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Estimating the Exposure–Response Relationship between Fine Mineral Dust Concentration and Coccidioidomycosis Incidence Using Speciated Particulate Matter Data: A Longitudinal Surveillance Study

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Background: Coccidioidomycosis, caused by inhalation of *Coccidioides* spp. spores, is an emerging infectious disease that is increasing in incidence throughout the southwestern US. The pathogen is soil-dwelling, and spore dispersal and human exposure are thought to co-occur with airborne mineral dust exposures, yet fundamental exposure–response relationships have not been conclusively estimated.

Objectives: We estimated associations between fine mineral dust concentration and coccidioidomycosis incidence in California from 2000 to 2017 at the census tract level, spatiotemporal heterogeneity in exposure–response, and effect modification by antecedent climate conditions.

Methods: We acquired monthly census tract-level coccidioidomycosis incidence data and modeled fine mineral dust concentrations from 2000 to 2017. We fitted zero-inflated distributed-lag nonlinear models to estimate overall exposure–lag–response relationships and identified factors contributing to heterogeneity in exposure–responses. Using a random-effects meta-analysis approach, we estimated county-specific and pooled exposure–responses for cumulative exposures.

Results: We found a positive exposure–response relationship between cumulative fine mineral dust exposure in the 1–3 months before estimated disease onset and coccidioidomycosis incidence across the study region [incidence rate ratio (IRR) for an increase from 0.1 to 1.1 $\mu g/m^3 = 1.60$; 95% CI: 1.46, 1.74]. Positive, supralinear associations were observed between incidence and modeled fine mineral dust exposures 1 [IRR = 1.13 (95% CI: 1.10, 1.17)], 2 [IRR = 1.15 (95% CI: 1.09, 1.20)] and 3 [IRR = 1.08 (95% CI: 1.04, 1.12)] months before estimated disease onset, with the highest exposures being particularly associated. The cumulative exposure–response relationship varied significantly by county [lowest IRR, western Tulare: 1.05 (95% CI: 0.54, 2.07); highest IRR, San Luis Obispo: 3.01 (95% CI: 2.05, 4.42)]. Season of exposure and prior wet winter were modest effect modifiers.

Discussion: Lagged exposures to fine mineral dust were strongly associated with coccidioidomycosis incidence in the endemic regions of California from 2000 to 2017. https://doi.org/10.1289/EHP13875

Introduction

Coccidioidomycosis is an emerging infectious disease with the highest burden of disease in the southwestern US. Recent decades have seen a more than 8-fold increase (2.4 to 18.8 cases/100,000 population) in age-adjusted incidence in California between 2000 and 2018.[1] Infection occurs following the inhalation of the fungal arthroconidia (2–4 μm)[2] of the genus *Coccidioides*, including *C. immitis*, most prevalent in California, and *C. posadasii*, most prevalent in Arizona.[3,4] *C. immitis* is endemic to arid and semi-arid, alkaline desert regions in California, particularly in the San Joaquin Valley.[1] Symptoms of coccidioidomycosis—including cough, fatigue, fever, headache, muscle aches, night sweats, rashes, and shortness of breath—can appear between 1 and 3 wk after spore inhalation and typically last from a few weeks to a few months.[5] Infection may occur following the inhalation of as few as one spore.[6] Prior infection generally results in acquired immunity, although chronic disease can occur.[6–8] Reactivation of infection is rare.[9] Approximately 60% of people with coccidioidomycosis are asymptomatic,[6] 5%–10% have chronic lung involvement, and 1% have dissemination outside of the lungs.[5,10] Dissemination causes significant morbidity, with a disseminated case fatality rate of ∼30%.[11]

Substantial increases in both annual incidence and geographic range of coccidioidomycosis in California have been observed over the past two decades,[1] with most cases occurring in the counties of the southern San Joaquin Valley, including Kern, San Luis Obispo, Kings, Madera, Fresno, and Tulare counties.[1] Increases in incidence have also recently been observed outside of the highly endemic region. Comparing the incidence in 2018 with that in 2000, the highest rate ratios were observed in the northern San Joaquin Valley and the Southern Coast (15.3 and 8.8, respectively), and the highest rate ratio comparing 2018 to 2014 was observed in the Central Coast (8.1).[1] However, the underlying factors driving these phenomena are not well understood.[12–14]

Coccidioidomycosis is thought to primarily occur following anthropogenic (e.g., excavation) or natural (e.g., wind erosion) disturbance of the soil matrix, leading to aerosolization and inhalation of *Coccidioides* arthroconidia.[6,15] Moreover, dispersion occurs through the air for many other species of fungi.[16] Acute occupational exposures to dust during soil disturbance activities have been associated with outbreaks among agricultural workers,[17] construction crews,[18–20] and wildland firefighters.[21–23] Further,

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socioeconomic factors, including income,[24,25] have been associated with an elevated risk of coccidioidomycosis. Individuals with a lower income or individuals who are engaged in these outdoor occupations may reside in areas with greater dust exposure. There is serious academic debate as to whether dust storms are associated with incidence, fueled by difficulties in accurately characterizing exposures.[26–30] Furthermore, the association between ambient dust concentrations and incidence in the general population is not well established. Ambient all-source particulate matter ≤ 10 μm in aerodynamic diameter (PM_{10}) and near-surface dust concentration have been positively associated with coccidioidomycosis incidence,[31–33] although others have found negative associations.[34] Despite these findings, the specific exposure–response relationship between ambient fine mineral dust concentration and coccidioidomycosis incidence remains poorly characterized, particularly as it relates to climatological modifiers of risk, which may influence the concentrations of *Coccidioides* arthroconidia within dust.

Prior research has generally focused on the association between all-source PM_{10}—which comprises many constituents, including organic carbon, elemental carbon, metals, sulfate, nitrate, ammonium, mineral dust, sea salt, and others—and coccidioidomycosis incidence.[30,31,35] Because mineral dust emissions are viewed as the main source of *Coccidioides* arthroconidia exposures (spores within the soil matrix are mobilized with mineral dust through wind-driven saltation or manual disturbance[6]), analysis of the effects of exposures that include many nonmineral dust components of PM_{10} is expected to be subject to significant measurement error and may prevent accurate estimation of lag–exposure–response relationships. Further, nonmineral dust components of PM_{10} of anthropogenic origins (e.g., sulfate, nitrate, ammonia, black carbon) differ widely from mineral dust concentrations in their spatiotemporal distribution and sources; thus, when PM_{10} is used as a surrogate for mineral dust, associations with *Coccidioides* incidence may be biased. Although estimates of the dust fraction of PM_{10} are not available, recent advances in air pollution modeling have allowed for compositional analysis of PM ≤ 2.5 μm in diameter ($PM_{2.5}$),[36] enabling estimation of the association between fine mineral dust and coccidioidomycosis incidence as pursued in the present study. Further, *C. immitis* arthroconidia are similar in size (2–4 μm) to fine particles and thus likely aerosolize and transport under similar conditions.

Spores are expected to be mixed with mineral dust when dust emissions originate from soils containing established *Coccidioides* populations. Meteorological and other environmental conditions (e.g., rodent populations, other soil nutrients[4,37]) that facilitate the proliferation of *Coccidioides* in soils may be important effect modifiers of the relationship between fine mineral dust concentrations and coccidioidomycosis incidence by increasing or decreasing the concentration of spores aerosolized in equivalent concentrations of dust. One dominant theory—termed the "grow and blow" hypothesis—posits that alternating cool/wet and hot/dry seasons support pathogen growth and dispersal by supporting mycelial growth in the wet months and arthroconidia dispersion in the dry months (Figure S1).[34,38,39] Neglecting to account for these climatic conditions may explain why some studies found mixed relationships between dust, PM concentrations, and coccidioidomycosis incidence. In California, coccidioidomycosis incidence typically exhibits a strong seasonal pattern, peaking during the fall. Precipitation during the winter and spring preceding the fall is associated with an increased incidence of disease in the fall, potentially by providing moisture to support fungal growth in soils.[40] Although recent studies have advanced our understanding of the role of temperature and precipitation cycling in *Coccidioides* growth and risk of coccidioidomycosis,[31,32,34,38,40] we still do not know how these factors modify the risk conferred by dust exposures. The substantial intrinsic variation in incidence across regions complicates our understanding of *Coccidioides* exposure and the associated risk of coccidioidomycosis. The estimation of fine mineral dust and coccidioidomycosis exposure–response relationships across locations may provide information on regional variation in *Coccidioides* spore concentrations in dust. County-specific exposure–response relationships may also inform local health jurisdictions as to the degree of risk posed by dust in their specific county.

In this study, we estimated the exposure–response relationship between modeled fine mineral dust concentration and coccidioidomycosis incidence in California and explored the role of climate conditions as modifiers of the association. We fitted zero-inflated distributed-lag nonlinear models (DLNMs) to census tract-level fine mineral dust concentrations and coccidioidomycosis incidence data across the study region, as well as on a per-county basis, using data on confirmed incident cases of coccidioidomycosis reported to the California Department of Public Health (CDPH) from January 2000 to December 2017. The results yielded a robust characterization of the risks of coccidioidomycosis posed by fine mineral dust exposure and provided the means of targeting mitigation actions to minimize *Coccidioides* arthroconidia exposure that may accompany dust emissions in areas where coccidioidomycosis is endemic or emerging.

Methods

Study Region

We analyzed coccidioidomycosis risk in endemic transmission counties in California, as detailed elsewhere.[40] Briefly, the study region consisted of counties in the San Joaquin Valley and surrounding areas (cases are infrequently reported outside this region).[1] We defined endemic transmission counties as counties or subcounties with at least 500 cases and a mean annual incidence rate of >5 cases/100,000 people over the period of 2000–2017 as reported to CDPH. This resulted in the inclusion of 14 total counties: 8 counties (Kings, Stanislaus, Ventura, Monterey, San Luis Obispo, San Joaquin, Merced, and Santa Barbara) and 6 subdivided counties (termed subcounties; eastern and western Kern, western Fresno, western Madera, western Tulare, and northern Los Angeles; Figure 1A). Subcounties were created to capture the variation in temperature and precipitation observed across several counties affected by the Sierra Nevada and San Emigdio-Tehachapi mountains. Subcounties were split following a 500-m isocline. Cases with estimated onset dates between 1 January 2000 and 31 December 2017 were included to align with the availability of fine mineral dust concentration data. Counties and subcounties are henceforth referred to as counties.

Highly urbanized census tracts, defined as census tracts above the 40th percentile of mean population density (defined as number of residents per kilometer squared) by year over the study period, were excluded from the study region (Figure S2) to minimize exposure misclassification, which is likely to be highest in highly urbanized census tracts where populations frequently leave their residential census tract for work and other activities. In addition, urbanized environments are characterized by high levels of paved, impervious surfaces that are not suitable habitat for *Coccidioides*. Overall, we excluded 60% (N excluded = 771; N included = 515) of census tracts that were defined as highly urbanized, corresponding to 64% of person-years (N excluded 71,409,888; N included = 40,837,222), 62% of cases (N excluded = 29,663; N included = 17,897), and 2% of surface area (in kilometers squared) in the study region (N excluded = 1,967.58; N included = 90,250.55) (Figure S2). We conducted sensitivity analyses varying the level of population density required to be classified as urban, including all census tracts and excluding census tracts above

the 60th percentile of mean population density, thus excluding 40% of census tracts compared with 60% in the main analysis.

