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Association between wildfires and coccidioidomycosis incidence in California, 2000–2018: a synthetic control analysis

Sophie Phillips[a], Isabel Jones[b], Gail Sondermyer-Cooksey[c], Alexander T. Yu[c], Alexandra K. Heaney[b], Bo Zhou[d], Abinash Bhattachan[e], Amanda K. Weaver[b], Simon K. Campo[b], Whitney Mgbara[b], Robert Wagner[f], John Taylor[f], Dennis Lettenmaier[d], Gregory S. Okin[d], Seema Jain[c], Duc Vugia[c], Justin V. Remais[b*], Jennifer R. Head[a,b]

Background: The frequency and severity of wildfires in the Western United States have increased over recent decades, motivating hypotheses that wildfires contribute to the incidence of coccidioidomycosis, an emerging fungal disease in the Western United States with sharp increases in incidence observed since 2000. While coccidioidomycosis outbreaks have occurred among wildland firefighters clearing brush, it remains unknown whether fires are associated with an increased incidence among the general population.
Methods: We identified 19 wildfires occurring within California's highly endemic San Joaquin Valley between 2003 and 2015. Using geolocated surveillance records, we applied a synthetic control approach to estimate the effect of each wildfire on the incidence of coccidioidomycosis among residents that lived within a hexagonal buffer of 20 km radii surrounding the fire.
Results: We did not detect excess cases due to wildfires in the 12 months (pooled estimated percent change in cases: 2.8%; 95% confidence interval [CI] = –29.0, 85.2), 13–24 months (7.9%; 95% CI = –27.3, 113.9), or 25–36 months (17.4%; 95% CI = –25.1, 157.1) following a wildfire. When examined individually, we detected significant increases in incidence following three of the 19 wildfires, all of which had relatively large adjacent populations, high transmission before the fire, and a burn area exceeding 5,000 acres.
Discussion: We find limited evidence that wildfires drive increases in coccidioidomycosis incidence among the general population. Nevertheless, our results raise concerns that large fires in regions with ongoing local transmission of *Coccidioides* may be associated with increases in incidence, underscoring the need for field studies examining *Coccidioides* spp. in soils and air pre- and post-wildfires.

Keywords: California; Climate change; Coccidioidomycosis; *Coccidioides*; Drought; Synthetic control; Valley fever; Wildfires

Introduction

Coccidioidomycosis is an infection caused by inhalation of spores from the soil-dwelling fungi *Coccidioides immitis* or *C. posadasii*.[1] Infection can lead to localized disease in the lung, and in a small proportion of cases can cause systemic disease, including meningitis or death.[1] Coccidioidomycosis is endemic across much of the southwestern United States and Mexico, with the incidence highest in California and Arizona. Between 2000 and 2014, the age-adjusted incidence in California nearly tripled, from 2.4 cases per 100,000 to 6.0 cases per 100,000.[2] Since 2014, the incidence rate of coccidioidomycosis in California has more than doubled,[2] with 2017 through 2019 witnessing the highest incidence on record.[3] Alongside social and demographic

What this study adds

Amid the growing intensity of wildfires in California and rising coccidioidomycosis incidence, this study fills a gap in the literature by examining potential associations between wildfire activity and coccidioidomycosis transmission in populations residing around wildfire burn areas. Our findings suggest that public health efforts to mitigate the impact of wildfires on coccidioidomycosis risk should continue to focus on prevention and worker protection during wildland firefighting. Although we do not find evidence that increasing wildfire severity and frequency play an important role in driving observed increasing trends in coccidioidomycosis incidence in the state, our findings underscore the need for a focal study of *Coccidioides* spp. in soils and air pre- and post-fire in populous regions with known local transmission.

[a]Department of Statistics, University of California, Los Angeles, Los Angeles, California; [b]Division of Environmental Health Sciences, School of Public Health, University of California, Berkeley, Berkeley, California; [c]Infectious Diseases Branch, California Department of Public Health, Richmond, California; [d]Department of Geography, University of California, Los Angeles, Los Angeles, California; [e]Department of Geosciences, Texas Tech University, Lubbock, Texas; [f]Department of Plant and Microbial Biology, College of Natural Resources, University of California, Berkeley, Berkeley, California; [g]Division of Epidemiology, School of Public Health, University of California, Berkeley, Berkeley, California

Justin V. Remais and Jennifer R. Head contributed equally to this work.

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The R script used to conduct the data analysis will be made available in a publicly available GitHub repository (https://github.com/sp8268/Fires_and_Cocci) before publication. Human case data are protected health information with access restricted to authorized California Department of Public Health (CDPH) staff. More complete human disease data can be obtained by submitting a formal request to the CDPH, Infectious Disease Branch, Surveillance and Statistics Section. All environmental predictors are publicly available.

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*Corresponding Author. Address: Division of Environmental Health Sciences, School of Public Health, University of California, 2121 Berkeley Way West #5301, Berkeley, CA 94720. E-mail: jvr@berkeley.edu (J.V. Remais).

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factors, environmental conditions are suspected to play an important role in the emergence and re-emergence of the disease.[4] *Coccidioides* is a filamentous fungus that grows and sporulates during wet conditions. The autolysis process begins to liberate spores during hot and dry conditions, conditions that additionally facilitate spore dispersal during wind erosion of soils,[4–7] allowing inhalation of spores and subsequent infection.

As coccidioidomycosis incidence has increased in recent years, so too has wildfire activity in California.[8] Wildfire burned area increased over five-fold in California from 1972 to 2018, an increase attributed to warmer spring and summer temperatures, reduced precipitation, changing wind patterns, and increased atmospheric aridity promoting fuel drying.[8–10] These trends are expected to continue under the influence of anthropogenic climate change.[9,10] Public health officials and researchers have speculated that wildfires contribute to coccidioidomycosis transmission by depleting vegetation cover and increasing dust emissions.[11,12] Although reports of coccidioidomycosis among wildland firefighters[12–14] have led to occupational health warnings for first responders to wildfires in endemic counties,[15,16] population-level research has been lacking on the potential association between wildfires and coccidioidomycosis incidence in the general population.

