areas such as Los Angeles and the Bay Area, and antagonistic effects in the northern coast (Fig. 3).

To explore how community characteristics might explain the observed heterogeneity in ZCTA-specific synergistic effects, we ran meta-regressions using 918 ZCTAs after removing ZCTAs with missing any community characteristics. Communities with lower synergistic effects had higher education attainment, higher health insurance coverage, higher income, higher proportion of automobile ownership, higher tree canopy coverage, and higher proportion of white residents (Fig. 4). On the other hand, we observed higher synergistic effects among communities with higher population density, and higher proportions of Black, Asian, Hispanic, American Indian or Alaska Native, and Native Hawaiian or Other Pacific Islander residents. Since air conditioning (AC) prevalence varies drastically across California due to the varied climate zones (fig. S5A), we evaluated the effect modification of AC prevalence on synergistic effects by climate zone and found lower synergistic effects among communities with higher AC prevalence in 10 of 15 climate zones (not enough data for estimation in Brawley), with exceptions for Eureka, San Jose, Santa Maria, Fresno, and LA Civic Center (fig. S5B).

To assess the robustness of our conclusions, we conducted extensive sensitivity analyses. First, we included all 1772 California ZCTAs in the statewide case-crossover analysis. The spatial distribution of compound exposure days is similar to the main analysis (fig. S6A), and so were the RERI estimates (table S3). Second, including non-wildfire smoke $PM_{2.5}$ in the conditional logistic model of the state-level analyses did not change the results for RERI, effect of wildfire smoke alone, or joint effect of both climate hazards (fig. S7). The effect of extreme heat decreased slightly after accounting for non-wildfire smoke $PM_{2.5}$, which might be due to the removal of the effect of

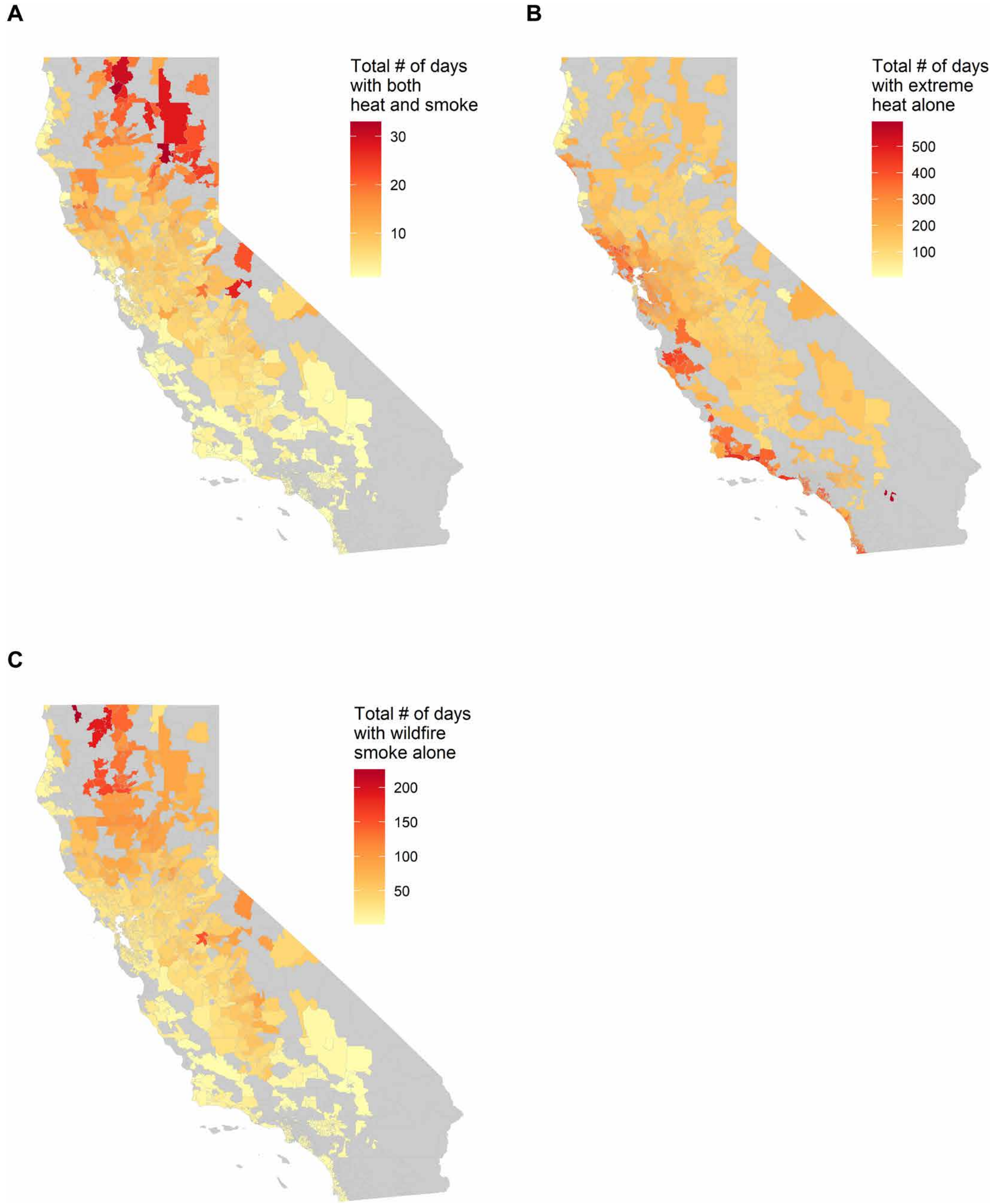

Fig. 1. Spatial distribution of the total number of exposed days in 995 California ZCTAs from 2006 to 2019 under the main analysis definition for climate hazards (85th percentile for extreme heat and 15 μg/m^3 for wildfire $PM_{2.5}$). (**A**) Compound exposure, (**B**) extreme heat alone, and (**C**) wildfire smoke alone. Gray color represents excluded ZCTA that has a population of ≤1000 or lacks any exposed day (extreme heat alone, wildfire smoke alone, or both).

extreme heat mediated through non-wildfire smoke $PM_{2.5}$ (*50*). Third, using three different control selection and estimation methods for the within-community matched designs to obtain ZCTA-specific estimates, we observed similar pre- and post-pooling synergistic effect estimates in spatial patterns in all matched designs explored (figs. S4 and S8). Inferences for effect modification of synergistic effects by community characteristics were also similar (fig. S9). Last, inferences remained the same for effect modification of synergistic effects by community characteristics under different analytical decisions: (i) using community characteristics based on averages of American Community Survey between 2011 and 2015, (ii) using Department of Housing and Urban Development (HUD) crosswalk to convert census tract data to ZCTA level for community characteristics, (iii) incorporating minimal prior knowledge into the spatial BHM, and (iv) ignoring potential spatial autocorrelation (fig. S10).

DISCUSSION

Using daily time-series dataset of compound exposures and cardiorespiratory hospitalizations for 995 ZCTAs in California from