Epidemiologic Data and Ethical Approval

Data on incident cases of coccidioidomycosis were obtained from the CDPH coccidioidomycosis surveillance system. Coccidioidomycosis cases have been reportable to local health departments and CDPH since 1995. Prior to 1 January 2019, case definitions required both laboratory and clinical criteria to be met. Post-2019, only laboratory criteria were used. Laboratory criteria included cultural, histopathological, or molecular evidence of the presence of *Coccidioides* species or a positive serological test for coccidioidal antibodies in serum, cerebrospinal fluid, or other body fluids. Clinical criteria were defined by the Council of State and Territorial Epidemiologists (CSTE). For the full case definition and associated changes, see the referenced CDPH and CSTE reports.[41,42] Within the surveillance data, cases are reported once, so patients with more than one reported positive *Coccidioides* test are only recorded upon their initial positive result. A geocoded census tract was obtained for $\sim 90\%$ ($N = 16{,}107$) of cases based on reported residence. For cases that could not be matched to a residential address (10%; $N = 1{,}790$), the centroid of their ZIP code or city was used.

When possible, dates of onset were recorded for each case, although these were available for only 24% of cases ($n = 4{,}295$). In the absence of an onset date, the earliest clinical or laboratory date collected was used as the estimated onset date. Thus, the estimated date of onset reflects reporting delays between symptom onset and diagnosis, specimen collection, record creation, or patient death. Among coccidioidomycosis surveillance reports, the median time between estimated disease onset and record creation for patients who recalled the estimated date of disease onset was 29 d. Such reporting delays are common in the endemic states in which coccidioidomycosis is reportable. A recent study in Arizona estimated that the median time between symptom onset and diagnosis from 2007 to 2008 was 55 d.[43] All case data were deidentified prior to analysis.

Patients with residence in prison facilities were excluded from study case records to minimize exposure misclassification, given that incarcerated individuals are occasionally transferred among facilities,[44,45] potentially obscuring the true location of exposure. Estimated disease onset data were aggregated to onset month, and residential address was aggregated to the census tract level, yielding incident cases per census tract-month. The study received approval from the Committee for Protection of Human Subjects of the California Health and Human Services Agency (protocol no. 17-05-2993). Approval by the University of California, Berkeley, was provided by reliance on the California State approval.

Exposure and Climatic Data

We obtained estimates of the fine mineral dust concentration (in micrograms per meter cubed) present within surface fine particulate matter (i.e., $PM_{2.5}$) for our study region using a model developed by van Donkelaar et al.,[36] which provides $0.01^\circ \times 0.01^\circ$ monthly $PM_{2.5}$ concentrations, as well as composition by sulfate, nitrate, ammonium, black carbon, organic matter, sea salt, and mineral dust. Briefly, the model used ground-based observations of $PM_{2.5}$ mass and composition from multiple monitoring networks in combination with the Goddard Earth Observing System chemical transport model, GEOS-Chem [as a data source for aerosol optical depth (AOD) and to simulate the relationship between AOD and $PM_{2.5}$], to produce monthly mean geoscience-based $PM_{2.5}$ surfaces. Component mass concentrations were estimated using a modification of the simulated relative contribution approach by Philip et al. 2014.[46] Further, van Donkelaar et al. validated results using 10-fold cross-validation against ground-based monitors of speciated $PM_{2.5}$ (Figure S3). Across the US, modeled fine mineral dust had a mean annual R^2 of 0.42 (5th annual: 0.34; 95th annual: 0.55) and a root mean square deviation (RMSD) of 0.2 (5th annual: 0.2, 95th annual: 0.3) with *in situ* measurements of fine mineral dust. In the southwestern US, modeled fine mineral dust had a mean annual R^2 of 0.21 (5th annual: 0.07; 95th annual: 0.37) and an RMSD of 0.4 (5th annual: 0.3, 95th annual: 0.5) with *in situ* measurements of fine mineral dust.[36] For the full model specification and validation statistics, see van Donkelaar et al.[36] We additionally tested the correlation between model and monitor data from the Interagency Monitoring of Protected Visual Environments (IMPROVE) program using 5- and 10-km buffers surrounding all monitors within the study region. We averaged site-level correlations between IMPROVE monitors and buffers to obtain a regional correlation. IMPROVE monitors estimate dust concentrations within the $PM_{2.5}$ fraction using X-ray fluorescence and a mineral component analysis method.[47,48]

To estimate exposure to mineral dust, we extracted modeled monthly average fine mineral dust concentration at the census tract level.[36] Because the effects of dust exposure on reported disease incidence are likely to be delayed due to both incubation periods (1–3 wk) and significant reporting delays,[43,49,50] we analyzed the relationship between monthly census tract-level incidence and fine mineral dust exposures at 0–6 month lags. We extracted monthly mean daily temperature and total precipitation at a 4-km spatial resolution from the Parameter-elevation Regression on Independent Slopes Model (PRISM)[51] and assigned monthly means to each census tract.

County-Level Covariates

To obtain annual population estimates at the census tract level, we combined annual county-level population estimates from the California Department of Finance with the 2010 US decennial census.[52,53] Because census tract-level population estimates are directly measured only by the decennial census, we used the decennial census to calculate the proportion of county residents living in each census tract. We assumed a constant proportion of residents by census tract over the 10-y periods between censuses and multiplied each proportion by the annual county-level population estimates from the Department of Finance. We thus obtained population estimates for each census tract year and estimated population density by dividing the total population of a census tract by its total area. Population estimates were used as the denominator to calculate county-level incidence rates per 100,000 people and as the log-transformed in an offset term in the DLNMs, described below.

We estimated the proportion of workers in construction and agriculture at the county level from 2000 to 2017 using data from the 1-y American Community Survey (ACS[54]), accessed via the R package *tidycensus* (https://walker-data.com/tidycensus/). Because the 1-y ACS was initiated in 2005, we linearly interpolated county-level proportions for the years 2000 to 2004. This method was selected as a conservative approach given that quadratic and spline models yielded highly variable estimates of occupation proportions. We also summarized the percentage of the population in each county living below the poverty line (defined as the number of people with income below the poverty line per county divided by the total county population) from 2000 to 2017 using the 1-y ACS data and the interpolation methods described above.

Statistical Analysis

To estimate the overall association between fine mineral dust concentrations and incidence in the study region, we used zero-inflated negative binomial DLNMs. DLNMs are commonly

applied in time-series studies where the effect of an exposure may occur over several time periods.[55] Zero-inflated models were used due to the high proportion of zeros within our data, given that coccidioidomycosis is both a rare and highly seasonal disease. The resulting models accounted for overdispersion, thus preventing the underestimation of standard errors.

Our outcome variable was the number of incident cases of coccidioidomycosis reported per census tract-month. We also included the log annual population of each census tract, estimated as described in the county-level covariate section, as an offset in the model. Including log population as an offset term within the negative binomial model serves to normalize the case count per census tract and month, thereby permitting model coefficients to be interpreted as the log difference in incidence rates associated with a unit change in a covariate (and, when exponentiated, the IRR). The exposure variables were average monthly fine mineral dust concentrations (in micrograms per meter cubed) spanning 6 months prior to 2 months after the estimated disease onset to capture the effect of variation in duration of reporting delays, examine potentially diminishing associations at further lags, and include negative controls for confounding.

To model the exposure–response and lag–response dimensions simultaneously, we created a two-dimensional cross-basis matrix of the predictor and lags using the crossbasis function in the R package *dlnm*.[56] We modeled both the lag–response and exposure–response relationships using natural cubic splines with 3 and 2 equally spaced knots, respectively. A natural spline function of continuous time with 2 knots per year (selected to capture seasonal fluctuations without overfitting) was included to control for long-term and strong seasonal trends in both fine dust concentrations and coccidioidomycosis incidence. To control for spatial confounding, we included a natural cubic spline on both the latitude and longitude of the centroid of each census tract as variables in our model with 35 and 25 equally spaced knots, respectively. The number of knots was picked to be ~ 1 knot per 10 miles (16.09 kilometers) across the study region's length and width while minimizing the Akaike information criterion. We additionally included a fixed effect on county to account for confounding factors that may vary less smoothly across space, including medical provider knowledge and the distribution of occupations. For the zero-inflated portion of the model, dummy variables for the month of estimated disease onset were used as predictors. See Equations 1 and 2 below for reduced and full model specifications:

$$\begin{aligned}\log\left(Y_{i,t}\right) &= \log\left(population_{i,t}\right) + \beta_0 + \beta_1(county_i) \\ &+ ns(latitude_i, df = 34) + ns(longitude_i, df = 24) \\ &+ ns(t, df = 35) + cb(dust) \\ \log it(p_{i,t}) &= \beta_0 + \sum_{j=1}^{11} \beta_j \mathbb{I}(month = j)\end{aligned} \quad (1)$$

and

$$\begin{aligned}\log\left(Y_{i,t}\right) &= \log\left(population_{i,t}\right) + \beta_0 + \beta_1(county_i) \\ &+ ns(latitude_i, df = 34) + ns(longitude_i, df = 24) \\ &+ ns(t, df = 35) + \beta_2(\%agriculture) + \beta_3(\%construction) \\ &+ \beta_4(\%BPL) + cb(dust) \\ \log it(p_{i,t}) &= \beta_0 + \sum_{j=1}^{11} \beta_j \mathbb{I}(month = j),\end{aligned} \quad (2)$$

where, $Y_{i,t}$ represents the number of observed coccidioidomycosis cases in census tract i at time t; *population* represents the residential population in census tract i at time t; *ns* represents the natural cubic spline; *df*, represents degrees of freedom; *BPL* represents the annual county-level proportion below poverty line; $\%agriculture$ and $\%construction$ represent the annual county-level proportion employed in these industries; $cb(\bullet)$ denotes the crossbasis DLNM functions;[56] $p_{i,t}$ represents the probability of an observation in census tract i at time t being equal to zero; and $\beta\mathbb{I}(indicator)$ represents dummy variables for month of onset of disease.

We conducted several additional sensitivity analyses, including varying the level of population density required to be classified as urban (i.e., including all census tracts, excluding census tracts above the 60th percentile of mean population density), knot placement within the crossbasis (i.e., at the 25th and 75th percentiles of dust concentrations observed over the study region and period), and inclusion of confounders (i.e., including sociodemographic covariates; Equation 2).

From this model, we extracted exposure–response relationships for each lagged month, as well as the cumulative exposure over lags 1, 2, and 3 months prior to estimated disease onset. Further lags were not included in our cumulative measure because they were not significantly associated with coccidioidomycosis incidence and thus would not contribute to the exposure–response. We did not consider the concurrent month in calculating our cumulative exposure because the concurrent month incorporated fine dust concentrations potentially experienced after a patient's estimated disease onset. We limited our analyses to fine dust concentrations within the 0th to the 99th percentile range of all observations (0 to 2.52 $\mu g/m^3$) to avoid overinterpretation of results with limited data support.