There are several plausible mechanisms by which wildfire may influence the environmental biology of *Coccidioides* spp. and the epidemiology of coccidioidomycosis across time scales spanning months to years (Figure 1). First, wildfires may affect the mobilization and dispersion of the pathogen, leading to both immediate and sustained increases in exposure to pathogenic spores. Wildfires can be accompanied by convective thermodynamics, including strong updrafts, that may disperse *Coccidioides* spores to surrounding areas, as has been seen for other fungal spores.[17] Although it is unknown whether *Coccidioides* spp. can travel and remain viable in wildfire smoke, other fungal spores have been found to survive in the smoke emitted from prescribed wildland fires.[18] In the longer term, wildfires may contribute to expansive loss of vegetation, soil organic matter, soil-stabilizing root networks, and naturally occurring soil crusts that retain soils.[19] Wildfires may further induce water repellency, leading to overland runoff, increased erodibility of surface soil,[20–22] and decreased aggregate stability of soils.[23] These changes following a wildfire may lead exposed regions to be more susceptible to wind erosion,[24] potentially facilitating the redistribution of spores within the landscape and aerosolization of spores for years following the fire. What is more, extreme temperatures from wildfires may inactivate other microbial competitors in the soil, potentially releasing *Coccidioides* spp. from competitive pressures and enabling more prolific growth in the years following the fire. Indeed, prior research has found high mean surface temperatures to be associated with incidence rates in California counties, leading to the theory that *Coccidioides* spp. survives beneath the soil at high temperatures that sterilize the soil of other competitors.[25,26]

On the other hand, plausible mechanisms may contribute to reductions in *Coccidioides* transmission. High temperatures and depletion of nutrients may lead to immediate or sustained declines in *Coccidioides* presence in soils. Exposure to temperatures of 80 °C for between 10 and 30 minutes has been shown to inactivate *Coccidioides* spores and mycelia,[27] although *Coccidioides* spp. can survive more than 1 week at 50 °C,[28] and can persist many centimeters beneath the surface[29] where they may be insulated from extreme heat. Second, wildfires may deplete carbohydrates and proteins derived from vegetation and small mammals that are needed to support *Coccidioides* mycelial growth.[28,30,31] *Coccidioides* presence is strongly associated with mammalian host populations,[29–31] which can dramatically decline when wildfires deplete food sources and reduce cover from predators.[32] Depending on rodent diet and habitat preferences, some rodent populations have been observed to remain low for over a year following wildfires.[32]

As wildfires across California increase in frequency and intensity,[33,34] their potential influence on the epidemiology of coccidioidomycosis is of increasing interest, particularly in endemic areas where *Coccidioides* transmission may accompany or follow wildfire events. Here, we estimate the effect of wildfires on coccidioidomycosis incidence between 2000 and 2018 using a synthetic control approach, with the goal of informing the public health response to wildfires.

Methods

Study area

Our study area comprised the six counties within California that reported the most cases of coccidioidomycosis between 2000 and 2018 and had a mean annual incidence of at least 10 cases per 100,000 population: Fresno, Kern, Kings, San Joaquin, San Luis Obispo, and Tulare (Figure 2A). Several of these counties, including Tulare, San Luis Obispo, western Fresno, and western Kern are projected to experience frequent wildfires in the coming decades.[35] In this region, county annual incidence ranged from 11.5 cases per 100,000 in San Joaquin County to 183 cases per 100,000 in Kern County.

Epidemiologic outcome

We obtained California Department of Public Health (CDPH) reportable disease surveillance data on confirmed coccidioidomycosis cases reported among California residents with estimated onset between 1 January 2000 and 21 December 2018. Patients meeting both the laboratory and clinical criteria for coccidioidomycosis as defined by the Council of State and Territorial Epidemiologists are required to be reported by health care providers and laboratories to local health departments and then the CDPH.[36] Although case definition compliance varied by local health jurisdiction, no sudden shifts in case definition occurred over this time period. Per CDPH protocols, if patients are diagnosed multiple times with coccidioidomycosis, only the first report is used. Using a locally implemented ArcGIS geocoding service and geodatabase of addresses in the contiguous United States,[37] each case residence was georeferenced and assessed for address match accuracy. We matched 96% of addresses. Where street addresses could not be identified, we used the centroid of the zip code. Case numbers were aggregated monthly within hexagonal grids across the study extent, with radii of 15, 20, or 25 km (Figure 2B).

Exposure definition

Data on wildfires that occurred within the study area between 2003 and 2015 were obtained from the Monitoring Trends in Burn Severity project,[38] which derived burn area boundaries and severity through remote sensing. The project has mapped all wildfires larger than 1000 acres since 1984 in the continental US and provides information on the size, in acres, of the burn area, date of ignition, and burn severity. We considered eligible wildfires as those where: (1) the burn area boundary was >2000 acres; and (2) the fire-exposed region did not overlap with another wildfire within 3 years before ignition.

To establish populations exposed to wildfires, hexagonal areas were delineated with radii of 20 km (area: 535 square miles or 342,000 acres) centered around the centroid of each fire burn area (Figure 2B). The 20 km radius accommodates cases that may be attributable to exposure to dispersing windborne spores that originated from the fire region, while at the same time limiting the inclusion of areas unaffected by fire. Within the synthetic control analysis, hexagonal areas centered on each wildfire were considered "exposed" units.