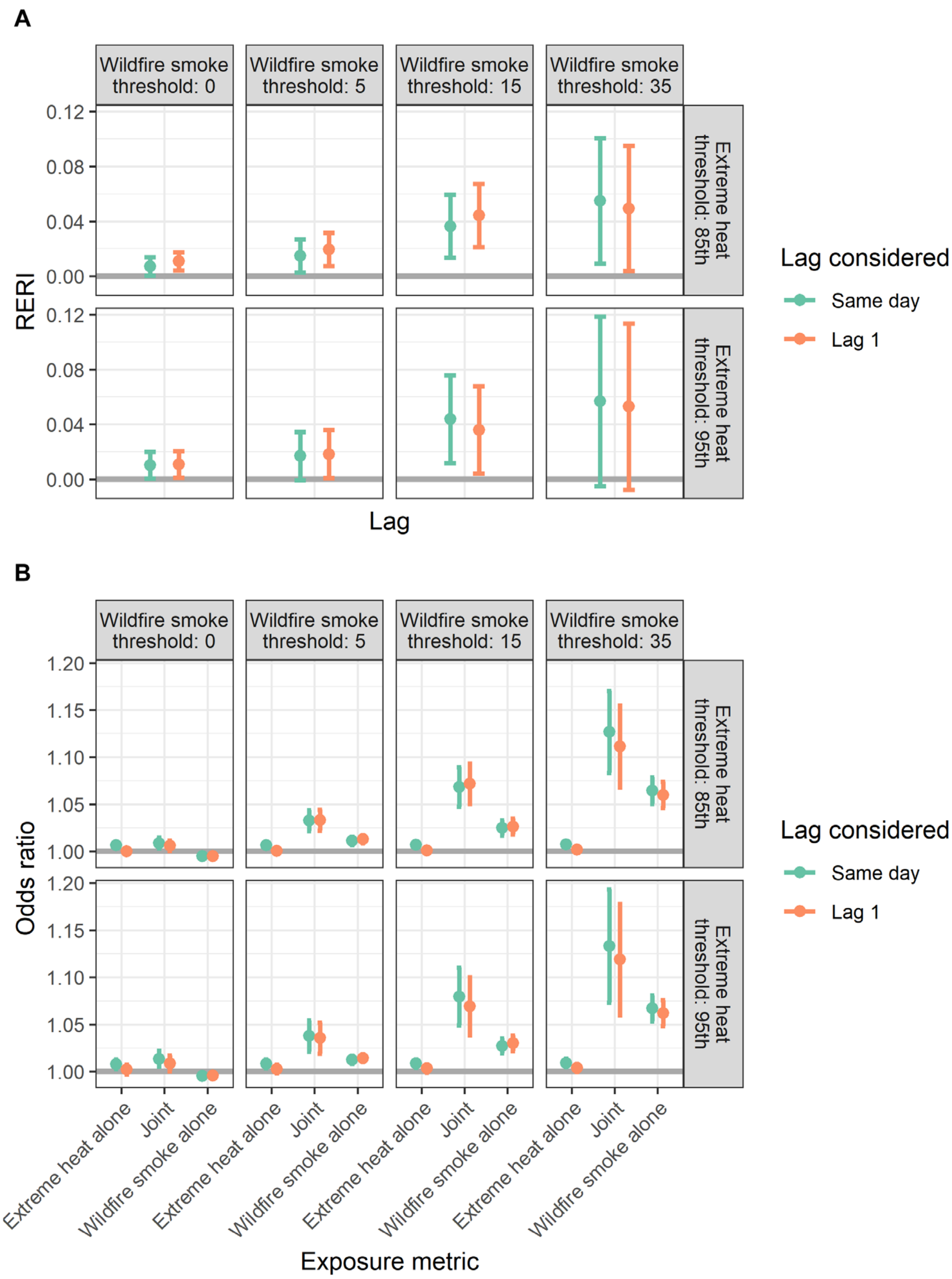

Fig. 2. State-level estimates by varying definitions of climate hazards. (**A**) Additive synergistic effect of wildfire smoke and extreme heat summarized in relative excess risk due to interaction (RERI). (**B**) Associations between risk of cardiorespiratory hospitalization and wildfire smoke alone, extreme heat alone, and joint of both climate hazards. Note: Numerical results are available in table S3.

2006 to 2019, we found evidence of synergistic effects between extreme heat and wildfire smoke at the state level. In other words, we observed a higher statewide joint effect when both hazards co-occur compared to the sum of individual effects of either hazard alone. Furthermore, using a within-community matched design and a spatial-temporal model, we also found that such synergistic effects vary spatially within California, with higher values in the northern mountains, central valley, and large coastal metropolitan areas. This spatial heterogeneity is correlated with socioeconomic and demographic characteristics; we observed higher synergistic effects in communities less affluent, more crowded, or with higher proportions of racial/ethnical minority residents. In 10 of 15 California climate zones, AC prevalence was negatively associated with the synergistic effect. Our results are robust to various climate hazard definitions and analytical methods. These results support the need to incorporate consideration of synergistic effects in evaluation of health impacts and development of action plans and adaptation efforts. Our results could also aid decision-making for targeted efforts in communities with higher vulnerability toward the synergistic effects.

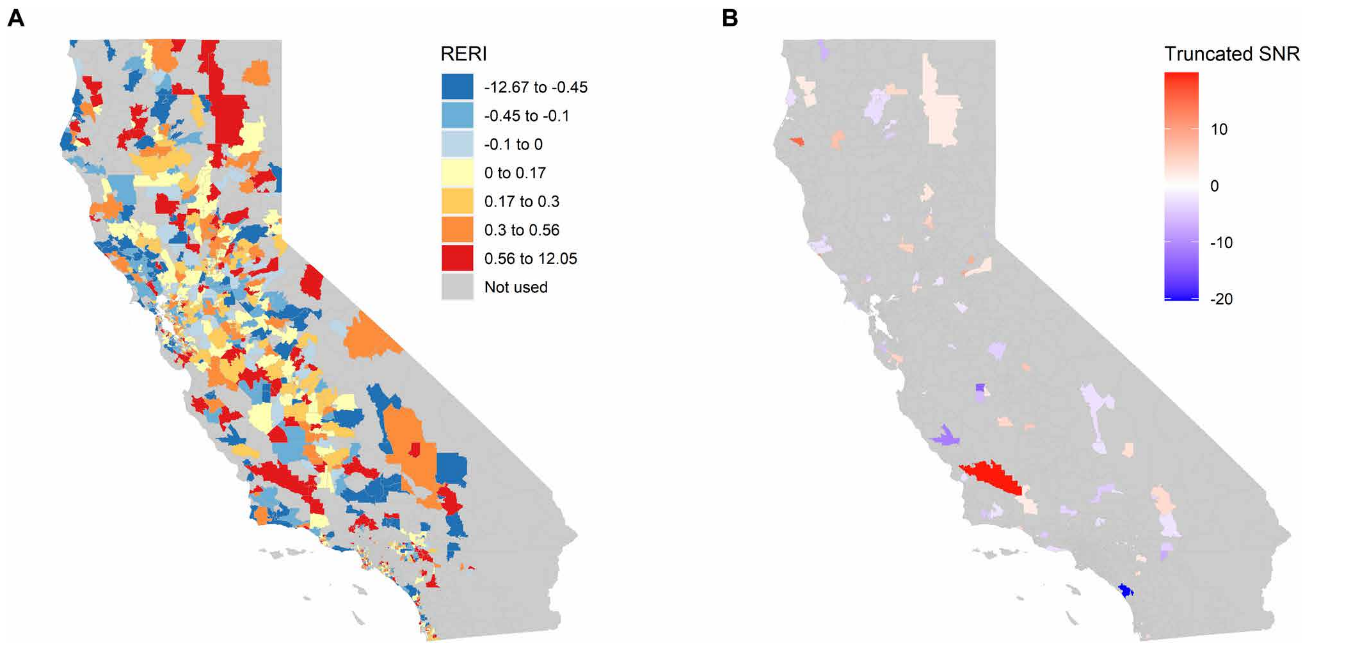

Fig. 3. Spatial distribution of ZCTA-level pooled additive synergistic effects of wildfire smoke and extreme heat. (**A**) Pooled RERI estimated using monthly weighting method under the main definition for climate hazards. (**B**) Corresponding signal-to-noise ratio (SNR) for the pooled estimates, which represents the significance of the effect estimates, with absolute values smaller than 2 marked as missing (gray). Note: Four ZCTAs were removed due to no hospitalization in control days and failure in the estimation of ZCTA-specific RERI. Color categories in (A) are based on septiles of the RERIs with minor adjustment to ensure that zero serves as one of the boundary values.

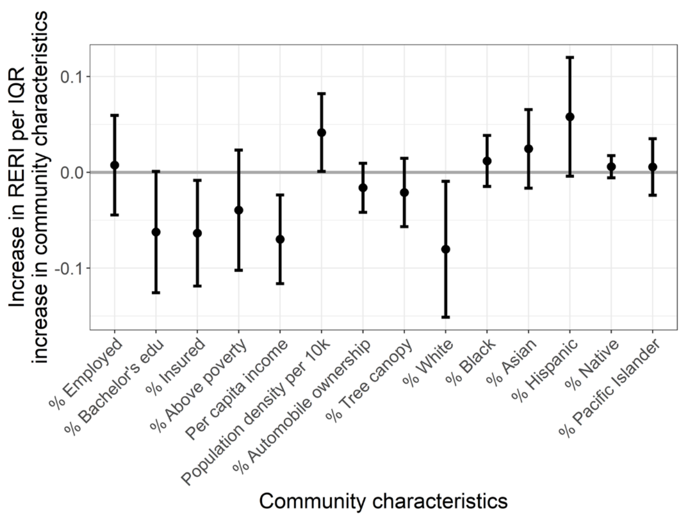

Fig. 4. Effect modification of community characteristics on the additive synergistic effect of wildfire smoke and extreme heat [increase in RERI per interquartile range (IQR) increase in community characteristics]. RERIs were estimated using monthly weighting method under the main definition for climate hazards.