Fine dust exposures of 0.1 $\mu g/m^3$ were set as the IRR centering reference value (the value at which IRR = 1) to express IRRs in relation to the 10th percentile of fine dust concentrations observed across the study region and period. Exposure–response relationships for a given lag may be interpreted as the relative increase in incidence associated with increasing uniform exposure to fine mineral dust relative to 0.1 $\mu g/m^3$ (i.e., the centering reference value) at the specified lag, across the range of dust concentrations experienced in the study region (limited to the 0th to 99th percentile range). Cumulative exposure–response relationships may be similarly interpreted as the increase in incidence associated with increasing exposure to fine mineral dust relative to 0.1 $\mu g/m^3$ during *all* the included lagged months (i.e., 1, 2, and 3 months prior to the estimated disease onset). Cumulative exposure–responses were calculated to combine effects over multiple months because variable reporting delays were expected to cause a distribution of lags between exposure and estimated disease onset.

Negative Control Exposure

Negative control exposures can be used to check for residual confounding in time-series and observational studies.[57] A negative control exposure is conditionally independent of the outcome in the absence of confounding, model misspecification, and measurement error but is associated with the exposure and potential unmeasured confounders. In the context of air pollution epidemiology, air pollution exposures that occur *following* estimated disease onset (e.g., in the future) are often used as negative controls given that they are expected to be associated with the exposure (current or lagged air pollution levels) and conditionally independent of the outcome in the absence of the sources of bias described above. More recent research has demonstrated that if controlling for confounders is not possible owing to measurement constraints, the inclusion of negative controls contributes to the partial correction of unmeasured confounding.[58] We incorporated

negative control exposures into our regression analysis to check for residual confounding. In our main model of the association between fine mineral dust exposure and coccidioidomycosis incidence in the study region, we included fine mineral dust exposures lagged up to 6 months prior to estimated disease onset and, as negative controls, up to 2 months after estimated disease onset.

Examination of Effect Modification

To account for the influence of climate cycling on *Coccidioides* growth, and in turn on the concentration of spores within fine dust, we examined how the season of exposure and preceding winter total precipitation and how summer average temperature modified the exposure–response relationship. To do so, we multiplied the basis function for the cubic spline on fine dust concentration by a series of indicators for the season (spring, summer, fall, winter, and dry vs. wet season) of fine mineral dust exposure, wet vs. dry preceding winters, and hot vs. cool preceding summers (Equations 3–6) and ran separate models with each indicator. For example, four separate models were run using Equation 3, with indicators for spring, summer, fall, and winter multiplied by the crossbasis. Cross prediction of each interacted model represents the exposure–response relationship for each indicator condition. Equations 3–6 are shown below.

$$\begin{aligned}\log(Y_{i,t}) &= \log(population_{i,t}) + \beta_0 + \beta_1(county_i) \\ &+ ns(latitude_i, df = 34) + ns(longitude_i, df = 24) \\ &+ ns(t, df = 35) + cb(dust) * \mathbb{I}(season\ of\ dust\ exposure)\end{aligned}$$

$$\log it(p_{i,t}) = \beta_0 + \sum_{j=1}^{11} \beta_j \mathbb{I}(month = j), \tag{3}$$

$$\begin{aligned}\log(Y_{i,t}) &= \log(population_{i,t}) + \beta_0 + \beta_1(county_i) \\ &+ ns(latitude_i, df = 34) + ns(longitude_i, df = 24) \\ &+ ns(t, df = 35) + cb(dust) * \mathbb{I}(dry\ season)\end{aligned}$$

$$\begin{aligned}\log(Y_{i,t}) &= \log(population_{i,t}) + \beta_0 + \beta_1(county_i) \\ &+ ns(latitude_i, df = 34) + ns(longitude_i, df = 24) \\ &+ ns(t, df = 35) + cb(dust) * \mathbb{I}(wet\ season)\end{aligned}$$

$$\log it(p_{i,t}) = \beta_0 + \sum_{j=1}^{11} \beta_j \mathbb{I}(month = j), \tag{4}$$

$$\begin{aligned}\log(Y_{i,t}) &= \log(population_{i,t}) + \beta_0 + \beta_1(county_i) \\ &+ ns(latitude_i, df = 34) + ns(longitude_i, df = 24) \\ &+ ns(t, df = 35) + cb(dust) * \mathbb{I}(> 75th\ precip)\end{aligned}$$

$$\begin{aligned}\log(Y_{i,t}) &= \log(population_{i,t}) + \beta_0 + \beta_1(county_i) \\ &+ ns(latitude_i, df = 34) + ns(longitude_i, df = 24) \\ &+ ns(t, df = 35) + cb(dust) * \mathbb{I}(< 25th\ precip)\end{aligned}$$

$$\log it(p_{i,t}) = \beta_0 + \sum_{j=1}^{11} \beta_j \mathbb{I}(month = j), \tag{5}$$

and

$$\begin{aligned}\log(Y_{i,t}) &= \log(population_{i,t}) + \beta_0 + \beta_1(county_i) \\ &+ ns(latitude_i, df = 34) + ns(longitude_i, df = 24) \\ &+ ns(t, df = 35) + cb(dust) * \mathbb{I}(> 75th\ temp)\end{aligned}$$

$$\begin{aligned}\log(Y_{i,t}) &= \log(population_{i,t}) + \beta_0 + \beta_1(county_i) \\ &+ ns(latitude_i, df = 34) + ns(longitude_i, df = 24) \\ &+ ns(t, df = 35) + cb(dust) * \mathbb{I}(< 25th\ temp)\end{aligned}$$

$$\log it(p_{i,t}) = \beta_0 + \sum_{j=1}^{11} \beta_j \mathbb{I}(month = j). \tag{6}$$

We restricted effect modification analyses to exposures lagged 2 months prior to estimated disease onset because this month had the strongest individual association with coccidioidomycosis incidence. Given that reporting delays create a distribution of lags, this restriction was applied to capture the strongest signal for usage in effect modification analyses, which can often be underpowered. To test the statistical significance of interaction more formally, we employed a resampling approach, using the mean and standard error for each 1- and 2-unit comparison of interest to create normal distributions that we sampled 10,000 times with replacement. We then compared the means of these vectors of possible coefficient values with the Student *t*-test. We reported *p*-values and considered the effect modification to be statistically significant at the 95% level.

For seasonal analyses, we considered spring to be March–May, summer to be June–August, fall to be September–November, and winter to be December–February. To estimate exposure–response relationships in the wet season as compared with the dry season in California, we considered the dry season to be May–October, and the wet season to be November–April. We considered dry and wet winters and cool and hot summers to be below the 25th or above the 75th percentile for precipitation and temperature for each county over the study period, respectively. This was done to both identify extreme climate conditions and maintain coverage for effect modification analysis. Winter months were not assigned a total winter precipitation given that the effects of precipitation on *Coccidioides* growth and subsequent spore presence in dust are expected to be more temporally delayed to allow for fungal population growth.[32,34] Summer months were assigned their concurrent summer average because temperature is expected to have an acute impact on spore autolysis and thus potential spore dust mobilization.[34,40]

We hypothesized that fine mineral dust exposures in the summer and fall, as well as in the dry season, would exhibit the strongest associations with coccidioidomycosis incidence rate, given that *Coccidioides* theoretically aerosolizes at greater concentrations during these seasons owing to the elevated temperatures facilitating spore autolysis.[31,32,34,40] We further hypothesized that, consistent with the grow and blow hypothesis,[38,40] fine mineral dust exposures that follow wet winters would be more highly associated with coccidioidomycosis incidence rates as compared with fine mineral dust exposures following dry winters, because *Coccidioides* fungal growth is supported by elevated soil moisture in the winter months.[32,34] Elevated summer temperatures may reduce the relative fitness of microbial competitors,[31,39] clearing the ecological niche for *Coccidioides* fungal growth in the following months.[13] *Coccidioides* is thought to be a poor competitor[59] but able to survive climatological extremes.[60] Thus, we hypothesized that fine dust exposures that follow hot summers would also be more highly associated with the

coccidioidomycosis incidence rate as compared with those that follow cooler summers.

Estimating County-Specific Exposure–Response Relationships

Because both dust concentrations and the annual incidence of coccidioidomycosis vary across the study region, we estimated county-specific exposure–response relationships. We fit zero-inflated DLNMs within each county to estimate the associations between lagged 1–3 month cumulative fine mineral dust exposures and coccidioidomycosis incidence (Equation 7).

$$\log\left(Y_{i,t}\right) = \log\left(population_{i,t}\right) + \beta_0 + ns(latitude_i, df = 2) + ns(longitude_i, df = 1) + ns(t, df = 35) + cb(dust)$$

$$\log it(p_{i,t}) = \beta_0 + \sum_{j=1}^{11} \beta_j \mathbb{I}(month = j). \quad (7)$$

As before, we used logged population in census tracts to interpret exponentiated coefficients from models as IRRs. Zero-inflation was modeled using dummy variables for the month of estimated disease onset. We included 2 knots placed at the 25th and 75th percentiles of dust concentrations across the study region for the exposure–response relationship because not all counties experienced dust concentrations high enough to use equally spaced knots as we did in our region-wide model. We kept 3 equally spaced knots across the lag–response relationship. Because models were run at the county level, we did not include a fixed effect on county. We additionally reduced the number of knots that were included on the latitude and longitude to accommodate the smaller size of counties as compared with the entire study region. We included 3 equally spaced knots on latitude and 2 on longitude because the model would not converge with a greater number. We then conducted a meta-analysis to pool county-specific exposure–response relationships, following prior work.[61,62] We used a random-effects approach to obtain the pooled estimate and subsequently calculated the best linear unbiased predictors (BLUP) for each county. The BLUP estimates balance bias and variance by allowing counties to borrow information from each other.[62] We identified a 1- and 2-$\mu g/m^3$ increase in cumulative fine dust concentration relative to 0.1 $\mu g/m^3$ and extracted the associated IRR for the pooled region, as well as for individual counties. For all analyses, we considered statistical significance at $p < 0.05$. All statistical analyses and mapping were conducted in R (version 4.2.0; R Development Core Team). The analytic code may be found in the file "DLNM demo.Rmd" in the Supplemental Material.