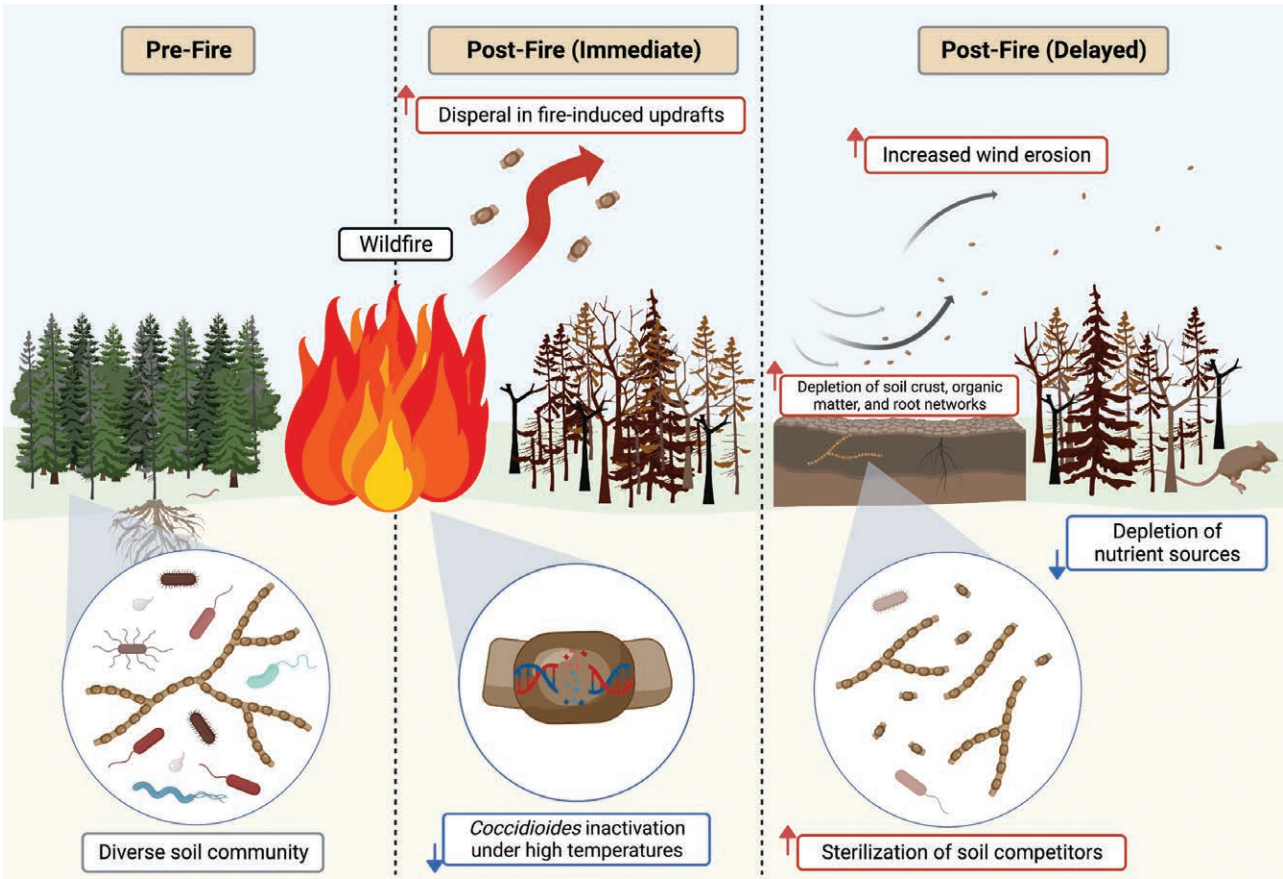

Figure 1. Potential mechanisms via which wildfire may increase or decrease transmission of *Coccidioides* over both immediate or delayed timelines.

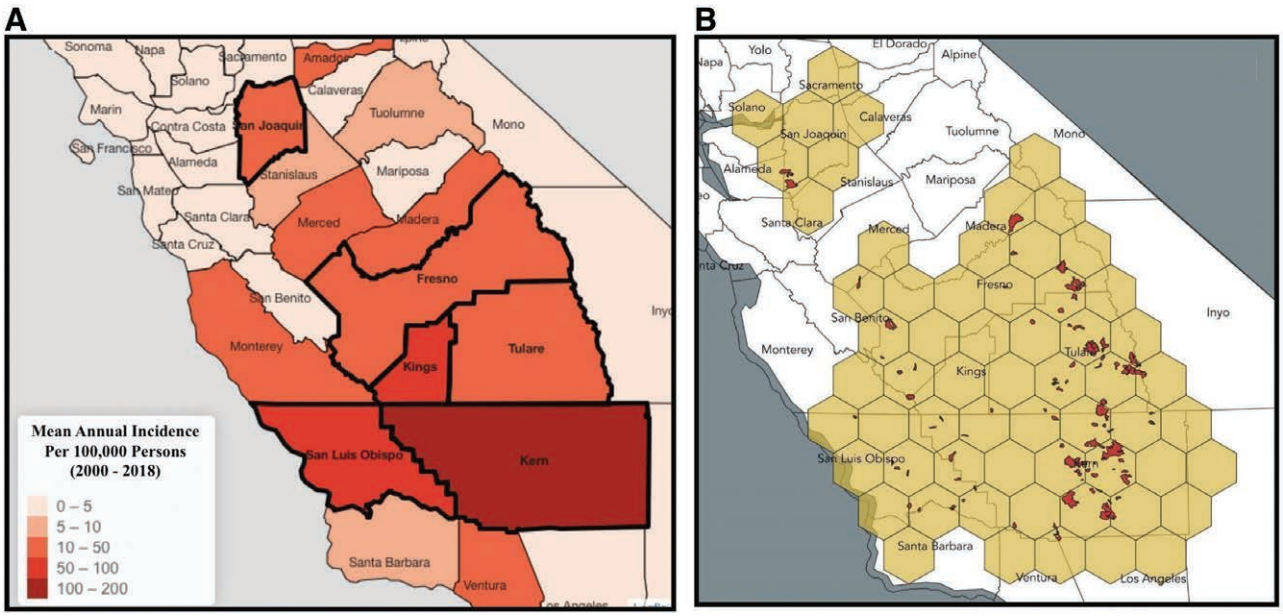

Figure 2. A, Mean annual coccidioidomycosis incidence rate (cases per 100,000 persons) across California's San Joaquin Valley from 2000 to 2018. We studied associations between wildfire and coccidioidomycosis incidence within the six counties outlined in bold. B, Burn area boundaries for all wildfires occurring within our study region between 2003 and 2015. We used regions in the hexagonal grid as controls. Identically sized hexagonal regions were delineated around the centroid of the burn areas (not shown).