Notably, we explicitly evaluated the synergistic effects of extreme heat and wildfire smoke events while exploring spatial heterogeneity and environmental justice implications of such impacts. Although we cannot directly compare with previous studies due to our unique focus on wildfire smoke instead of all-source $PM_{2.5}$, our findings are consistent with previous studies qualitatively. A systematic review found evidence supporting the synergistic effects of heat and air pollutants (ozone and particulate matter) on all-cause mortality, non-accidental mortality, and morbidity outcomes (*22*). Synergistic effects between air pollution and heat were further supported by recent studies, including a global study that found higher effects of extreme heat on cardiorespiratory mortality in areas with higher levels of PM_{10}, $PM_{2.5}$, O_3, and NO_2 (*31*), and a California study that found positive RERI between extreme $PM_{2.5}$ exposure and extreme heat for all-cause mortality (*51*).

Our finding that hospitalizations on days with concurrent extreme heat and wildfire smoke events exceeded the combined hospitalizations from days with either hazard alone motivates the consideration of compound climate hazards in public health planning. Although government agencies are becoming more aware of the increase in concurrent exposure to wildfire smoke and extreme heat, and some attempted to promote individual behavior changes specific to such compound exposure to mitigate adverse health impacts (*52*, *53*), a better understanding of the magnitude of the synergistic effect could promote more proactive top-down initiatives to protect public health. For example, the health impact of the compound exposure in days with wildfire $PM_{2.5}$ above 15 μg/m^3 (WHO 24-hour standard) is close to the health impact of the wildfire smoke alone in days with wildfire $PM_{2.5}$ above 35 μg/m^3 (U.S. EPA 24-hour standard). In other words, a joint early warning system using more stringent standards (e.g., 15 μg/m^3 instead of 35 μg/m^3) to account for the synergistic effect is needed to achieve the same level of protection using less stringent standards in days with single hazard when compound exposures exist.

We found spatial heterogeneity in the synergistic effects of extreme heat and wildfire smoke events across California, with higher synergistic effects in communities with lower education attainment, lower health insurance coverage, lower income, lower proportion of automobile ownership, lower tree canopy coverage, higher population density, and higher proportions of racial and ethnic minorities. This is consistent with vulnerable communities identified separately for wildfire and extreme heat in previous studies (*23*, *32*, *35*, *39*). These results confirmed spatial variations in the effects of extreme weather events and shed light on how to understand such heterogeneity and develop targeted interventions toward vulnerable subpopulations. For example, we observed higher synergistic effects in communities with higher proportions of racial/ethnic minority groups, who may be more vulnerable to the impacts of such compounded impacts due to the intersection with other social determinants of health such as lack of access to health care, lower financial capacity to protect themselves against exposure to the hazards, lower awareness of the compound hazards, or higher prevalence of comorbidities. On the other hand, the effect modification by AC prevalence varies across climate zones, with lower synergistic effects observed in communities with higher AC prevalence in 10 of 15 California climate zones. The counterintuitive positive effect modification by AC in the five climate zones could be due to behavior factors or other building infrastructure factors that affect infiltration of wildfire smoke or heat insulation (*33*). For example, Eureka and Santa Maria are coastal areas with mild climate and low AC prevalences (median of 0% and 11.8%, respectively), and extreme heat days there might have temperatures in the 80° to 90°F range, during which people might be less likely to use AC. Such uncertainties in the effect modification by community characteristics emphasized the ecological nature of this study and the importance to consider intersectionality of social characteristics at individual level in the future. Although uncertainty exists in the mechanism behind such vulnerability, updating existing heat action plans to incorporate considerations of wildfire smoke could still help mitigate the joint effects of compound hazards, such as implementing focused educational outreaches and establishing clean air and cooling centers near the most affected subpopulations.

There are a few limitations in this study that should be explored in future research. First, we identified wildfire smoke day using a threshold value for modeled daily wildfire-specific $PM_{2.5}$ concentrations. Since the emission, formation, and evolution of ozone and other pollutants are different from $PM_{2.5}$ in wildfire smoke (*54*, *55*), the co-occurrence of such components might also contribute to the spatial heterogeneity of individual effect of wildfire smoke and synergistic effects with other climate hazards. Future studies should consider such components to better understand their specific effects, but we focus on wildfire $PM_{2.5}$ in this study as it has been shown to be the most health relevant component of wildfire smoke. Second, being exposed to ambient air pollution or extreme heat for multiple consecutive days might lead to different health impacts than single-day compound exposure (i.e., excess effect from long heat waves or cumulative effect of air pollution) (*56*, *57*), which we did not consider in this study due to the limited size of our sample. Third, we focused on acute effects of extreme heat and wildfire smoke on unscheduled cardiorespiratory hospitalizations, while both hazards could have long-term health impacts or less clearly defined health outcomes like increased mental stress. Exploring the potential synergistic effects of both hazards on different time scales and mental health outcomes warrants future research. Fourth, although we accounted for seasonality and confounding from variables that are stable within 2 months by design in estimating ZCTA-specific synergistic effects, we could not rule out the possibility of residual confounding. However, consistent results from different control selections (e.g., yearly matching controlled for seasonality in outcomes more stringently than the monthly matching in the main analysis) and estimation methods (e.g., Poisson method assigned the same weights to all control days) alleviated this concern (fig. S9). Fifth, because the amplitude of RERI may be driven by both baseline risks and synergistic effects on the additive scale, we focused on qualitative interpretation of RERIs based on their direction and statistical precision. Future studies could explore other metrics for synergistic effects like risk difference due to additive interaction (*49*). Sixth, we were also constrained by aggregated data at ZCTA level and therefore can only investigate effect modifications by ZCTA-level community characteristics. Last, we assumed isotropy (i.e., same spatial relationships regardless of direction) in the spatial BHM due to methodological limitation, which might not hold in data with complex geographies and climates like California. For example, coastal marine-layer clouds could modulate extreme heat expression and synergistic effects of climate hazards in the coastal area (*58*). Two communities in the coastal area might be more similar in their synergistic effects than two communities of the same distance but located in the coastal area and inland area, respectively. However, by using relative thresholds for extreme heat, we account for some of these spatial differences by defining these exposure events as extreme days based on the temperature distribution at the ZCTA level. Future studies should aim to develop and apply more flexible spatial methods allowing anisotropy in explorations of climate hazards.

Extreme heat and wildfire smoke are both harmful exposures that are increasingly co-occurring in the context of climate change. As the number of compound exposure days increases, the synergistic effects between extreme heat and wildfire smoke identified in this study will become more important for accurate health burden estimation and should be incorporated in the development of the hazard warning system. For example, a joint warning system could offset the excess risk due to the synergistic effect by considering exposure to both climate hazards and issuing health warnings at lower air pollution levels when extreme heat co-occurs. Moreover, we found spatially varying synergistic effects between wildfire smoke and extreme heat on cardiorespiratory hospitalization and identified vulnerable communities to such effects in California. This finding highlights the need to incorporate environmental justice considerations into evidence-based mitigation and adaptation policy development, which could guide the siting of clean air and cooling centers and the implementation of focused educational outreaches.

MATERIALS AND METHODS

Data sources

We explored the synergistic effects of two climate-related hazards, extreme heat and wildfire smoke, in California using the case-crossover design and the within-community matched design for observational daily time-series data (*59*–*61*). We studied California ZCTAs from 2006 to 2019 that satisfied the following criteria: (i) having a population larger than 1000 in the 2010 U.S. decennial census (statistical power consideration) and (ii) having at least 1 day in each of the four exposure categories (necessary for obtaining ZCTA-specific effect estimates and applied in state-level analysis to ensure consistent population throughout this study). We chose the ZCTA as the spatial unit for analysis because health data were collected at ZIP code level. Since ZCTAs are areas created by the U.S. Census Bureau to represent populated areas of the ZIP code service routes, we only differentiated them when describing the data sources and used ZCTA in the rest of the article.

Health outcome

We identified the ZIP code–specific daily sum of unscheduled hospital visits and emergency department visits (referred to as non-prearranged hospitalizations in this article) by cause using the Patient Discharge Data and Emergency Department Data collected by the California Department of Health Care Access and Information (*62*). The ZIP code is based on the patients' residential address. We defined the cardiorespiratory hospitalization as either circulatory or respiratory hospitalization, based on primary diagnosis codes (see Supplementary Text for the list of codes included to identify the cause-specific hospitalizations). The ethics approval of this study was granted by the California Health and Human Services Agency's Committee for the Protection of Human Subjects (CPHS) (project number: 2021-116).