Results

There were 17,897 reported cases of coccidioidomycosis reported in the study region from 2000 to 2017. Kern (172 cases/100,000 people), Kings (72 cases/100,000 people), San Luis Obispo (46 cases/100,000 people), and Tulare counties (45 cases/100,000 people) had the highest annual incidence rates. Incidence rates were calculated using all census tracts and combined regions (i.e., eastern and western) to protect patient confidentiality in line with CDPH policy (Figure 1A). Within the study region, fine mineral dust concentration was highly seasonal, peaking on average in the late summer and fall months across the region. Fine dust concentrations were consistently highest in the western Tulare (monthly average over the study period $= 1.09\ \mu g/m^3$), western Kern (0.95 $\mu g/m^3$), Kings (0.92 $\mu g/m^3$), and western Fresno (0.92 $\mu g/m^3$) counties (Figure 1B). The minimum monthly fine dust concentration observed over the study period was 0 $\mu g/m^3$, and the maximum was 4.00 $\mu g/m^3$. The 0th–99th percentile range of monthly fine dust concentrations observed in the study region ranged from 0 to 2.52 $\mu g/m^3$. Selected summary statistics of annual mean and cumulative fine mineral dust concentrations are presented in Table 1. Modeled fine mineral dust

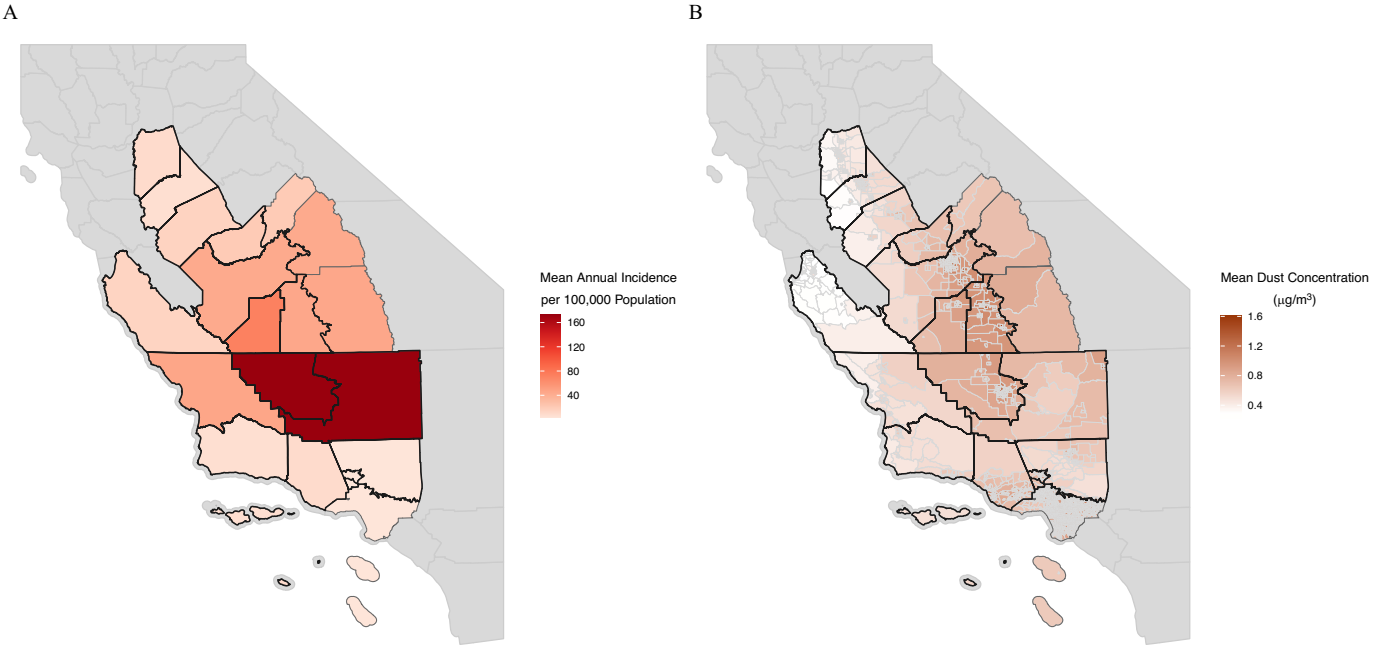

Figure 1. Maps of the study region, highlighting coccidioidomycosis incidence and fine mineral dust concentration over the study period (2000–2017) in California. The thick black outline denotes the included counties and subcounties in the study region (*N* counties = 14; *N* census tracts = 515). Census tracts and county subregions outside of the thickest black lines were not included in the analysis. (A) Full counties colored by their mean annual incidence of coccidioidomycosis per 100,000 population over the study period (2000 to 2017). Incidence is calculated at the county level as opposed to the subcounty level in accordance with CDPH policy. (B) Average monthly fine mineral dust concentrations ($\mu g/m^3$) across the study region and period at the census tract level. Corresponding numerical data are shown in Excel Table S1. Note: CDPH, California Department of Public Health.

Table 1. Summary statistics (selected percentiles) of fine mineral dust exposure metrics within the study region, California, 2000–2017.

	5th		25th		50th		75th		95th	
Year	Cumulative	Mean	Cumulative	Mean	Cumulative	Mean	Cumulative	Mean	Cumulative	Mean
2000	4.6	0.38	6.23	0.52	8.66	0.72	12.31	1.03	14.54	1.21
2001	6.17	0.51	8.71	0.73	11	0.92	15.11	1.26	17.52	1.46
2002	5.79	0.48	8.54	0.71	10.83	0.9	14.47	1.21	18.09	1.51
2003	4.36	0.36	6.51	0.54	8.6	0.72	12.58	1.05	16.49	1.37
2004	4.83	0.4	7.01	0.58	9.35	0.78	12.53	1.04	15.66	1.31
2005	2.61	0.22	4.63	0.39	6.33	0.53	9.34	0.78	13.44	1.12
2006	4.71	0.39	6.93	0.58	9.46	0.79	13.42	1.12	16.96	1.41
2007	3.93	0.33	6.3	0.52	8.72	0.73	13.18	1.1	16.52	1.38
2008	5.06	0.42	7.73	0.64	11.26	0.94	16.27	1.36	20.42	1.7
2009	4.47	0.37	6.54	0.55	9.92	0.83	13.57	1.13	17.18	1.43
2010	3.69	0.31	5.56	0.46	7.68	0.64	10.39	0.87	12.49	1.04
2011	2.88	0.24	5.39	0.45	7.66	0.64	11.9	0.99	16.87	1.41
2012	4.15	0.35	6.68	0.56	9.82	0.82	13.2	1.1	16.74	1.39
2013	5.28	0.44	8.59	0.72	11.57	0.96	15.11	1.26	21.01	1.75
2014	4.27	0.36	8.02	0.67	12.13	1.01	16.34	1.36	18.46	1.54
2015	4.15	0.35	6.78	0.57	9.09	0.76	12.38	1.03	15.04	1.25
2016	4.55	0.38	7.6	0.63	10.84	0.9	14.09	1.17	17.42	1.45
2017	4.59	0.38	8.35	0.7	10.8	0.9	14.57	1.21	18.61	1.55

Note: Monthly census tract-level fine mineral dust concentrations ($\mu g/m^3$) are summarized annually into census tract-level cumulative and mean exposure measures.

had a median annual R^2 of 0.42 (5th annual: 0.34; 95th annual: 0.55) and 0.21 (5th annual: 0.07; 95th annual: 0.37) with *in situ* measurements of fine mineral dust (Figure S3) in the US and the southwestern US, respectively.[36] When comparing monthly fine dust concentrations as estimated by the van Donkelaar et al. model[36] and concentrations estimated by IMPROVE monitors within our study region, we found a high degree of correlation overall (5-km $R^2 = 0.82$; 10-km $R^2 = 0.82$). At low fine dust concentrations (defined as $<0.75\ \mu g/m^3$), the 5- and 10-km correlations were 0.56 and 0.55, respectively. At high fine dust concentrations (defined as $>2\ \mu g/m^3$), the degree of correlation was lower (5-km $R^2 = 0.39$; 10-km $R^2 = 0.38$). Precipitation and temperature were highly seasonal, with precipitation peaking in the winter and temperatures peaking in the summer. On average, counties in the Central Valley had less precipitation, higher temperatures (Figure S4), and higher fine mineral dust concentrations (Figure 1B) as compared with northern and coastal counties, which were generally wetter, cooler, and less dusty. For the full annual census tract and county-level summaries of average fine mineral dust concentrations, annual temperature, and total precipitation, see Excel Table S1.

Overall Associations in the Study Region

Overall, we found that elevated fine dust concentrations lagged 1–3 months prior to estimated disease onset exhibited the strongest associations with coccidioidomycosis incidence (Figure 2). Sensitivity analyses indicated that these associations were robust to variations in the quantile of population density (including all census tracts, excluding fewer urban census tracts; Excel Table

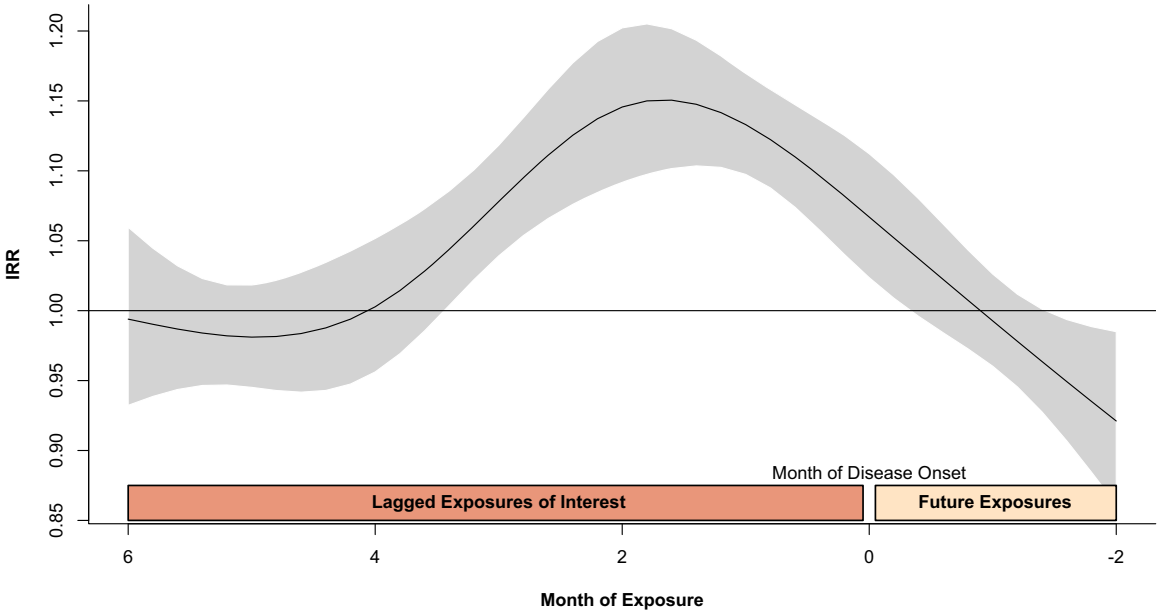

Figure 2. Overall lag–response relationship for a 0.1- to 1.1-$\mu g/m^3$ increase in fine mineral dust concentration (N observations = 105,564) from this time-series ecological study based in California (2000–2017). IRRs were obtained from the DLNM testing the association between fine mineral dust concentration and coccidioidomycosis incidence using Equation 1. All models were adjusted for spatiotemporal trends. The x-axis represents the lag or lead of exposure comparison, with the month of zero indicating the month of estimated disease onset. Negative months indicate future exposures, which are used as negative controls. The y-axis represents the associated IRR. The solid line represents point estimates, and shading represents the 95% confidence interval. Corresponding numerical data are shown in Excel Table S2. Note: DLNM, distributed-lag nonlinear model; IRR, incidence rate ratio.