To establish control units, a tessellated hexagonal grid with radii 20 km was applied to the study region, with placement set so as to minimize the number of grid cells necessary to completely cover the region. Within the synthetic control framework, control units from this grid were considered eligible to be matched to an exposed unit if they met the following criteria: (1) did not spatially overlap with the fire-exposed region and (2) did not contain a wildfire event

within the 3 years before or following the ignition date of the fire. In this manner, the set of eligible control units differed slightly for each wildfire considered, ranging from 26 to 34.

Statistical analysis

Synthetic control analysis

We used the generalized synthetic control (GSC) method to estimate the effect of each wildfire individually on monthly coccidioidomycosis incidence in the 3 years following the fire.[39] Similar to the classic synthetic control method,[40] the GSC method uses a weighted average of eligible control regions to construct a counterfactual region (a synthetic control) for each fire-exposed region that resembles the exposed region in terms of pre-fire incidence and other covariates determined to be confounders (Figure S1; http://links.lww.com/EE/A222; here: mean temperature, total precipitation, percent vegetation cover, and maximum wind velocity). We included population as a time-varying covariate to match on to ensure an appropriate comparison of incident cases between the synthetic control and the fire-exposed region. Compared to the traditional method, GSC permits the estimation of easily interpretable uncertainty parameters (e.g., standard error) on the target parameter of interest.[39]

We used the GSC method to estimate counterfactual monthly cases for each fire-exposed region, representing the expected cases in that region if the wildfire had not occurred. We then estimated the monthly treatment effect of each wildfire $\left(\hat{\psi}_{j,t}\right)$ by taking the difference in observed cases in month t in fire-exposed region j $\left(Y_{j,t}\right)$ and its counterfactual cases $\left(\hat{Y}^N_{j,t}\right)$ over the period after the fire, such that:

$$\hat{\psi}_{j,t} = Y_{j,t} - \hat{Y}^N_{j,t} \quad [1]$$

For each wildfire, we then summed across months to obtain the cumulative effect $\left(\hat{\psi}_j\right)$ of each individual fire, j, over a specified postfire period, from t_0 to T:

$$\hat{\psi}_j = \sum_{t=t_0}^{T} \left(Y_{j,t} - \hat{Y}^N_{j,t}\right) \quad [2]$$

Vegetation, soil crusts, root networks, and small mammal communities disrupted by fires generally begin to rebound within 2–3 years postfire.[19,32] We thus considered the postfire period to span 1–36 months postignition date to capture longer-term effects of the fire on incidence. Within the 1–36 months, we examined fire effects across four specific periods or subperiods: 1–36 months after fire, 1–12 months; 13–24 months, and 25–36 months. Because most fires occurred early in fall, and cases typically rise and peak in late fall to early winter, each yearly period following the fire roughly captures a full transmission season.

We used a parametric bootstrap with 10,000 runs to generate 95% confidence intervals (CI) around the fire effect estimate (eSupplement; http://links.lww.com/EE/A222). We applied this method to each fire individually to obtain an individual-level treatment effect $\left(\hat{\psi}_j\right)$ and standard error for each fire. The average treatment effect across all wildfires was obtained using a fixed effects model meta-analysis that applied the meta-analysis to calculate both monthly effects ($\hat{\psi}_t$; Equation 3) and period effects ($\hat{\psi}$; Equation 4), such that:

$$\hat{\psi}_t = \frac{1}{\sum_j^J w_j} \sum_{j=1}^{J} w_j \hat{\psi}_{j,t} \quad [3]$$

$$\hat{\psi} = \frac{1}{\sum_j^J w_j} \sum_{j=1}^{J} \sum_{t=t_0}^{T} w_j \hat{\psi}_{j,t} \quad [4]$$

Analyses were conducted using R version 3.5.[41] The GSC method was implemented using the gsynth package,[42] and the meta-analysis was implemented using the meta package.[43]

Secondary and sensitivity analyses

To determine whether the effect of the wildfire was modified by environmental or demographic factors, we applied a fixed-effects meta-analysis to regress the individual treatment effect of the fire against fire-specific covariates, such as population, baseline level of transmission, and other environmental covariates. We applied an interrupted time series analysis (equation 5 in eSupplement; http://links.lww.com/EE/A222) as well as a synthetic control analysis using vegetation cover (as measured by MESMA) as the outcome to characterize the changes in vegetation postfire, to examine whether any potential effect of fire could be mediated by sustained decreases in vegetative land cover. Finally, to determine whether increases in cases after fire may have been mediated by acute increases in wind concurrent with the fire, the number of days per month where the wind speed was greater than five meters per second was regressed against an interaction term between being a fire-exposed region during the month of the fire. These analyses are described in detail in the eSupplement; http://links.lww.com/EE/A222.

We examined whether results were sensitive to the size of the hexagon demarcating fire-exposed and control regions by repeating the analysis using hexagonal regions with radii 15 km and 25 km to define the fire-exposed and control regions. We also tested whether results were sensitive to the pool of eligible controls[44,45] by removing each control one at a time from the eligible control pool and calculating the effect of the wildfire with this control excluded.

Results

Descriptive

Between 2000 and 2018, there were 42,125 reported cases of coccidioidomycosis within the six study counties. Of these, 3,323 patients resided within an area surrounding a fire that met the eligibility criteria. There were 22 wildfires within the study region between 2003 and 2015 that satisfied the eligibility criteria. Seven wildfires overlapped with another wildfire within 3 years of ignition. Three of these seven were nearly overlapping with another wildfire less than 6 months after ignition, and thus we defined a single event for each spanning the period delineated by the ignition date of the earlier fire and the end date of the later fire. For the remaining four, we determined the effect of the earlier wildfire until the ignition date of the later fire.