Climate hazards

We identified wildfire smoke ZCTA-days as days in which the daily wildfire-specific $PM_{2.5}$ concentration in the ZCTA is equal to or higher than a pre-specific threshold. We explored four threshold values: >0 μg/m^3, ≥5 μg/m^3 [2021 air quality guideline for annual $PM_{2.5}$ by WHO (*47*)], ≥15 μg/m^3 [2021 air quality guideline for 24-hour $PM_{2.5}$ by WHO (*47*)], and ≥35 μg/m^3 [National Ambient Air Quality Standard for 24-hour $PM_{2.5}$ by U.S. EPA (*63*)]. Although adverse health impacts were observed below such thresholds (*64*, *65*), maintaining $PM_{2.5}$ concentrations lower than these threshold values is considered sufficient to protect public health from a regulatory perspective and serves as a good starting point to dichotomize the wildfire-specific $PM_{2.5}$. Most local air quality management agencies also issue air quality warnings or promote "action days" if the standards were exceeded. In the main analysis, we will use the ≥15 μg/m^3 threshold to define the smoke ZCTA-day.

The daily time-series dataset of ZCTA-specific wildfire-specific $PM_{2.5}$ concentration was previously developed (*66*) and used in other epidemiological study (*67*). Briefly, Aguilera *et al.* (*66*) first estimated ZCTA-specific daily total $PM_{2.5}$ concentration from a stacked ensemble model using data from U.S. EPA's Air Quality System monitors, aerosol optical depth from NASA satellite measurements, smoke plume observations from the NOAA Hazard Mapping System, meteorological variables from the Gridded Meteorological (GRIDMET) reanalysis product, and other land-use variables from the National Land Cover Database. Next, they imputed non-wildfire–specific $PM_{2.5}$ concentration in ZCTA-days with wildfire smoke plume using chained random forest algorithm and $PM_{2.5}$ concentration in ZCTA-days without wildfire smoke plume. Last, they calculated wildfire-specific $PM_{2.5}$ concentration as the difference between the generated daily total $PM_{2.5}$ concentration and non-wildfire–specific $PM_{2.5}$ concentration in each ZCTA. The ensemble model for total $PM_{2.5}$ concentration had a prediction R^2 of 0.78 in the hold-out test set (*66*). Evaluations of randomly selected wildfire events also found the modeled wildfire-specific $PM_{2.5}$ concentrations reasonable in intensity and spatial distribution (*66*).

We identified extreme heat ZCTA-days as days in which the daily maximum heat index of the ZCTA is higher than a ZCTA-specific threshold. Following a modified definition of heat wave day used by the U.S. EPA (*48*), we defined the ZCTA-specific threshold as the 85th percentile of the summertime (July and August) daily maximum heat index from the year 1980 to the year 2005 in the ZCTA, which captured unusually hot days in each ZCTA and allowed adaptation and acclimation to local climates. In other words, this definition uses the local climate norms as reference and emphasizes the influence of climate change in recent decades by allowing ZCTAs with larger increases in heat index during the study period compared to the historical period to have more extreme heat days. We modified the EPA's definition by shortening the historical period from 1980–2010 to 1980–2005 to exclude years in our study period. When using different historical periods (1980–2010 and 1990–2005), the ZCTA-specific threshold values correlated well with the threshold value based on 1980–2005 (Spearman's correlation coefficients of 0.994 and 0.992) and demonstrated similar spatial patterns (fig. S2). Another modification is that we used the daily maximum heat index instead of apparent temperature as the threshold, which combines maximum absolute temperature and minimum relative humidity, proxies biological heat stress, and is of higher health relevance than absolute temperature (*68*, *69*). We obtained daily temperature and humidity from the GRIDMET reanalysis product at a 4-km resolution and assigned to each ZCTA values of the grid into which the ZCTA population-weighted centroid falls for the calculation (*70*). Since most heat index algorithms produce numerically similar results, we choose the National Weather Service's Weather Prediction Center's adaptation of the Rothfusz regression model for heat index calculation (*71*, *72*). To avoid implausible threshold values, we also replaced ZCTA-specific threshold values higher than 105°F or lower than 80°F with absolute cutoff values of 105°F or 80°F to define extreme heat days (*46*). Details and codes of the implementation of this algorithm in Google Earth Engine were reported elsewhere (*46*).

Combining designations of extreme heat ZCTA-day and wildfire smoke ZCTA-day, we categorized ZCTA-days within California into four types of ZCTA-days: extreme heat alone, wildfire smoke alone, compound exposure to both hazards, and no exposure to either hazard (control/unexposed). These exposure categories were used in selecting ZCTAs for the study and in ZCTA-level matched design to evaluate spatial heterogeneity in synergistic effects. We summarized spatial distribution and the total number for the three types of exposed days.

Community characteristics

To explore the effect modification of spatial heterogeneities in synergistic effects from extreme heat and wildfire smoke by community characteristics, we obtained ZCTA level community characteristics from the U.S. Decennial Census in 2010 (*73*) and the Healthy Places Index (HPI) report version 3.0 (*74*, *75*). All community characteristics were coded in a way that higher values indicate more affluent subpopulations or better environment except for population density and racial/ethnic compositions. Specifically, we included variables for race/ethnicity (proportion of non-Hispanic white, non-Hispanic Black, non-Hispanic Asian, Hispanic, non-Hispanic American Indian or Alaska Native, non-Hispanic Native Hawaiian, or Other Pacific Islander), employment (proportion of employment among those ages 20 to 64), education attainment (proportion of 25 and older with a bachelor degree or higher), health insurance coverage (proportion of insured among those aged 18 to 64), income (proportion of the population with an income that is greater than 200% of the federal poverty level and per capita income in U.S. dollars), population density per 10,000 population, assets and utilities (percentage of households with central AC or access to an automobile), and tree canopy coverage (population-weighted percentage of area with tree canopy). Most socioeconomic variables are based on the averages of the American Community Survey in 2015–2019 summarized by the HPI, while racial/ethnical variables are based on the Decennial Census survey in

2010. Details of all data sources are summarized in table S4. Since California has a highly varied climate with drastically different average temperatures, we also obtained the designation of ZCTAs into 16 climate zones in California from the Pacific Energy Center for stratified analysis (*76*).

Although the HPI provided community characteristics at ZCTA level, they did not provide details on their crosswalk from the census tract (the spatial unit where most survey data were measured) to the ZCTA (the spatial unit for our health outcome). As a sensitivity analysis, we calculated the ZCTA level community characteristics manually from census tract values except for population density, racial/ethnic compositions, and AC prevalence, which were available at ZCTA level from other data sources (see table S4). We downloaded the census tract–level HPI data for the relevant indicators (*75*), census tract population sizes from the U.S. Decennial Census in 2010 (*73*), and the HUD crosswalk file (*77*). Specifically, we calculated the ZCTA-level values as weighted averages of census tract–level values. The weight is the census tract population within the ZCTA, which was calculated as the product of the census tract population and the ratio of the census tract addresses that fall within the ZCTA. For automobile ownership, we created an ordinal variable with 10 categories based on deciles of ZCTA's automobile ownership percentile among census tracts within each ZCTA.

To explore the sensitivity of our results toward the time period used on community characteristics, we also used the HPI 2.0 dataset (*75*). The HPI 2.0 dataset is based on averages of the American Community Survey in 2011–2015 and Decennial Census survey in 2010. In analysis using the HPI 2.0 dataset, we used ZCTA-specific racial/ethnical variables provided instead of obtaining them from the Decennial Census survey. Besides, HPI 2.0 dataset lacks a few important variables included in HPI 3.0 dataset: per capital income, percentage of automobile ownership, and percentage insured.

Statistical analyses

In the main analysis, we used $\geq 15\ \mu g/m^3$ daily wildfire-specific $PM_{2.5}$ concentration as the threshold for wildfire smoke and 85th percentile historical daily maximum heat index as the threshold for extreme heat in the definition of hazards.