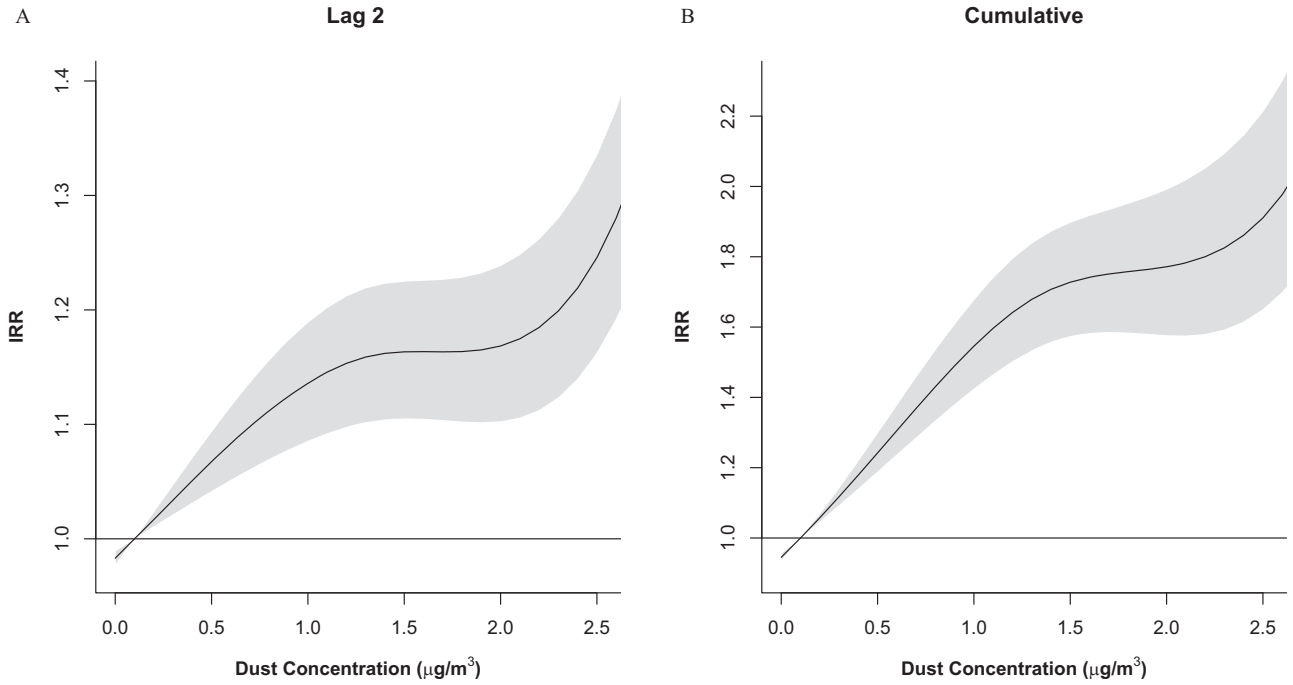

Figure 3. Exposure–response relationships comparing 0.1 $\mu g/m^3$ to a range of dust concentration values (N observations = 105,564) from this time-series ecological study based in California (2000–2017). IRRs estimated from the DLNM using Equation 1. All models were adjusted for spatiotemporal trends. The x-axis (fine mineral dust concentration) ranges from 0 $\mu g/m^3$ to the 99th percentile of dust concentrations across the region (2.52 $\mu g/m^3$). The y-axis represents the associated IRR. (A) Exposure–response for lag 2 months. (B) Cumulative exposure–response over lag 1 to lag 3 months before disease onset. The solid line represents point estimates, and shading represents the 95% confidence interval. Corresponding numerical data are shown in Excel Table S3. Note: DLNM, distributed-lag nonlinear model; IRR, incidence rate ratio.

S8) used to define urban areas for exclusion, with consistency of lags most strongly associated with incidence (Figure S5 and Excel Tables S9 and S10). Knot placement did not have a major influence on the exposure–response relationship (Figure S6 and Excel Table S11). The inclusion of occupation and economic vulnerability measures as confounders did not meaningfully affect the association between coccidioidomycosis incidence rate and fine mineral dust exposure (Figure S7 and Excel Table S12). Thus, we considered our model that contained only spatiotemporal controls, defined as fixed effects on county, splines on time, latitude, and longitude, as constituting our primary analysis. In our main model (Equation 1), the association between fine dust concentration and coccidioidomycosis incidence attenuated to the null at a lag of 4 months, and associations at further lags were also null. When examining associations with negative controls, we found evidence that future fine dust concentrations were unassociated with coccidioidomycosis incidence (future lag 1) and weakly associated (future lag 2), indicating a low risk for residual confounding (Figure 2).

Positive, supralinear relationships with upticks at the highest exposures were found for fine dust exposures from 1 to 3 months lagged from the month of estimated disease onset (Figure 3A; Figure S8). Specifically, the IRR for an increase from 0.1 to 1.1 $\mu g/m^3$ at 1 month lag was 1.13 [95% confidence interval (CI): 1.10, 1.17], 1.15 (95% CI: 1.09, 1.20) at the 2 month lag, and 1.08 (95% CI: 1.04, 1.12) at the 3 month lag. The IRR for a 2-unit increase at a 1-month lag was 1.19 (95% CI: 1.14, 1.24), 1.17 (95% CI: 1.11, 1.25) at the 2-month lag, and 1.11 (95% CI: 1.06, 1.17) at the 3-month lag. The cumulative exposure–response relationship between fine mineral dust concentration and coccidioidomycosis incidence across 1- to 3-month lags showed a positive, supralinear association, with a 1-$\mu g/m^3$ increase from 0.1 to 1.1 $\mu g/m^3$ associated with an IRR of 1.60 (95% CI: 1.46, 1.74). The highest cumulative exposures to fine mineral dust were highly associated with coccidioidomycosis incidence, exhibiting an upward curve in exposure–response [2-unit IRR = 1.78 (95% CI: 1.57, 2.02); Figure 3B].

Modifiers of Risk

We found that the season of exposure modified the exposure–response relationship (Figure 4). In terms of shape, all seasons exhibited different patterns. Exposure–response curves for the summer mostly reflected supralinearity, with positive divergence at the highest exposures. Fall exposure–response curves were linear. Spring exposure–response curves were supralinear with high exposures negatively associated with coccidioidomycosis incidence, although CIs encompassed the null hypothesis (Figure 4). Controlling for long-term secular and seasonal trends, we found that the IRR for a 1 $\mu g/m^3$ increase from 0.1 to 1.1 $\mu g/m^3$ in fine dust exposure during the summer months was 1.42 (95% CI: 1.29, 1.56). Fine dust exposures in the fall were associated with a 16% increase in incidence [IRR = 1.16 (95% CI: 1.04, 1.29)]. The equivalent 1-$\mu g/m^3$ increase in the spring was not significantly associated with coccidioidomycosis incidence, with an IRR of 1.11 (95% CI: 1.00, 1.24; Figure 4). The model for winter exposures to dust did not converge, likely because of outcome data sparsity, and thus was not included in Figure 4. At higher exposures, similar patterns were observed, namely that summer exposures [2-unit IRR = 1.42 (95% CI: 1.27, 1.58)] conferred the most risk, followed by fall [IRR = 1.29 (95% CI: 1.13, 1.47)] and spring exposures [IRR = 1.10 (95% CI: 0.91, 1.34)]. However, p-values calculated per interaction were not statistically significant for any combination of season or unit comparison, although the summer–spring comparison was the most statistically significant ($p = 0.28$; Table S1).

One-unit increases (0.1–1.1 $\mu g/m^3$) in fine dust concentration during the dry season were more highly associated with coccidioidomycosis incidence as compared with increases during the wet season at lag 2 months. Accordingly, the IRR during the dry season was 1.21 (95% CI: 1.13, 1.30), and the equivalent IRR during the wet season was 1.10 (95% CI: 1.02, 1.18), representing a 10% increase in risk during the dry season as compared with the wet season. The dry season exposure–response relationship was supralinear until $\sim 1.7\,\mu g/m^3$, with a slight decrease followed by an increase in association at the highest exposures. At these higher exposures, IRRs for the wet season exceeded those for the dry season. By comparison, the exposure–response relationship for the wet season was linear. For a 2-unit comparison, the dry season IRR was 1.19 (95% CI: 1.10, 1.29), and the wet season IRR was 1.28 (95% CI: 1.10, 1.48) (Figure 5). This represents a 7% increase in risk during the wet season as compared with the dry season, a reversal of the pattern observed at a 1-unit comparison. *p*-Values calculated for 1- and 2-unit comparisons were not statistically significant (Table S1).

We also found that preceding winter precipitation weakly modified the exposure–response relationship (Figure 6). When split by wet vs. dry preceding winters, the exposure–response relationships had similar shapes across the range of fine mineral dust concentrations analyzed, although the wet winters exposure–response exceeded that of dry winters, particularly at higher exposures. The IRRs for a 1-$\mu g/m^3$ increase in fine dust exposure from 0.1 to 1.1 $\mu g/m^3$ for a preceding wet winter and dry winter were equivalent [IRR = 1.20 (95% CI: 1.09, 1.32)]. However, a 2-unit increase in fine mineral dust concentration following a wet winter was 1.28 (95% CI: 1.11, 1.48), and the equivalent IRR following a dry winter was 1.15 (95% CI: 1.01, 1.30; Figure 6), representing an 11% increase in risk following wet winters as compared with dry winters. *p*-Values calculated for 1- and 2-unit comparisons were not statistically significant (Table S1). The model comparing preceding hot and cool summers did not converge.

Meta-Analysis

Using a meta-analysis approach to arrive at a pooled estimate of association across counties, we found a similar positive, nonlinear association between cumulative exposure to fine mineral dust concentration and coccidioidomycosis incidence (Figure 7A). A 1-$\mu g/m^3$ increase in cumulative fine dust exposure relative to 0.1 $\mu g/m^3$ was associated with a 43% increase in coccidioidomycosis incidence across the study region [IRR = 1.43 (95% CI: 1.10, 1.88)]. A 2-unit increase in fine mineral dust concentration was associated with an IRR of 2.34 (95% CI: 1.07, 5.09). The models for Stanislaus and Ventura counties did not converge, and thus these counties were excluded from further county-level analyses ($N = 12$). Counties varied greatly in their estimated BLUP-derived exposure–response relationships (Figure 7A). The highest risk associated with a 1-$\mu g/m^3$ increase in cumulative fine dust exposure relative to 0.1 $\mu g/m^3$ was observed in San Luis Obispo County [IRR = 3.01 (95% CI: 2.05, 4.42)]. High risk associated with the equivalent increase was also observed in western Madera [IRR = 2.19 (95% CI: 1.59, 3.02)] and western Kern counties [IRR = 1.51 (95% CI: 1.04, 2.20)], whereas the lowest risk was observed in western Tulare County [IRR = 1.05 (95% CI: 0.54, 2.07)] (Figure 7B). All IRR point estimates for a 1-$\mu g/m^3$ increase in fine dust exposure were positively associated with coccidioidomycosis incidence, although exposures in 9 of the 12 counties were not statistically significant (Table S2). We did not observe any relationship between mean annual incidence and strength of association between fine mineral dust and coccidioidomycosis incidence. Exposure–response relationships and point estimates for 1- and 2-unit comparisons for all counties are shown in Figures S9–S20 and Table S2.