Among the 22 wildfires, five (22%) were larger than 10,000 acres; the largest was 17,238 acres. Based on changes in spectral indices indicating photosynthetically healthy versus burned vegetation calculated from satellite imagery,[38] 13 wildfires (57%) were classified as low severity while 9 (40%) were classified as moderate/high burn severities. Eighteen (78%) of the wildfires occurred in the summer months. Three wildfires were excluded for failing to achieve the goodness of fit criterion in the pre-fire period, leaving a total of 19 wildfires for further analysis (Table 1). Across the 19 wildfire regions included in the analysis, an average of 19.1 (SD = 21.6) incident cases were reported over the 3 years before the fire within each 20 km buffer region around the fire. An estimated 558,200 individuals lived within these 19 regions during the study period.

Table 1.

Total differences in cases between the fire-exposed region and its synthetic control over the 3-year post-fire period among the 19 fires analyzed

	Excess cases attributable to fire (CI)	RMSE	Ignition date	Fire acres	Burn severity
Tulare, Aug, 2004[a]	0.2 (–16.4, 16.8)	0.5	12-08-2004	3371	3
Fresno, Jun, 2005[a]	–6.9 (–22.9, 9.1)	0.2	04-06-2005	2620	2
Tulare, Jul, 2005	–4 (–31.9, 24.0)	1	07-07-2005	2997	3
Fresno, Aug, 2005	–6 (–32.0, 20.1)	0.2	01-08-2005	3825	2
Kern, Sept, 2005	–9.4 (–38.0, 19.2)	0.5	03-09-2005	2439	2
San Joaquin, Jul, 2006[b]	32.5 (6.3, 58.7)	0.8	11-07-2006	6344	2
Kern, Aug, 2006[a]	3.0 (–14.6, 20.6)	0.3	05-08-2006	2386	2
Tulare, Jun, 2007	3.1 (–15.6, 21.7)	0.5	03-06-2007	6246	2
Kern, Jun, 2007	2.4 (–16.1, 20.9)	0.9	24-06-2007	11784	2
Fresno, Jul, 2008[a]	1.2 (–15.0, 17.4)	0.2	19-07-2008	12205	2
San Joaquin, Jun, 2009	–6.7 (–54.1, 40.7)	1.6	19-06-2009	14156	2
San Luis Obispo, May, 2010	–11.6 (–50.2, 27.0)	0.1	15-05-2010	2083	2
Tulare, Jul, 2010	29.4 (–5.9, 64.7)	0.6	16-07-2010	17238	3
Kern, Jun, 2011	0.4 (–47.9, 48.8)	0.4	19-06-2011	5262	2
Kern, Jun, 2011 (2)	8.5 (–38.8, 55.8)	0.6	21-06-2011	3256	3
Kern, Sept, 2011[b]	26.4 (–20.7, 73.5)	1.3	04-09-2011	14707	2
Kern, Aug, 2012	–1.7 (–36.8, 33.4)	0.3	10-08-2012	12212	3
Kern, Jun, 2014[b]	–62 (–99.1, –24.8)	1.1	13-06-2014	6053	3
San Luis Obispo, Jun, 2015[b]	55.5 (3.2, 107.7)	0.7	20-06-2015	5785	3

The root mean squared error (RMSE) is defined as the difference in incident cases between the fire-exposed region and its synthetic control during the pre-fire period.

Burn severity is an ordinal variable between 1 and 3 with higher values representing more severe depletion of vegetation.

[a]Fires measured over a period shorter than 36 months due to overlap with another fire.

[b]Fires where a statistically significant difference in cases occurred over some 12-month period or longer following the fire.

Average treatment effect of wildfire on coccidioidomycosis cases

When pooling the effect of the 19 wildfires across four time periods following the fire (1–12 months; 13–24 months; 25–36 months; and 0–36 months), we found no significant association between wildfires and coccidioidomycosis incidence among the general population. The average number of excess cases in surrounding populations attributable to a wildfire over the 3 years following the fire was 2.5 (95% CI = –5.4, 10.3), representing an 8.6% (95% CI = –14.8, 50.2) increase in cases relative to the estimated counterfactual cases (Figure 3). Among regions with ≥10 cases across the 3 years before the wildfire, we estimated an average of 6.9 (95% CI = –3.8, 17.5) excess cases over the 3 years following a fire, representing a 14.5% (95% CI = –16.4, 45.5) increase above expected. In other words, the total cases observed following wildfires were not significantly higher than the number of cases that would be expected had the fires not occurred.

Examining the pooled effect of wildfires across each month of the 36-month postfire period, we found that among the general population, cases were elevated compared with their synthetic controls during peak transmission months (typically, late fall) occurring in the second and third years following a wildfire, but not significantly so (Figure 4). In the first year (months 1–12) following a wildfire, there was an average of 0.2 (95% CI = –3.2, 3.3) excess cases per fire-exposed region, representing a 2.8% (95% CI = –29.0, 85.2) increase in cases relative to the estimated counterfactual cases. In the second (months 13–24) and third years (months 25–36) following wildfires, the average number of cases attributable to the fires was 0.7 (95% CI = –3.7, 5.1) and 1.3 (95% CI = –2.8, 5.3), respectively, representing a 7.9% (95% CI = –27.3, 113.9) and 17.4% (95% CI = –25.1, 157.1) increase in cases compared with the estimated counterfactuals (Figure S2; http://links.lww.com/EE/A222).