State-level case-crossover analysis

We first evaluated the synergistic effect of extreme heat and wildfire smoke on the risk of daily cardiorespiratory hospitalizations at the state level using the time-stratified case-crossover design and the metric RERI. The time-stratified case-crossover design is a widely used method in evaluating short-term health impacts of environmental hazards, which compared an individual's exposure in the day with an event to the individual's exposures in the same weekdays in other weeks of the month without the event to account for individual-level confounding and seasonality, and estimates OR using conditional logistic regression to account for the matching (*78*, *79*). The OR approximates the ratio of hospitalization risks among those exposed and not exposed because hospitalization is rare in the general population and an OR larger than one indicates an increase in the risk of hospitalization from exposure to environmental hazards. RERI quantifies the relative difference between the joint effect of two co-occurring hazards (extreme heat and wildfire smoke) and the sum of individual effects of the two hazards (*49*). A positive RERI value indicates an increase in risk due to interaction between the two hazards.

Specifically, for each ZCTA-day that had cardiorespiratory hospitalizations, we first identified controls as the same weekdays from other weeks of the same month and year in the same ZCTA. When multiple ZCTA-days in the same weekday of the same month and year experienced cardiorespiratory hospitalizations, we would create multiple matched sets with case as the day when the hospitalization occurred and weight equal to the number of deaths. Next, we applied conditional logistic models to estimate the statewide OR for the effect of extreme heat alone, wildfire smoke alone, and the combined exposure to both hazards on cardiorespiratory hospitalizations by including an interaction term between indicators for either hazard. The conditional logistic model accounted for the matching procedure by comparing the exposures of each matched case and control set and calculating a weighted average across all matched sets. The OR approximates the effect of the climate hazard (compound or individual) on the risk of hospitalization; in other words, an OR larger than one indicates a detrimental effect of the climate hazard (compound or individual) on the risk of hospitalization. Since this study design controls for individual-level covariates such as age, race, and sex, as well as time-varying covariates like season (*80*, *81*), we did not include covariates other than indicators for the hazards of interest and an interaction term between the two hazards. Effects of individual hazard alone (OR_{H0S1} and OR_{H1S0}) were exponentiated coefficients from the conditional logistic model, while the joint effect of both hazards (OR_{H1S1}), or effect of compound climate hazards, was calculated as the exponentiated sum of three coefficients (two for individual hazards and one for the interaction term) in the conditional logistic model. Since assessing interaction on the additive scale has been recommended as the appropriate scale to inform potential public health benefits of hypothetical interventions (*49*), we evaluated whether a synergistic effect exists between extreme wildfire smoke and heat on the additive scale using the RERI in our main analysis. We calculated the RERI as $(OR_{H1S1} - 1) - (OR_{H0S1} - 1) - (OR_{H1S0} - 1)$, where subscript H1 indicates days with extreme heat and S0 indicates days without wildfire smoke. We also assessed interaction on the multiplicative scale using the ratio of the OR (exponentiated coefficient for the interaction term) as a secondary analysis. We calculated the 95% CIs for RERI and the joint effect using the delta method (*49*). We used the "survival" for conditional logistic regression and the "msm" package for the delta method (*82*, *83*).

ZCTA-level matched design with spatial BHM

Since the state-level analysis assumed the same effect of extreme heat and wildfire smoke (individual, joint, or synergistic) across all ZCTAs while spatial heterogeneity might exist, we applied a modified version of the previously developed method that uses within-community matched design to estimate ZCTA-specific effects and spatial BHM to incorporate considerations of spatial autocorrelation (*61*). We chose the within-community matched design for ZCTA-specific estimates instead of the time-stratified case-crossover design used for state-level estimates because the number of days exposed to compound hazards is too low in many ZCTAs to efficiently use the latter (Fig. 1). Since the within-community matched design estimates rate ratios and the case-crossover design approximates rate ratios with ORs, the effect estimates and RERIs in both designs are comparable when confounding is properly controlled.

In the within-community matched design, we quantified the ZCTA-specific effects of the climate hazards on cardiorespiratory hospitalizations for each ZCTA separately. For each ZCTA, we first identified matched controls for three types of exposed days separately (extreme heat alone, wildfire smoke alone, and compound exposure to both hazards). For each exposed day, controls are days of the same year and ZCTA, not exposed to either hazard and within the window of 30 calendar days before or after the exposed day (*61*). To reduce the spillover effect from other exposed days and make the controls more representative of non-exposed day, we excluded days within 3 days of any exposed days (either extreme heat or wildfire smoke) from the potential controls (*84*, *85*). Next, we calculated the rate ratio for each exposed day as the ratio of hospitalization counts in the exposed day divided by the weighted average of the hospitalization counts in all selected control days, with weight equal to the inverse distance to the exposed day (i.e., 1/number of days to exposed day). Since this study design resembles a matched cohort design, we directly calculated the ZCTA-specific rate ratios for extreme heat alone (RR_{H1S0}), wildfire smoke alone (RR_{H0S1}), and combined exposure to both hazards (RR_{H1S1}) as the average rate ratios from all corresponding pairs of matched exposed days and control days in each ZCTA. We used the ratio of the hospitalization counts to approximate the rate ratio because the population size of a ZCTA is unlikely to change dramatically within 2 months. Last, we calculated the ZCTA-specific synergistic effects, RERI, as $(RR_{H1S1} - 1) - (RR_{H0S1} - 1) - (RR_{H1S0} - 1)$. This within-community matched design accounted for potential confounding that does not vary remarkably within 2 months by design (e.g., population composition regarding sex and age), while giving more weight to control days closer to the exposed day in calculation reduced the potential influence of seasonal trend. We removed ZCTAs from the next-step analysis if the estimation of individual or joint effects failed.

Since areas closer together are more likely to be exposed to the same wildfire smoke or extreme heat events, we expect the ZCTA-specific RERIs to be more similar among closer ZCTAs. To increase the precision of our ZCTA-specific estimates, we used a spatial BHM to leverage this spatial autocorrelation in our estimates. The theoretical development of this model was described elsewhere (*61*). On the basis of the empirical semivariogram, we selected the spherical shape for the covariance structure and specified starting values of the covariance structure as 2, 0.75, and 2 for sill, nugget, and range, respectively. We also specified the priors as inverse gamma distributions (2 for shape and 1/starting value for scale) for the sill and nugget, and uniform distribution (0.001 to 6) for the range; the tuning parameters are $^1/_{20}$ of the starting values. We used 10,000 Monte Carlo Markov chain samples with 75% burn-in to estimate parameters and sample weights in the spatial BHM. We recovered sample weights in the BHM to obtain pooled ZCTA-specific RERIs, which incorporated information from spatial autocorrelation into the pre-pooling ZCTA-specific RERIs. We also computed the signal-to-noise ratio (SNR) as the ratio between the mean of the recovered samples (either for the parameters or for the weights) and the corresponding SD of the recovered samples, representing the precision of the estimates. This method assumes isotropy (i.e., the same spatial relationship in all directions). We used the "spBayes" package in R for the spatial BHM (*86*).

Effect modification by community characteristics

To evaluate the potential effect modification of community characteristics on the synergistic effect, we ran meta-regressions of the pooled ZCTA-specific RERIs on each community characteristic selected separately. We reported results as the increase in RERI per IQR change in the community characteristics. For AC prevalence, we also evaluated the effect modification for each climate zone separately because AC prevalence varies dramatically across climate zones in California (fig. S5A). We conducted meta-regressions using the "meta" package (*87*).

Sensitivity analyses

Since we restricted our study to ZCTAs having at least 1 day in each of the four exposure categories to ensure population consistency throughout this study, we excluded some ZCTAs that could have contributed to the state-level effect estimates. To evaluate the robustness of our state-level estimates toward the inclusion of ZCTAs, we conducted the time-stratified case-crossover analysis using all California ZCTAs (1772) after removing two ZCTAs due to exposure data missingness (one for extreme heat and the other for wildfire smoke). We also explored seven combinations of hazard definitions other than the definition used in the main analysis (threshold of $>0\ \mu g/m^3$, $\geq 5\ \mu g/m^3$, $\geq 15\ \mu g/m^3$, and $\geq 35\ \mu g/m^3$ daily wildfire-specific $PM_{2.5}$ concentration for wildfire smoke; threshold of 85th and 95th percentiles of historical daily maximum heat index for extreme heat). Although it is unlikely that non-wildfire $PM_{2.5}$ would affect the probability of experiencing wildfire smoke or extreme heat (*50*), we might have created an association between wildfire $PM_{2.5}$ and non-wildfire $PM_{2.5}$ through the modeling process. Thus, we conducted sensitivity analyses by including non-wildfire $PM_{2.5}$ in the conditional logistic regression to estimate state-level effects in the case-crossover design. Last, we conducted the main analyses using the exposure of the previous day (lag1).