Discussion

This study found significant, positive associations between coccidioidomycosis incidence and exposure to fine mineral dust in California (Figure 3). While accounting for significant reporting delays that are inherent in surveillance data, we identified the temporal window over which fine mineral dust exposures are associated with increased risk. We found that fine mineral

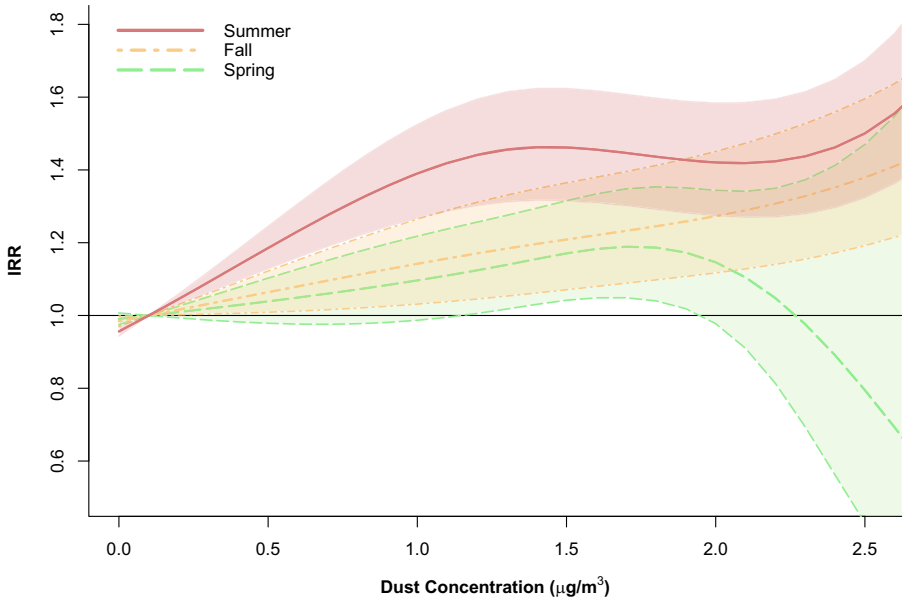

Figure 4. Exposure–response relationship for increasing dust concentration at lag 2 months prior to estimated disease onset by season of dust exposure using DLNM Equation 3 (N observations = 105,564) from this time-series ecological study based in California (2000–2017). All models were adjusted for spatiotemporal trends. The *x*-axis (fine mineral dust concentration) ranges from 0 $\mu g/m^3$ to the 99th percentile of dust concentrations across the region (2.52 $\mu g/m^3$). The *y*-axis represents the associated IRR. The months of March–May were coded as spring, June–August as summer, September–November as fall, and December–February as winter. Center lines are patterned by season of exposure and represent point estimates. The shading represents the 95% confidence interval. Corresponding numerical data are shown in Excel Table S4. Note: DLNM, distributed-lag nonlinear model; IRR, incidence rate ratio.

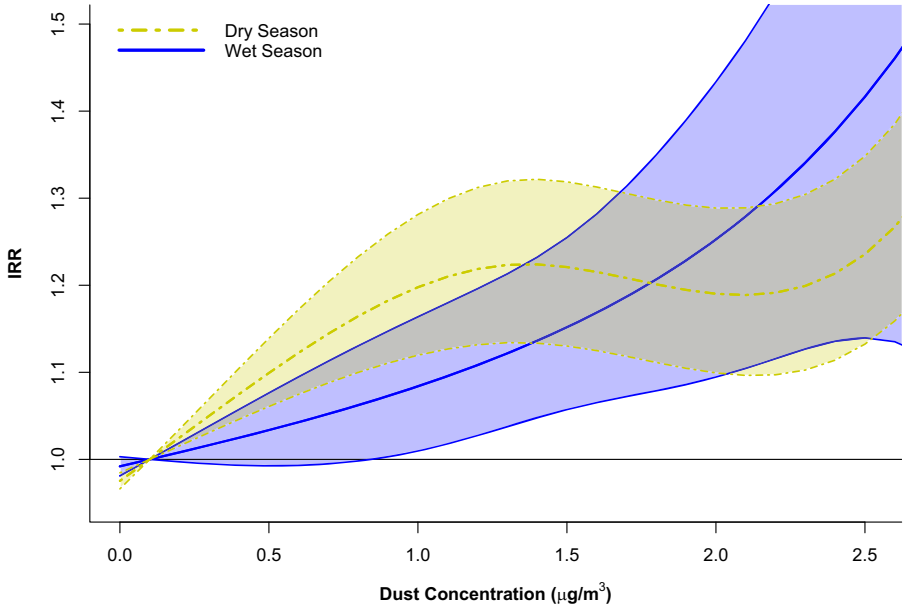

Figure 5. Exposure–response relationship for increasing dust concentration at lag 2 months prior to estimated disease onset by precipitation season of dust exposure using DLNM Equation 4 (N observations = 105,564) from this time-series ecological study based in California (2000–2017). All models were adjusted for spatiotemporal trends. The x-axis (fine mineral dust concentration) ranges from 0 $\mu g/m^3$ to the 99th percentile of dust concentrations across the region (2.52 $\mu g/m^3$). The y-axis represents the associated IRR. May–October was considered the dry season, and November–April the wet season. Center lines are patterned by season of exposure and represent point estimates. The shading represents the 95% confidence interval. Corresponding numerical data are shown in Excel Table S5. Note: DLNM, distributed-lag nonlinear model; IRR, incidence rate ratio.

dust exposures 1–3 months prior to estimated disease onset were positively associated with increased coccidioidomycosis incidence, with the strongest association observed for exposures that occurred 2 months prior to estimated disease onset (Figure 2).

We also found limited evidence to support the grow and blow hypothesis. For one, while controlling for long-term trends and seasonality in coccidioidomycosis incidence, we found evidence that fine mineral dust exposures during the summer months were most strongly associated with coccidioidomycosis incidence (Figure 4). Fall and spring fine mineral dust exposures were less strongly associated with coccidioidomycosis incidence. Further, when comparing exposures during the dry and wet seasons in California, we also found modest effect modification by season

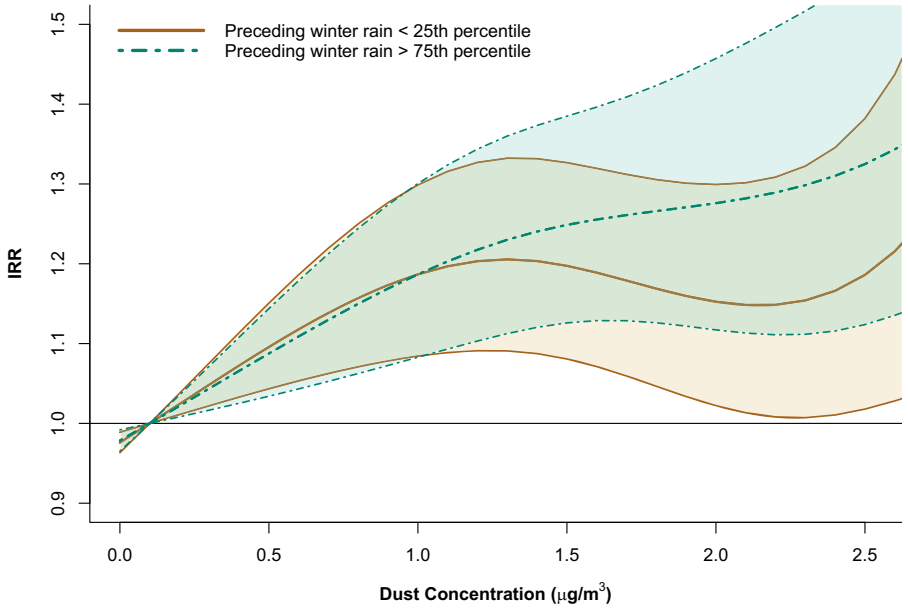

Figure 6. Exposure–response relationships comparing wet and dry winters as defined by exceeding the 75th percentile or falling below the 25th percentile of county-level winter precipitation using DLNM Equation 5 (N observations = 105,564) from this time-series ecological study based in California (2000–2017). All models were adjusted for spatiotemporal trends. The x-axis (fine mineral dust concentration) ranges from 0 $\mu g/m^3$ to the 99th percentile of dust concentrations across the region (2.52 $\mu g/m^3$). The y-axis represents the associated IRR. Exposure–response curves are for increases in dust concentration at lagged 2 months prior to estimated disease onset. Center lines are patterned by winter precipitation category and represent point estimates. The shading represents the 95% confidence interval. Corresponding numerical data are shown in Excel Table S6. Note: DLNM, distributed-lag nonlinear model; IRR, incidence rate ratio.