Individual treatment effects of wildfires on coccidioidomycosis cases

We assessed the effects of individual wildfires across the 3 years following the fire and detected significant increases in incidence relative to that expected based on the counterfactual estimate in at least one annual period following three of the 19 wildfires studied (Figure 3; Figure S2; http://links.lww.com/EE/A222). The 2006 Midway Fire in San Joaquin and the 2015 Park Hill Fire in San Luis Obispo exhibited higher incidence across the full 3-year post-fire period (Table 1 and Figure 3). The 2011 Canyon Fire in Kern demonstrated higher incidence only during months 13–24 after the fire (Figure S2; http://links.lww.com/EE/A222).

We examined characteristics of the fires and surrounding populations that may explain the heterogeneity in the treatment effect across the 19 fires. Unlike most of the other 16 fire-exposed regions, the three regions that were associated with increases in incidence were: (1) relatively more populous (home to over 36,000 people, or 67 persons per square mile); (2) had relatively more cases reported during the 3 years before the fire (18 or more); and (3) had burn areas greater than 5,000 acres (Figures S3–S5; http://links.lww.com/EE/A222). The three fires also primarily burned grass and/or brush. The Park Hill and Midway fires occurred within grasslands at lower elevations (below 500 meters) within the San Joaquin Valley (Figure S3; http://links.lww.com/EE/A222). The fire-exposed hexagons encompassed nearby cities of Tracy and San Luis Obispo, respectively. The Canyon fire in southeastern Kern County burned through grass and brush within the Kern River Canyon, at a higher elevation (~1500 m; Figures S3 and S4; http://links.lww.com/EE/A222). However, only the San Joaquin Midway fire retained significant postfire effects under sensitivity analyses that varied the control donor pool (Figure S9; http://links.lww.com/EE/A222). In univariate meta-analyses, we did not detect consistent trends between the effect of fire and meta-predictors such as prefire vegetative land cover, mean temperature, and precipitation pre- and post-fire (Figure S5; http://links.lww.com/EE/A222).

The 2014 Shirley fire, occurring in the southern part of Sequoia National Forest in eastern Kern County, was associated with lower incidence than expected in months 25–36 following the fire (Figure S2; http://links.lww.com/EE/A222) and across the 3 years following the fire (Figure 3). This fire had average levels of vegetative land cover before the fire (Figure S5; http://links.lww.com/EE/A222), but we detected a significant decline in

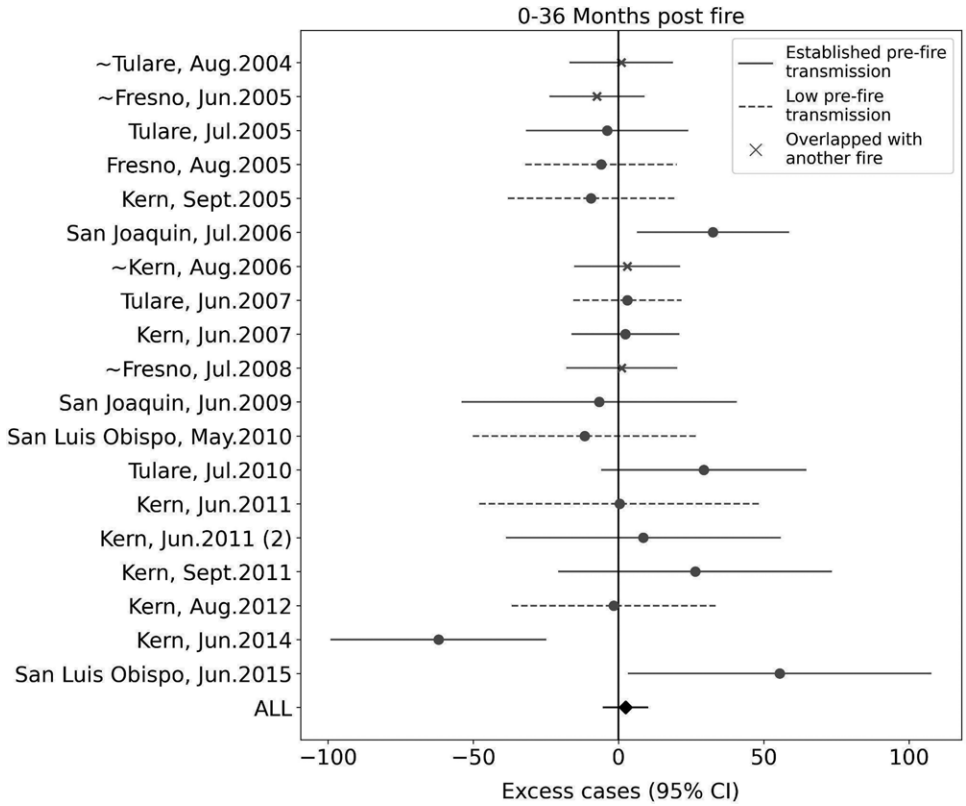

Figure 3. Individual and averaged fire effects demonstrating the difference in cases between fire-exposed regions and their synthetic control across the 3 years following the fire. Horizontal bars indicate 95% confidence intervals. Dashed lines represent fires where the surrounding region experienced fewer than 10 coccidioidomycosis cases during the 3 years before the fire. Effects marked with tildes (~) were measured over a period shorter than 36 months due to overlap with another fire. The average effect across all fires was calculated using a fixed-effects meta-analysis.