For ZCTA-specific RERIs, we explored three different within-community matched designs with varying assumptions (yearly weighting, monthly Poisson, and yearly Poisson) other than the within-community matched design described in the main analysis (monthly Poisson). The first part of the method name describes the control identification method, while the second part describes the estimation method. Specifically, in the "yearly" methods, we adopted the control identification method used by Liu *et al.* (*84*) studying wildfire smoke events. We identified matched controls for each exposed day as days of the same ZCTA, not exposed to either hazard and within the window of seven calendar days before or after the exposed day in a different year. This control identification method provides better control for seasonal trends by design than the "monthly" method used in the main analysis but might experience more inter-year confounding. For "yearly weighting," the calculation of the rate ratio is the same as the main analysis except that the unit for the distance between matched control and the exposed day is year instead of day. We also adopted a different rate ratio calculation method modified from Liu *et al.* (*84*), which takes a random sample of four controls from the matched controls of each exposed day and runs a Poisson regression of the count of hospitalization on an indicator of exposed among all matched pairs in each ZCTA ("Poisson"). Compared to the weighting method that gives more weight to days closer to the event, the Poisson method treats all matched controls equally. We leveraged spatial information into these estimations through the spatial BHM while restricting the analyses to ZCTAs that succeeded in all four matched designs and had a plausible RERI (<50). We also evaluated effect modification by community characteristics for all matched designs explored.

Last, we evaluated the robustness of the combination of our spatial BHM and effect modification evaluation method by conducting four analyses other than the main analysis: (i) we used ZCTA-level community characteristics obtained from the HPI 2.0 dataset in the meta-regression, which is mostly based on averages of American Community Survey in 2011 to 2015 but has fewer variables and ZCTAs with complete data than the HPI 3.0 dataset used in main analysis (HPI 2.0); (ii) we converted census tract community characteristics data to ZCTA level using the HUD crosswalk instead of using ZCTA-level data directly provided by HPI in meta-regression to confirm the robustness toward community characteristic dataset (HUD crosswalk); (iii) we ran the spatial BHM using flat priors for the sill and nugget to introduce minimal prior information into the Bayesian model (inverse gamma distributions with shape and scale equal to 0.001) (flat prior); and (iv) we ignored the potential spatial autocorrelation and ran linear regressions of ZCTA RERI from the within-community matched design and community characteristics (non-spatial linear). Because of discrepancy in available variables in HPI 2.0 and HPI 3.0 dataset, we did not run effect modification evaluations for per capital income, percentage of automobile ownership, and percentage insured in HPI 2.0 analysis.

All analyses were performed in R Studio with R version 4.1.0 (*88*). The R code to replicate these analyses is archived at Zenodo (10.5281/zenodo.10330291) and is available at the following link: https://github.com/benmarhnia-lab/synergistic_effect_wildfire_extremeheat_ca.