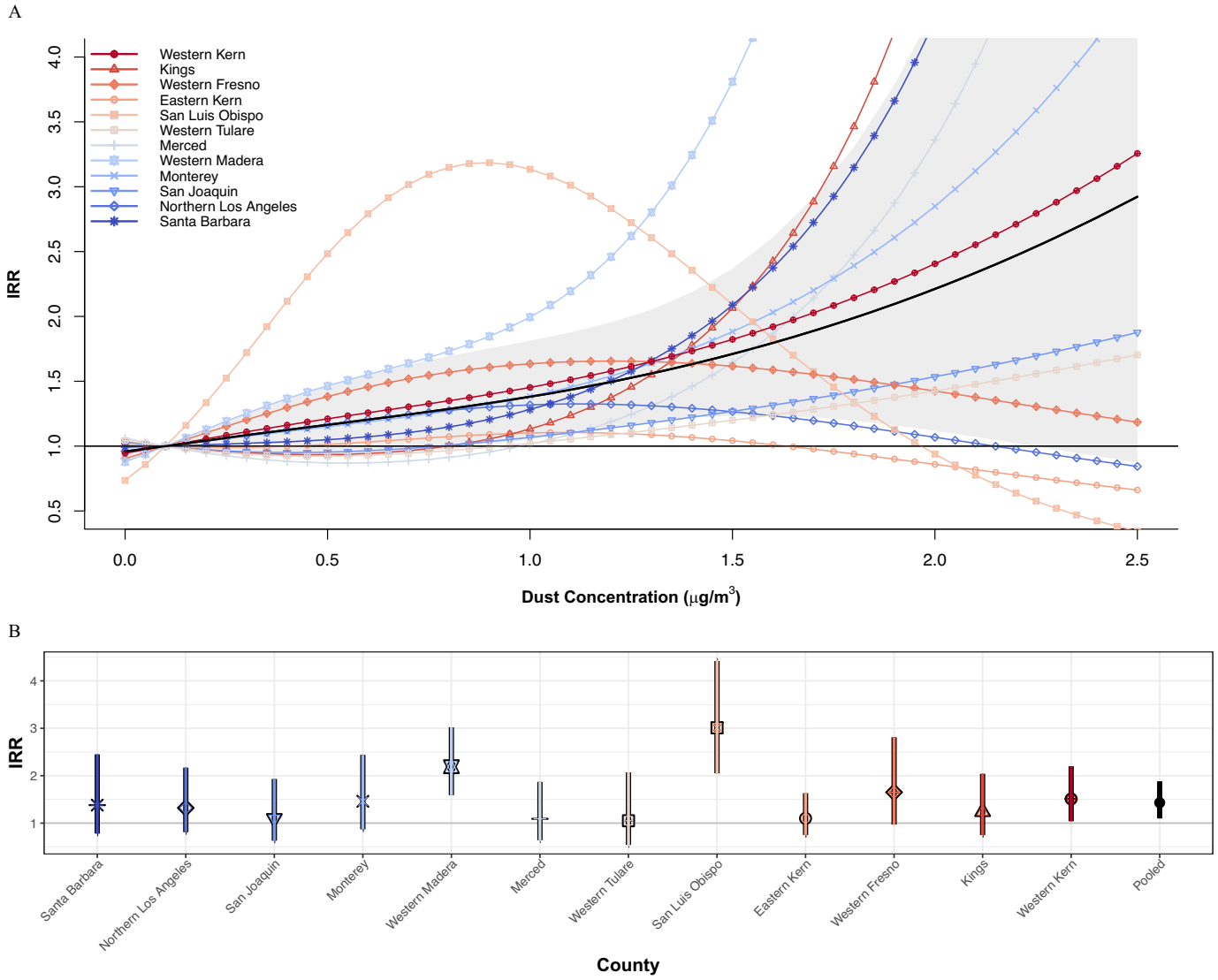

Figure 7. (A) County-specific best linear unbiased predictions and pooled region-wide estimate for cumulative dust exposures from 1 to 3 months prior to estimated disease onset using DLNM Equation 7 (N observations = 105,564) from this time-series ecological study based in California (2000–2017). All models were adjusted for spatiotemporal trends. The x-axis (fine mineral dust concentration) ranges from 0 $\mu g/m^3$ to the 99th percentile of dust concentrations across the region (2.52 $\mu g/m^3$). The y-axis represents the associated IRR. Lines and symbols represent county-specific exposure–response relationships and are colored by subcounty annual incidence over the study period (i.e., including by eastern and western regions). Counties with high total cases during the study period are in red, and lower total cases in blue. The thick black line represents the pooled association. The solid lines represent point estimates, and shading represents the 95% confidence interval for the pooled estimate. (B) Point estimates and 95% confidence intervals for a 1-unit comparison centered at 0.1 $\mu g/m^3$. Point estimates are colored according to subcounty annual incidence as in (A) and use the same symbol. Corresponding numerical data are shown in Excel Table S7. Note: DLNM, distributed-lag nonlinear model; IRR, incidence rate ratio.

(Figure 5), with dust exposures during the dry season more highly associated with coccidioidomycosis incidence as compared with exposures in the wet season at lower exposure levels. However, this relationship was reversed at higher exposure levels and was not statistically significant. As suggested by the grow and blow hypothesis, exposures during drier, hotter periods, when elevated temperatures may facilitate the autolysis of spores, were more highly associated with coccidioidomycosis incidence as compared with exposures during cooler, wetter periods, when mycelial growth may dominate.

We further examined whether wet winters modified the association between fine mineral dust exposures and coccidioidomycosis incidence. We hypothesized that aerosolized dust may contain a higher concentration of arthroconidia during months that followed wetter winters because mycelial growth and sporulation, which is thought to occur during the wet spring and winter months (i.e., the grow period), could result in greater quantities of spores available for dispersal (i.e., the blow period).[31,32,34,40] We found wetter preceding winters were associated with a stronger exposure–response at higher exposure levels, although the difference was not statistically significant (Figure 6). These findings indirectly support the grow and blow hypothesis in that greater fungal growth due to a wet winter would be expected to increase the risk associated with dust in the following months, as we observed. We were unable to find evidence that preceding hot summers significantly modified the association between fine mineral dust exposures and coccidioidomycosis incidence.

Our study had several limitations. Cases were assigned to the month of their estimated onset date, which reflects the date of specimen collection or, if available, the reported onset date. Thus, reporting delays were inherent in our data. However, such misclassification is likely to bias our results by attenuating the causal effect

of the true month exposure and inflating the associations for the surrounding months. We examined longer-term lags to capture the full distribution of reporting delays. Coccidioidomycosis remains underdiagnosed in the US, and medical provider knowledge can vary nationwide, although potentially less so within the highly endemic areas studied here.[63] However, even across the endemic region, providers may vary in time regarding testing for coccidioidomycosis. This may have affected our findings if counties with lower case burden, and thus potentially lower provider knowledge, experienced longer lags between the estimated onset date and true onset date. Thus, associations between fine mineral dust exposures and incidence may have been attenuated toward the null in these counties. However, by estimating county-specific relationships cumulatively, across 1, 2, and 3 months lagged, we may have captured much of the effect.

Given that the surveillance data provides only residential addresses, we were limited in our ability to estimate dust exposures of interest (i.e., to *Coccidioides* arthroconidia) that occur outside of the residential census tract. Dust exposures based directly upon residential address are the least accurate for census tracts with relatively high movement owing to work or travel. Further, acute occupational exposures were not well captured by the spatiotemporal resolution of this modeled product. As a result, our modeling framework did not attempt to assign individual-level or occupational fine dust exposure but, rather, focused on population-level outcomes and monthly ambient exposures to partially address this issue. Measurement error was still possible if the number of cases within a census tract was partially determined by dust concentrations outside of said census tract. This may occur if dust-associated arthroconidia are readily transported from one census tract to another or if people are routinely exposed to dust and arthroconidia outside of their residential census tract. We believe that this bias induced by movement is likely differential by census tract, given that the frequency with which people leave their census tracts varies by factors including occupation, income, and census tract size. Outdoor jobs like construction and agriculture may necessitate longer commute times. Thus, census tracts with high proportions of these occupations may have more nonresidentially acquired cases. Accordingly, we hypothesize that differential measurement error may have biased our results toward the null under the assumption that census tracts where cases were truly acquired were dustier than highly residential census tracts. However, dust concentrations within the study region are spatially autocorrelated, and thus we expect this effect to be relatively small. We attempted to minimize this bias by excluding urban census tracts, which are typically small and more likely to experience intertract dust transport and human travel, as well as being relatively inhospitable environments for *Coccidioides*.

The usage of monthly fine mineral dust concentrations also prohibited the investigation of shorter-term, highly localized exposures to fine dust, particularly short-term occupational exposures (e.g., during digging or construction) that may be higher both in concentrations of dust and arthroconidia when compared with ambient exposures. We were also unable to draw any conclusions regarding dust storms, another source of exposure to extremely high concentrations of mineral dust, which have been associated with upticks in incidence.[27] Error in modeled fine mineral dust concentration may also have been an issue given that fine-scale air pollution models combine information from limited monitoring stations with circulation models. Modeled fine dust concentration data surrounding monitors, for example, are not perfectly predicted by monitor data. However, our overall correlations were relatively high. Advances in fine-scale dust concentration modeling and a resolution of reporting delays and exposure location will be needed to permit individual-level analysis. Doing so will enable even more accurate estimation of exposures and climate modifiers of importance to coccidioidomycosis.

Despite these limitations, our study had several notable strengths. Using newly available, modeled surface fine mineral dust represents a significant improvement in exposure measurement, allowing researchers to conduct analyses on the component of PM that directly originates from soils and plausibly co-occurs with the pathogen *Coccidioides*. Previous research estimating the association between mineral dust and coccidioidomycosis has used proxy measures, namely PM_{10}.[31,33,34] However, the evidence generated by these studies remains limited by the usage of correlations, which do not yield public health-relevant measures of effect. Further, the study designs previously applied cannot examine effects across time lags or estimate nonlinear exposure–responses, significantly hindering epidemiologic insight into the true timing and magnitude of effect of relevant exposures.

Our results here represent an important step forward in understanding the exposure route and spatiotemporal variation of risk of an emerging pathogen. We found that fine dust exposures were strongly associated with the incidence of coccidioidomycosis, lending credence to the theory that dust and arthroconidia exposures co-occur via soil mobilization. Our approach of time-series analysis allowed for the exploration of lag–response relationships, which is critical given the observed delays between exposure and reporting inherent in surveillance data. Both estimation of the exposure–response relationship and identification of risk modifiers are critical to understanding when and who is at greatest risk. We have shown that the risk associated with fine mineral dust exposures varies substantially across counties and seasons. Specifically, we found that dust exposures that occur in the summertime were more highly associated with coccidioidomycosis incidence as compared with other seasons. Further, dust exposures within San Luis Obispo, western Madera, and western Kern counties conferred the greatest degree of risk, as compared with other counties within the study region, suggesting greater proliferation and aerosolization of *Coccidioides* within these counties. However, other factors may be important drivers of the spatial variation of risk, including the distribution of soil-engaged occupations, underlying population susceptibility, and influxes of new California residents who may be immunologically naïve to coccidioidomycosis, although controlling for census tract-level occupational distribution did not significantly change our results. Data on underlying comorbidities and the influx of an immunologically naïve population were not available, and thus these questions remain beyond the scope of this article. What is more, DLNM methods facilitate the investigation of climatological risk modifiers, with which we have recently found evidence supporting the grow and blow hypothesis. We found that dust exposures following wetter winters were more highly associated with coccidioidomycosis incidence, supporting the theory that winter rains support *Coccidioides* growth and lead to greater quantities of spores available to be aerosolized.

Our results may support local health jurisdictions in their identification of locations and time periods of greatest risk. For example, our findings suggest that Valley fever awareness messaging in California should go out in early summer when the risk posed by dust exposures is greatest. It may also be beneficial to minimize major construction projects in the summer and fall months owing to the hypothetically higher concentrations of arthroconidia in the soil. Further, counties such as San Luis Obispo, Madera, and Kern may benefit the most from dust suppression and stabilizing projects. More recently, research has found that several soil microbes inhibit the growth of *Coccidioides* in the lab[64] and that restoration of biocrust communities may suppress spore aerosolization,[65] providing new

mitigation techniques. However, public awareness campaigns and dust suppression projects may have limited success in averting cases of coccidioidomycosis, and thus funding and development of the human vaccine should continue to be prioritized.