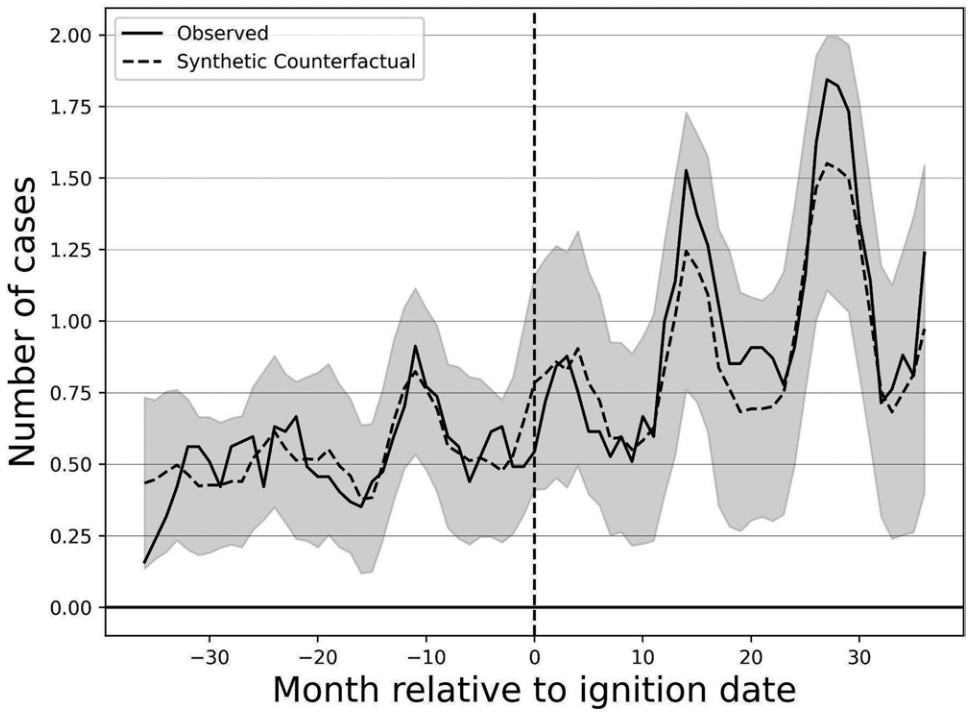

Figure 4. Average monthly cases observed in fire-exposed regions (solid line) compared to their synthetic controls (dashed line) based on 20 km hexagonal fire-exposed and control areas. The gray ribbon indicates the 95% confidence interval for the estimated counterfactual. Cases in the second and third years following a fire were elevated compared to their synthetic control, but not significantly so. Monthly deviations are smoothed using a 3-month rolling average.

vegetative cover following the fire (Figure S6; http://links.lww.com/EE/A222). Although the number of cases of coccidioidomycosis reported in the 3 years before the fire was relatively high (44 cases), this area within the Sierras is not classically expected to harbor *Coccidioides* in soils, in part due to the high elevation of the fire (2100 m) and colder temperature extremes. The rapid

spread and the proximity of the fire to houses prompted evacuation orders in nearby residences, potentially contributing to the observed decline.[46]

Secondary analyses

We did not find a significant association between the effect of individual wildfires and baseline climatic conditions (wind speed, temperature, and precipitation), elevation, vegetation, fire burn area, or population density (Figure S5; http://links.lww.com/EE/A222). Similarly, the effect of a wildfire on incident cases was not associated with differences in vegetative land cover in the fire-exposed region compared to the synthetic control region during the postfire period. In the synthetic control analysis with vegetation cover as the outcome, we saw a small but significant decrease in the percentage of soil in fire-exposed regions covered by vegetation (green or non-photosynthetic) around 12 months after the fires (Figure S7; http://links.lww.com/EE/A222). However, this decrease was not consistently observed among fires for which significant changes in coccidioidomycosis cases were noted using the interrupted time series model (Figure S6; http://links.lww.com/EE/A222). Furthermore, the differences in cases between a fire-exposed region and its estimated counterfactual were not associated with the differences in vegetative land cover across the 3 years following the fire. We also did not detect an acute increase in wind speed concurrent with fires. These results are presented in greater detail in the eSupplement; http://links.lww.com/EE/A222.

Sensitivity analyses

When the analysis was repeated using different radii for the hexagonal region, no fires exhibited a significant effect on incidence in the surrounding population (Figures S8 and S9; http://links.lww.com/EE/A222). However, smaller radii captured few cases and thus detected negligible changes following the fire, whereas larger radii measured effects with low precision, so both small and large radii, when compared with intermediate radii, may have had limited power to detect an effect.

Although individual effect estimates for several fires were sensitive to the controls included in the donor pool, the pooled effect of wildfires on coccidioidomycosis incidence remained null (Figure S8; http://links.lww.com/EE/A222). Of the four fires that were followed by significant changes in cases, only two consistently demonstrated significant effects under variations in the donor pool (Figure S9; http://links.lww.com/EE/A222). These findings support the results of the pooled analysis that wildfires do not generally exhibit strong associations with incidence at the population level.

Discussion

We examined the effect of wildfires on coccidioidomycosis incidence in adjacent populations in six endemic counties in California. When pooling the results across all 19 fires studied, we did not find a statistically significant association between wildfires and coccidioidomycosis incidence among the general population across the 3 years following fire events, even as we observed a nonsignificant amplification in seasonal transmission in the second and third years following fires across all fire-exposed regions. While wildfire activity has increased alongside coccidioidomycosis incidence in California over the past two decades,[2,24] our results suggest that wildfires may not be a major driver of increasing coccidioidomycosis incidence in the state. Prior research suggests that increasing aridity in the southwestern United States, among other factors, may be contributing to increases in incidence in the state.[4]

However, we did not find evidence that the majority (15) of the fires we analyzed influenced incidence in surrounding populations, our results motivate further investigation into the effect of larger fires that burn through areas with notable *Coccidioides* transmission. We detected significant increases in coccidioidomycosis incidence following three of the wildfires studied: the 2006 Midway fire in San Joaquin County, the 2011 Canyon Fire in Kern County, and the 2014 Park Hill fire in San Luis Obispo County. Unlike all but one of the other 16 fire-exposed regions, these fires had burn areas larger than 5,000 acres and occurred in more populous areas (>67 persons per square mile) where 18 or more cases of the disease were reported in the surrounding 20 km hexagonal buffer in the 3 years before the fire. Of note, the 2009 explosive fire in San Joaquin County also met these criteria but was not followed by significant changes in incidence (Figure S4; http://links.lww.com/EE/A222). Two of the three fires that were followed by significant increases in incidence occurred near major cities, and all three fires burned through grasslands or shrubland. However, only one of these fires (the 2006 Midway Fire in San Joaquin County) remained significantly associated with coccidioidomycosis incidence in sensitivity analyses (Figure S9; http://links.lww.com/EE/A222), underscoring the need for further study to confirm these findings.