Supplementary Materials

This PDF file includes:
Supplementary Text
Figs. S1 to S10
Tables S1 to S5

REFERENCES AND NOTES

1. B. Ford, M. Val Martin, S. E. Zelasky, E. V. Fischer, S. C. Anenberg, C. L. Heald, J. R. Pierce, Future fire impacts on smoke concentrations, visibility, and health in the contiguous United States. *Geohealth* **2**, 229–247 (2018).
2. Y. Li, D. Tong, S. Ma, X. Zhang, S. Kondragunta, F. Li, R. Saylor, Dominance of wildfires impact on air quality exceedances during the 2020 record-breaking wildfire season in the United States. *Geophys. Res. Lett.* **48**, e94908 (2021).
3. S. E. Perkins, L. V. Alexander, J. R. Nairn, Increasing frequency, intensity and duration of observed global heatwaves and warm spells. *Geophys. Res. Lett.* **39**, L20714 (2012).
4. T. T. Smith, B. F. Zaitchik, J. M. Gohlke, Heat waves in the United States: Definitions, patterns and trends. *Clim. Change* **118**, 811–825 (2013).
5. C. Tebaldi, M. F. Wehner, Benefits of mitigation for future heat extremes under RCP4.5 compared to RCP8.5. *Clim. Change* **146**, 349–361 (2018).
6. M. A. Krawchuk, M. A. Moritz, M.-A. Parisien, J. V. Dorn, K. Hayhoe, Global pyrogeography: The current and future distribution of wildfire. *PLOS ONE* **4**, e5102 (2009).
7. M. Senande-Rivera, D. Insua-Costa, G. Miguez-Macho, Spatial and temporal expansion of global wildland fire activity in response to climate change. *Nat. Commun.* **13**, 1208 (2022).
8. B. Clarke, F. Otto, R. Stuart-Smith, L. Harrington, Extreme weather impacts of climate change: An attribution perspective. *Environ. Res. Climate* **1**, 012001 (2022).
9. US EPA, Climate change indicators in the United States (2023); https://www.epa.gov/climate-indicators.
10. J. T. Abatzoglou, A. P. Williams, R. Barbero, Global emergence of anthropogenic climate change in fire weather indices. *Geophys. Res. Lett.* **46**, 326–336 (2019).
11. A. Gershunov, K. Guirguis, California heat waves in the present and future. *Geophys. Res. Lett.* **39**, (2012).
12. M. Goss, D. L. Swain, J. T. Abatzoglou, A. Sarhadi, C. A. Kolden, A. P. Williams, N. S. Diffenbaugh, Climate change is increasing the likelihood of extreme autumn wildfire conditions across California. *Environ. Res. Lett.* **15**, 094016 (2020).
13. A. P. Williams, J. T. Abatzoglou, A. Gershunov, J. Guzman-Morales, D. A. Bishop, J. K. Balch, D. P. Lettenmaier, Observed impacts of anthropogenic climate change on wildfire in California. *Earth's Future* **7**, 892–910 (2019).
14. A. L. Westerling, Increasing western US forest wildfire activity: Sensitivity to changes in the timing of spring. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **371**, 20150178 (2016).
15. V. Iglesias, J. K. Balch, W. R. Travis, U.S. fires became larger, more frequent, and more widespread in the 2000s. *Sci. Adv.* **8**, eabc0020 (2022).
16. B. B. Hanberry, Compounded heat and fire risk for future U.S. populations. *Sustainability* **12**, 3277 (2020).
17. K. L. Ebi, A. Capon, P. Berry, C. Broderick, R. de Dear, G. Havenith, Y. Honda, R. S. Kovats, W. Ma, A. Malik, N. B. Morris, L. Nybo, S. I. Seneviratne, J. Vanos, O. Jay, Hot weather and heat extremes: Health risks. *Lancet* **398**, 698–708 (2021).
18. K. G. Burkart, M. Brauer, A. Y. Aravkin, W. W. Godwin, S. I. Hay, J. He, V. C. Iannucci, S. L. Larson, S. S. Lim, J. Liu, C. J. L. Murray, P. Zheng, M. Zhou, J. D. Stanaway, Estimating the cause-specific relative risks of non-optimal temperature on daily mortality: A two-part modelling approach applied to the Global Burden of Disease Study. *Lancet* **398**, 685–697 (2021).
19. C. Black, Y. Tesfaigzi, J. A. Bassein, L. A. Miller, Wildfire smoke exposure and human health: Significant gaps in research for a growing public health issue. *Environ. Toxicol. Pharmacol.* **55**, 186–195 (2017).
20. F. H. Johnston, S. B. Henderson, Y. Chen, J. T. Randerson, M. Marlier, R. S. Defries, P. Kinney, D. M. J. S. Bowman, M. Brauer, Estimated global mortality attributable to smoke from landscape fires. *Environ. Health Perspect.* **120**, 695–701 (2012).
21. G. Roberts, M. J. Wooster, Global impact of landscape fire emissions on surface level PM2.5 concentrations, air quality exposure and population mortality. *Atmos. Environ.* **252**, 118210 (2021).
22. S. C. Anenberg, S. Haines, E. Wang, N. Nassikas, P. L. Kinney, Synergistic health effects of air pollution, temperature, and pollen exposure: A systematic review of epidemiological evidence. *Environ. Health* **19**, 130 (2020).
23. J.-Y. Son, J. C. Liu, M. L. Bell, Temperature-related mortality: A systematic review and investigation of effect modifiers. *Environ. Res. Lett.* **14**, 073004 (2019).
24. M. E. Marlier, N. Crnosija, T. Benmarhnia, Wildfire smoke exposures and adult health outcomes, *Landscape Fire, Smoke, and Health: Linking Biomass Burning Emissions to Human Well-Being* (American Geophysical Union, 2022).
25. R. Aguilera, T. Corringham, A. Gershunov, T. Benmarhnia, Wildfire smoke impacts respiratory health more than fine particles from other sources: Observational evidence from Southern California. *Nat. Commun.* **12**, 1493 (2021).
26. F. C. Curriero, K. S. Heiner, J. M. Samet, S. L. Zeger, L. Strug, J. A. Patz, Temperature and mortality in 11 cities of the Eastern United States. *Am. J. Epidemiol.* **155**, 80–87 (2002).
27. J. E. Bennett, M. Blangiardo, D. Fecht, P. Elliott, M. Ezzati, Vulnerability to the mortality effects of warm temperature in the districts of England and Wales. *Nat. Clim. Change* **4**, 269–273 (2014).
28. A. Gasparrini, P. Masselot, M. Scortichini, R. Schneider, M. N. Mistry, F. Sera, H. L. Macintyre, R. Phalkey, A. M. Vicedo-Cabrera, Small-area assessment of temperature-related mortality risks in England and Wales: A case time series analysis. *Lancet Planet. Health* **6**, e557–e564 (2022).
29. R. Aguilera, K. Hansen, A. Gershunov, S. D. Ilango, P. Sheridan, T. Benmarhnia, Respiratory hospitalizations and wildfire smoke: A spatiotemporal analysis of an extreme firestorm in San Diego County, California. *Environ. Epidemiol.* **4**, e114 (2020).
30. C. E. Reid, M. Jerrett, I. B. Tager, M. L. Petersen, J. K. Mann, J. R. Balmes, Differential respiratory health effects from the 2008 northern California wildfires: A spatiotemporal approach. *Environ. Res.* **150**, 227–235 (2016).
31. M. Rai, M. Stafoggia, F. de 'Donato, M. Scortichini, S. Zafeiratou, L. V. Fernandez, S. Zhang, K. Katsouyanni, E. Samoli, S. Rao, E. Lavigne, Y. Guo, H. Kan, S. Osorio, J. Kyselý, A. Urban, H. Orru, M. Maasikmets, J. J. K. Jaakkola, N. Ryti, M. Pascal, M. Hashizume, C. F. S. Ng, B. Alahmad, M. H. Diaz, C. De la Cruz Valencia, B. Nunes, J. Madureira, N. Scovronick, R. M. Garland, H. Kim, W. Lee, A. Tobias, C. Íñiguez, B. Forsberg, C. Åström, A. M. Vicedo-Cabrera, M. S. Ragettli, Y.-L. L. Guo, S.-C. Pan, S. Li, A. Gasparrini, F. Sera, P. Masselot, J. Schwartz, A. Zanobetti, M. L. Bell, A. Schneider, S. Breitner, Heat-related cardiorespiratory mortality: Effect modification by air pollution across 482 cities from 24 countries. *Environ. Int.* **174**, 107825 (2023).
32. I. P. Davies, R. D. Haugo, J. C. Robertson, P. S. Levin, The unequal vulnerability of communities of color to wildfire. *PLOS ONE* **13**, e0205825 (2018).
33. M. Burke, S. Heft-Neal, J. Li, A. Driscoll, P. Baylis, M. Stigler, J. A. Weill, J. A. Burney, J. Wen, M. L. Childs, C. F. Gould, Exposures and behavioural responses to wildfire smoke. *Nat. Hum. Behav.* **6**, 1351–1361 (2022).
34. C. Portier, K. Thigpen Tart, S. Carter, C. Dilworth, A. Grambsch, J. Gohlke, J. Hess, S. Howard, G. Luber, J. Lutz, T. Maslak, M. Radtke, J. Rosenthal, T. Rowles, P. Sandifer, J. Scheraga, D. Strickman, J. Trtanj, P.-Y. Whung, *A Human Health Perspective on Climate Change: A Report Outlining the Research Needs on the Human Health Effects of Climate Change* (National Institute of Environmental Health Sciences, 2010).
35. M. L. Bell, A. Zanobetti, F. Dominici, Evidence on vulnerability and susceptibility to health risks associated with short-term exposure to particulate matter: A systematic review and meta-analysis. *Am. J. Epidemiol.* **178**, 865–876 (2013).
36. G. C. Chi, A. Hajat, C. E. Bird, M. R. Cullen, B. A. Griffin, K. A. Miller, R. A. Shih, M. L. Stefanick, S. Vedal, E. A. Whitsel, J. D. Kaufman, Individual and neighborhood socioeconomic status and the association between air pollution and cardiovascular disease. *Environ. Health Perspect.* **124**, 1840–1847 (2016).
37. J. E. Clougherty, L. D. Kubzansky, A framework for examining social stress and susceptibility to air pollution in respiratory health. *Environ. Health Perspect.* **117**, 1351–1358 (2009).
38. C. J. Gronlund, Racial and socioeconomic disparities in heat-related health effects and their mechanisms: A review. *Curr. Epidemiol. Rep.* **1**, 165–173 (2014).
39. A. G. Berberian, D. J. X. Gonzalez, L. J. Cushing, Racial Disparities in Climate Change-Related Health Effects in the United States. *Curr. Envir. Health Rpt.* **9**, 451–464 (2022).
40. Public Policy Institute of California, California's population; https://www.ppic.org/publication/californias-population/.

41. Public Policy Institute of California, Income inequality in California; https://www.ppic.org/publication/income-inequality-in-california/.
42. B. KC, J. M. Shepherd, A. W. King, C. Johnson Gaither, Multi-hazard climate risk projections for the United States. *Nat. Hazards* **105**, 1963–1976 (2021).
43. M. D. Hurteau, A. L. Westerling, C. Wiedinmyer, B. P. Bryant, Projected effects of climate and development on California wildfire emissions through 2100. *Environ. Sci. Technol.* **48**, 2298–2304 (2014).
44. M. D. Mastrandrea, C. Tebaldi, C. W. Snyder, S. H. Schneider, Current and future impacts of extreme events in California. *Clim. Change* **109**, 43–70 (2011).
45. A. AghaKouchak, F. Chiang, L. S. Huning, C. A. Love, I. Mallakpour, O. Mazdiyasni, H. Moftakhari, S. M. Papalexiou, E. Ragno, M. Sadegh, Climate extremes and compound hazards in a warming world. *Annu. Rev. Earth Planet. Sci.* **48**, 519–548 (2020).
46. N. Rosenthal, T. Benmarhnia, R. Ahmadov, E. James, M. E. Marlier, Population co-exposure to extreme heat and wildfire smoke pollution in California during 2020. *Environ. Res. Climate* **1**, 025004 (2022).
47. World Health Organization, *WHO Global Air Quality Guidelines: Particulate Matter (PM2.5 and PM10), Ozone, Nitrogen Dioxide, Sulfur Dioxide and Carbon Monoxide* (World Health Organization, 2021).
48. US EPA, Climate change indicators: Heat waves (2021); https://www.epa.gov/climate-indicators/climate-change-indicators-heat-waves.
49. T. J. VanderWeele, M. J. Knol, A tutorial on interaction. *Epidemiol. Methods* **3**, 33–72 (2014).
50. J. P. Buckley, J. M. Samet, D. B. Richardson, Commentary: Does air pollution confound studies of temperature? *Epidemiology* **25**, 242–245 (2014).
51. M. M. Rahman, R. McConnell, H. Schlaerth, J. Ko, S. Silva, F. W. Lurmann, L. Palinkas, J. Johnston, M. Hurlburt, H. Yin, G. Ban-Weiss, E. Garcia, The effects of co-exposure to extremes of heat and particulate air pollution on mortality in California: Implications for climate change. *Am. J. Respir. Crit. Care Med.* **206**, 1117–1127 (2022).
52. Health Canada, Wildfire smoke 101: Combined wildfire smoke and heat (2021); https://www.canada.ca/en/health-canada/services/publications/healthy-living/combine-wildfire-smoke-heat.html.
53. Wildfire Smoke | Los Angeles County Department of Public Health - Environmental Health; http://www.publichealth.lacounty.gov/eh/safety/wildfire-smoke.htm.
54. D. A. Kalashnikov, J. L. Schnell, J. T. Abatzoglou, D. L. Swain, D. Singh, Increasing co-occurrence of fine particulate matter and ground-level ozone extremes in the western United States. *Sci. Adv.* **8**, eabi9386 (2022).
55. C. E. Buysse, A. Kaulfus, U. Nair, D. A. Jaffe, Relationships between particulate matter, ozone, and nitrogen oxides during urban smoke events in the Western US. *Environ. Sci. Technol.* **53**, 12519–12528 (2019).
56. G. B. Anderson, M. L. Bell, Heat waves in the United States: Mortality risk during heat waves and effect modification by heat wave characteristics in 43 U.S. communities. *Environ. Health Perspect.* **119**, 210–218 (2011).
57. X. Qiu, Y. Wei, Y. Wang, Q. Di, T. Sofer, Y. A. Awad, J. Schwartz, Inverse probability weighted distributed lag effects of short-term exposure to PM2.5 and ozone on CVD hospitalizations in New England Medicare participants - exploring the causal effects. *Environ. Res.* **182**, 109095 (2020).
58. R. E. S. Clemesha, K. Guirguis, A. Gershunov, I. J. Small, A. Tardy, California heat waves: Their spatial evolution, variation, and coastal modulation by low clouds. *Climate Dynam.* **50**, 4285–4301 (2018).
59. M. Maclure, The case-crossover design: A method for studying transient effects on the risk of acute events. *Am. J. Epidemiol.* **133**, 144–153 (1991).
60. E. Mostofsky, B. A. Coull, M. A. Mittleman, Analysis of observational self-matched data to examine acute triggers of outcome events with abrupt onset. *Epidemiology* **29**, 804–816 (2018).
61. L. Schwarz, K. Hansen, A. Alari, S. D. Ilango, N. Bernal, R. Basu, A. Gershunov, T. Benmarhnia, Spatial variation in the joint effect of extreme heat events and ozone on respiratory hospitalizations in California. *Proc. Natl. Acad. Sci. U.S.A.* **118**, e2023078118 (2021).
62. HCAI - Department of Health Care Access and Information; https://hcai.ca.gov/.
63. US EPA, NAAQS Table (2014); https://www.epa.gov/criteria-air-pollutants/naaqs-table.
64. L. Pinault, M. Tjepkema, D. L. Crouse, S. Weichenthal, A. van Donkelaar, R. V. Martin, M. Brauer, H. Chen, R. T. Burnett, Risk estimates of mortality attributed to low concentrations of ambient fine particulate matter in the Canadian community health survey cohort. *Environ. Health* **15**, 18 (2016).
65. Q. Di, Y. Wang, A. Zanobetti, Y. Wang, P. Koutrakis, C. Choirat, F. Dominici, J. D. Schwartz, Air pollution and mortality in the Medicare population. *N. Engl. J. Med.* **376**, 2513–2522 (2017).
66. R. Aguilera, N. Luo, R. Basu, J. Wu, R. Clemesha, A. Gershunov, T. Benmarhnia, A novel ensemble-based statistical approach to estimate daily wildfire-specific PM2.5 in California (2006–2020). *Environ. Int.* **171**, 107719 (2023).
67. H. McBrien, S. T. Rowland, T. Benmarhnia, S. Y. Tartof, B. Steiger, J. A. Casey, Wildfire exposure and health care use among people who use durable medical equipment in Southern California. *Epidemiology* **34**, 700–711 (2023).
68. G. B. Anderson, M. L. Bell, R. D. Peng, Methods to calculate the heat index as an exposure metric in environmental health research. *Environ. Health Perspect.* **121**, 1111–1119 (2013).
69. B. Jacklitsch, W. Williams, K. Musolin, A. Coca, J.-H. Kim, N. Turner, *NIOSH Criteria for a Recommended Standard: Occupational Exposure to Heat and Hot Environments* (National Institute on Drug Abuse, 2016).
70. J. T. Abatzoglou, Development of gridded surface meteorological data for ecological applications and modelling. *Int. J. Climatol.* **33**, 121–131 (2013).
71. National Weather Service, Heat index equation (2014); https://www.wpc.ncep.noaa.gov/html/heatindex_equation.shtml.
72. L. P. Rothfusz, "The heat index 'equation' (or, more than you ever wanted to know about heat index)" (Technical Attachment SR 90-23, NWS, 1990).
73. US Census Bureau, 2010 Census (2010); https://web.archive.org/web/20100320084325/http://2010.census.gov/2010census/.
74. N. Maizlish, T. Delaney, H. Dowling, D. A. Chapman, R. Sabo, S. Woolf, C. Orndahl, L. Hill, L. Snellings, California healthy places index: Frames matter. *Public Health Rep.* **134**, 354–362 (2019).
75. Data & reports—California healthy places index; https://healthyplacesindex.org/.
76. California Energy Commission, Climate zone tool, maps, and information supporting the California Energy Code; https://www.energy.ca.gov/programs-and-topics/programs/building-energy-efficiency-standards/climate-zone-tool-maps-and.
77. HUD USPS ZIP Code Crosswalk Files | HUD USER; https://www.huduser.gov/portal/datasets/usps_crosswalk.html.
78. S. Tong, X. Y. Wang, Y. Guo, Assessing the short-term effects of heatwaves on mortality and morbidity in Brisbane, Australia: Comparison of case-crossover and time series analyses. *PLOS ONE* **7**, e37500 (2012).
79. Y. Wei, Y. Wang, Q. Di, C. Choirat, Y. Wang, P. Koutrakis, A. Zanobetti, F. Dominici, J. D. Schwartz, Short term exposure to fine particulate matter and hospital admission risks and costs in the Medicare population: time stratified, case crossover study. *BMJ* **367**, l6258 (2019).
80. D. Levy, T. Lumley, L. Sheppard, J. Kaufman, H. Checkoway, Referent selection in case-crossover analyses of acute health effects of air pollution. *Epidemiology* **12**, 186–192 (2001).
81. H. Janes, L. Sheppard, T. Lumley, Overlap bias in the case-crossover design, with application to air pollution exposures. *Stat. Med.* **24**, 285–300 (2005).
82. T. Therneau, survival: A package for survival analysis in R (2022); https://CRAN.R-project.org/package=survival.
83. C. Jackson, Multi-State Models for Panel Data: The msm Package for R. *J. Stat. Softw.* **38**, 1–28 (2011).
84. J. C. Liu, A. Wilson, L. J. Mickley, F. Dominici, K. Ebisu, Y. Wang, M. P. Sulprizio, R. D. Peng, X. Yue, J.-Y. Son, G. B. Anderson, M. L. Bell, Wildfire-specific fine particulate matter and risk of hospital admissions in urban and rural counties. *Epidemiology* **28**, 77–85 (2017).
85. J. F. Bobb, Z. Obermeyer, Y. Wang, F. Dominici, Cause-specific risk of hospital admission related to extreme heat in older adults. *JAMA* **312**, 2659–2667 (2014).
86. A. O. Finley, S. Banerjee, A. E. Gelfand, spBayes for large univariate and multivariate point-referenced spatio-temporal data models. *J. Stat. Softw.* **63**, 1–28 (2015).
87. S. Balduzzi, G. Rücker, G. Schwarzer, How to perform a meta-analysis with R: a practical tutorial. *Evid. Based Ment. Health* **22**, 153–160 (2019).
88. R Core Team, *R: A Language and Environment for Statistical Computing* (R Foundation for Statistical Computing, 2021); https://www.R-project.org/.

Acknowledgments: We thank R. Aguilera for their support and expertise in the wildfire smoke–related fine particulate matter dataset, which is crucial to this research project. **Funding:** This work is supported by a seed grant from the UC Center for Climate Health Equity and by the National Institute on Aging (RF1AG080948). **Author contributions:** Conceptualization: C.C., M.E.M., and T.B. Methodology: C.C., L.S., N.R., M.E.M., and T.B. Investigation: C.C. and N.R. Visualization: C.C. and L.S. Supervision: M.E.M. and T.B. Writing—original draft: C.C., N.R., and L.S. Writing—review and editing: C.C., L.S., N.R., M.E.M., and T.B. **Competing interests:** The authors declare that they have no competing interests. **Data and materials availability:** All data and codes are available via links in the main text or Supplementary Materials except for the health outcome data, which cannot be shared to protect the privacy of patients. Access of the health outcome data could be requested directly at the California Department of Health Care Access and Information website (https://hcai.ca.gov/data-and-reports/research-data-request-information/).

Submitted 14 July 2023
Accepted 29 December 2023
Published 2 February 2024
10.1126/sciadv.adj7264