This study examines the effect of wildfires on coccidioidomycosis among the general population, without inferring risk among specific sub-populations, including wildland firefighters, among whom outbreaks of coccidioidomycosis have been reported.[12–14] Studies have found an elevated risk of infection among firefighters directly involved in or exposed to potentially dirt-disturbing activities such as clearing brush, cutting or constructing fire containment lines, or working directly with contaminated soils after a fire.[13,14] Accordingly, appropriate protections should be provided to individuals directly working in wildfire prevention and suppression activities, even as we failed to detect evidence for enhanced risk of infection among the general public during and following most fires. Future work should consider the risk of coccidioidomycosis infection that wildfires pose to individuals directly involved in the response, or those directly interacting with burned soils.

Although we did not identify an association between wildfires and incidence for most of the 19 wildfires, several factors may have limited our ability to detect a significant statistical association. First, wildfires that occurred during this time period tended to lie in higher elevations at the periphery of the San Joaquin Valley, whereas the highest coccidioidomycosis incidence rates are observed at lower elevations in the lower San Joaquin Valley. As such, the burned habitat may have differed from the *Coccidioides* soil niche, resulting in negligible changes in concentrations of *Coccidioides* in the burned soil. However, this may explain why we did not detect an effect in some regions, elevation alone does not explain the heterogeneity in effect as several fires at low elevation in endemic areas did not demonstrate an effect, while the Canyon fire in mountainous eastern Kern was followed by significant increases. Second, while these counties are highly endemic for coccidioidomycosis, some of the wildfire-exposed areas have low population density, and thus fewer cases, resulting in high uncertainty in some individual fire effects that, when pooled, may have contributed to our null findings. Nevertheless, when we pool results from fires with at least 10 cases in the prefire period, we continue to see nonsignificant associations between fires and incidence. What is more, while our models included annual population estimates, it is possible that fires led to short-term population displacement; such declines in population immediately following the fire could offset any increases in cases that might otherwise be observed.

Our analysis found neither strong evidence for associations between most wildfires and coccidioidomycosis, nor evidence for two of the mechanisms via which wildfire is hypothesized to affect coccidioidomycosis: vegetative cover and wind speed. Although we observed decreases in vegetative ground cover following fires, we did not find evidence that reduced vegetative cover mediated the relationship between fires and incidence.

We also did not detect acute increases in wind speed concurrent with the wildfire. However, most fugitive dust emissions are generated through short periods of extremely high wind activity,[47] which monthly aggregation of wind data may have obscured. Longitudinal field studies to examine changes in the presence of *Coccidioides* spp. in the soil before and after wildfires should be prioritized, as should ground monitoring to examine changes in soil erosion and dust following fires.

This analysis has other limitations. Because monthly cases in the exposed regions were typically fewer than 20 cases per month, monthly incidence rates were unstable. Thus, we modeled monthly incident cases as the outcome rather than monthly incidence rates and adjusted for population by including population as a covariate on which to match during the creation of the synthetic control. In doing so, we were unable to calculate incidence rate ratios, and cannot ensure an exact match between the population of fire-exposed regions and that of their synthetic control as the matching algorithm minimizes differences across several time-varying covariates. Nevertheless, this method for adjusting for the population is a common approach in synthetic control analyses, and it yielded near matches between the population in the observed and the counterfactual regions.[45,48] In our matching algorithm, we did not include demographic or other factors that may affect case reporting, either via differential care-seeking behaviors among the general population or differential diagnosis and reporting practices within healthcare facilities. However, this could have created residual confounding, matching on pre-fire trends helps control for trends in reporting, and creation of a synthetic control that includes multiple control regions minimizes the influence of any sudden shifts in reporting among any single control region.[39]

Wind directions may result in heterogeneous exposure to fugitive dust emissions from burned soils within the study regions, even as the size and shape of the hexagonal buffers were chosen based on a balance between the distance spores disperse through wind, individual movement patterns, and the risk of dilution of the fire effect. We centered our exposed regions on fire-burned areas rather than smoke plumes, as we hypothesized that fire-burned areas may emit more spore-laden dust over the long term. Spatial data on smoke plumes emitted during fires show that smoke plumes may cover a much wider area that may not be centered on the fire, with the size and shape of the plume changing depending on wind and atmospheric conditions.[49] Future work may thus consider examining whether exposure to smoke plumes is associated with acute changes in coccidioidomycosis incidence rates.

Finally, our eligibility criteria prevented us from examining the effect of a wildfire in an area where fires are highly common. Unexposed regions were only eligible as potential controls if they had not experienced a wildfire in the 3 years before or after the fire being considered. Similarly, fire-exposed regions were only eligible to be analyzed if they did not experience another wildfire before the fire. While this limits the generalizability of this analysis to areas that experience wildfires more frequently than once every few years, it enables us to examine the effect of a single fire over a longer postperiod.

Conclusions

Amid the growing intensity of wildfires in California and rising coccidioidomycosis incidence, this study fills a gap in the literature by examining potential associations between wildfire activity and coccidioidomycosis transmission in populations residing around wildfire burn areas. Using a synthetic control framework, we find limited evidence to support an association between wildfires and coccidioidomycosis incidence among the general population. Nevertheless, continued investigation of increased case counts among the local community following fires, as well as further epidemiologic studies among populations directly working with or exposed to wildfire are warranted, along with large-scale field studies comparing the probability of *Coccidioides* detection in soils and the air before, during, and after fires. With these findings, public health efforts to mitigate the impact of wildfires on coccidioidomycosis risk are likely best focused, as they are currently within California, on prevention and worker protections during wildland firefighting, particularly those who may be involved in or exposed to soil-distributing activities while fighting wildfires.

Conflicts of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

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