Given the wide-ranging impacts of climate change, the findings of this study should be considered in light of the projected expansion and intensification of coccidioidomycosis across the US.[66] Many studies have concluded that climate change is likely to produce drier, hotter seasons in the southwestern US, which could potentially lead to increases in dust emission.[67,68] A recent analysis of the US Southwest estimated that fine and coarse mineral dust levels could increase by 57% and 38%, respectively, by 2080–2099 under RCP8.5.[67] In California, the Sustainable Groundwater Management Act, which aims to protect groundwater resources, will lead to the mass fallowing of many acres of farmland over the coming decades, which may increase fugitive dust emissions.[69] At the same time, anthropogenic dust emissions due to urbanization have been increasing.[70] The San Joaquin Valley's population is growing rapidly, and increases in construction and expansion of urban areas are expected over the coming decades.[71] Considering these changes, dust is an emerging public health threat in this region, and the health risks of exposure to dust—including coccidioidomycosis—are expected to increase, even as projecting future dust concentrations in *Coccidioides*-endemic regions remains challenging.[72]

Conclusions

California is currently experiencing an increase in incidence of coccidioidomycosis, with the San Joaquin Valley and coastal counties exhibiting particularly rapid rises.[1] Other endemic states, including Arizona, have also seen upticks in incidence,[5,43] and coccidioidomycosis cases and positive soil samples are increasingly reported in noncontiguous areas in nonendemic states, including Oregon,[49] Utah,[73] and Washington.[6,74,75] The association between ambient mineral dust exposure and coccidioidomycosis incidence is fundamental to our understanding of the disease. In this study, we found consistent, nonlinearly positive associations between fine mineral dust concentrations and coccidioidomycosis incidence. We additionally found that this association varied by county, with fine mineral dust exposures within the counties of San Luis Obispo, western Madera, and western Kern posing the greatest risk. Finally, we found modest evidence to support the grow and blow hypothesis, most notably that fine dust exposures in the summer were the most highly associated with coccidiomycosis incidence. Thus, awareness messaging in California may be more effective if implemented in the summertime, when our results suggest risk posed by dust exposures is greatest. We further found that high fine mineral dust exposures following a wet winter conferred an 11% increase in risk as compared with exposures that follow a dry winter. Our results further clarify both the route of exposure to the emerging pathogen *Coccidioides* as well as spatiotemporal and climatologic risk modifiers. Our study suggests a need for further research characterizing the exposure–response across dust particle sizes, finer temporal scales, and acute dust events.

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Human case data are protected health information with access restricted to authorized California Department of Public Health (CDPH) staff. Limited, county-level, deidentified human case data are available via CDPH Data Reports and Epidemiologic Summaries for Valley fever.[76] More complete human disease data can be obtained for approved purposes by submitting a formal request to the CDPH Infectious Diseases Branch Surveillance and Statistics Section.[77]

The findings and conclusions in this article are those of the authors and do not necessarily represent the views or opinions of the CDPH or the California Health and Human Services Agency.

References

1. Sondermeyer Cooksey GL, Nguyen A, Vugia D, Jain S. 2020. Regional analysis of coccidioidomycosis incidence—California, 2000–2018. MMWR Morb Mortal Wkly Rep 69(48):1817–1821, PMID: 33270616, https://doi.org/10.15585/mmwr.mm6948a4.
2. Cox RA, Magee DM. 1998. Protective immunity in coccidioidomycosis: the life cycle and biology of *Coccidioides immitis*. Res Immunol 149(4–5):417–428, PMID: 9720959, https://doi.org/10.1016/s0923-2494(98)80765-7.
3. Kirkland TN, Fierer J. 2018. *Coccidioides immitis* and *posadasii*; a review of their biology, genomics, pathogenesis, and host immunity. Virulence 9(1):1426–1435, PMID: 30179067, https://doi.org/10.1080/21505594.2018.1509667.
4. Weaver E, Kolivras KN, Thomas RQ, Thomas VA, Abbas KM. 2020. Environmental factors affecting ecological niche of *Coccidioides* species and spatial dynamics of valley fever in the United States. Spat Spatiotemporal Epidemiol 32:100317, PMID: 32007282, https://doi.org/10.1016/j.sste.2019.100317.
5. CDC (Centers for Disease Control and Prevention). n.d. Valley Fever. https://www.cdc.gov/fungal/diseases/coccidioidomycosis/index.html [accessed 1 May 2022].
6. Crum NF. 2022. Coccidioidomycosis: a contemporary review. Infect Dis Ther 11(2):713–742, PMID: 35233706, https://doi.org/10.1007/s40121-022-00606-y.
7. Keckich DW, Blair JE, Vikram HR, Seville MT, Kusne S. 2011. Reactivation of coccidioidomycosis despite antifungal prophylaxis in solid organ transplant recipients. Transplantation 92(1):88–93, PMID: 21516063, https://doi.org/10.1097/TP.0b013e31821c1df6.
8. Walker MP, Brody CZ, Resnik R. 1992. Reactivation of coccidioidomycosis in pregnancy. Obstet Gynecol 79(5 pt 2):815–817, PMID: 1565375.
9. Pappagianis D. 1999. *Coccidioides immitis* antigen. J Infect Dis 180(1):243–244, PMID: 10353891, https://doi.org/10.1086/314835.
10. Thompson GR III. 2011. Pulmonary coccidioidomycosis. Semin Respir Crit Care Med 32(6):754–763, PMID: 22167403, https://doi.org/10.1055/s-0031-1295723.
11. Wilson L, Ting J, Lin H, Shah R, MacLean M, Peterson MW, et al. 2019. The rise of Valley fever: prevalence and cost burden of coccidioidomycosis infection in California. Int J Environ Res Public Health 16(7):1113, PMID: 30925716, https://doi.org/10.3390/ijerph16071113.
12. Crum NF, Lederman ER, Stafford CM, Parrish JS, Wallace MR. 2004. Coccidioidomycosis: a descriptive survey of a reemerging disease. Clinical characteristics and current controversies. Medicine (Baltimore) 83(3):149–175, PMID: 15118543, https://doi.org/10.1097/01.md.0000126762.91040.fd.
13. Kollath DR, Miller KJ, Barker BM. 2019. The mysterious desert dwellers: *Coccidioides immitis* and *Coccidioides posadasii*, causative fungal agents of coccidioidomycosis. Virulence 10(1):222–233, PMID: 30898028, https://doi.org/10.1080/21505594.2019.1589363.
14. Nguyen C, Barker BM, Hoover S, Nix DE, Ampel NM, Frelinger JA, et al. 2013. Recent advances in our understanding of the environmental, epidemiological, immunological, and clinical dimensions of coccidioidomycosis. Clin Microbiol Rev 26(3):505–525, PMID: 23824371, https://doi.org/10.1128/CMR.00005-13.
15. Galgiani JN, Ampel NM, Blair JE, Catanzaro A, Johnson RH, Stevens DA, et al. 2005. Coccidioidomycosis. Clin Infect Dis 41(9):1217–1223, PMID: 16206093, https://doi.org/10.1086/496991.
16. Wagner R, Montoya L, Gao C, Head JR, Remais J, Taylor JW. 2022. The air mycobiome is decoupled from the soil mycobiome in the California San Joaquin Valley. Mol Ecol 31(19):4962–4978, PMID: 35933707, https://doi.org/10.1111/mec.16640.
17. McCurdy SA, Portillo-Silva C, Sipan CL, Bang H, Emery KW. 2020. Risk for coccidioidomycosis among Hispanic farm workers, California, USA, 2018. Emerg Infect Dis 26(7):1430–1437, PMID: 32568046, https://doi.org/10.3201/eid2607.200024.
18. Cummings KC, McDowell A, Wheeler C, McNary J, Das R, Vugia DJ, et al. 2010. Point-source outbreak of coccidioidomycosis in construction workers. Epidemiol Infect 138(4):507–511, PMID: 19845993, https://doi.org/10.1017/S0950268809990999.
19. Sondermeyer Cooksey GL, Wilken JA, McNary J, Gilliss D, Shusterman D, Materna BL, et al. 2017. Dust exposure and coccidioidomycosis prevention among solar power farm construction workers in California. Am J Public Health 107(8):1296–1303, PMID: 28640687, https://doi.org/10.2105/AJPH.2017.303820.
20. Wilken JA, Sondermeyer G, Shusterman D, McNary J, Vugia DJ, McDowell A, et al. 2015. Coccidioidomycosis among workers constructing solar power farms,

California, USA, 2011–2014. Emerg Infect Dis 21(11):1997–2005, PMID: 26484688, https://doi.org/10.3201/eid2111.150129.
21. Das R, McNary J, Fitzsimmons K, Dobraca D, Cummings K, Mohle-Boetani J, et al. 2012. Occupational coccidioidomycosis in California: outbreak investigation, respirator recommendations, and surveillance findings. J Occup Environ Med 54(5):564–571, PMID: 22504958, https://doi.org/10.1097/JOM.0b013e3182480556.
22. de Perio MA, Materna BL, Sondermeyer Cooksey GL, Vugia DJ, Su C-P, Luckhaupt SE, et al. 2019. Occupational coccidioidomycosis surveillance and recent outbreaks in California. Med Mycol 57(suppl 1):S41–S45, PMID: 30690596, https://doi.org/10.1093/mmy/myy031.
23. Laws RL, Jain S, Sondermeyer Cooksey G, Mohle-Boetani J, McNary J, Wilken J, et al. 2021. Coccidioidomycosis outbreak among inmate wildland firefighters: California, 2017. Am J Ind Med 64(4):266–273, PMID: 33484179, https://doi.org/10.1002/ajim.23218.
24. Rios S. 2018. *Valley Fever: Environmental Racism and Health Justice* [dissertation]. Santa Barbara, CA: University of California, Santa Barbara.
25. Shriber J, Conlon KC, Benedict K, McCotter OZ, Bell JE. 2017. Assessment of vulnerability to coccidioidomycosis in Arizona and California. Int J Environ Res Public Health 14(7):680, PMID: 28644403, https://doi.org/10.3390/ijerph14070680.
26. Comrie AC. 2021. No consistent link between dust storms and Valley fever (coccidioidomycosis). Geohealth 5(12):e2021GH000504, PMID: 34877441, https://doi.org/10.1029/2021GH000504.
27. Pappagianis D, Einstein H. 1978. Tempest from Tehachapi takes toll or *Coccidioides* conveyed aloft and afar. West J Med 129(6):527–530, PMID: 735056.
28. Sprigg WA, Nickovic S, Galgiani JN, Pejanovic G, Petkovic S, Vujadinovic M, et al. 2014. Regional dust storm modeling for health services: the case of valley fever. Aeolian Res 14:53–73, https://doi.org/10.1016/j.aeolia.2014.03.001.
29. Tong DQ, Gorris ME, Gill TE, Ardon-Dryer K, Wang J, Ren L. 2022. Dust storms, Valley fever, and public awareness. Geohealth 6(8):e2022GH000642, PMID: 35949254, https://doi.org/10.1029/2022GH000642.
30. Tong DQ, Wang JXL, Gill TE, Lei H, Wang B. 2017. Intensified dust storm activity and Valley fever infection in the southwestern United States. Geophys Res Lett 44(9):4304–4312, PMID: 30166741, https://doi.org/10.1002/2017GL073524.
31. Comrie AC. 2005. Climate factors influencing coccidioidomycosis seasonality and outbreaks. Environ Health Perspect 113(6):688–692, PMID: 15929890, https://doi.org/10.1289/ehp.7786.
32. Gorris ME, Cat LA, Zender CS, Treseder KK, Randerson JT. 2018. Coccidioidomycosis dynamics in relation to climate in the southwestern United States. Geohealth 2(1):6–24, PMID: 32158997, https://doi.org/10.1002/2017GH000095.
33. Kollath DR, Mihaljevic JR, Barker BM. 2022. PM10 and other climatic variables are important predictors of seasonal variability of coccidioidomycosis in Arizona. Microbiol Spectr 10(2):e01483-21, PMID: 35319247, https://doi.org/10.1128/spectrum.01483-21.
34. Weaver EA, Kolivras KN. 2018. Investigating the relationship between climate and valley fever (coccidioidomycosis). Ecohealth 15(4):840–852, PMID: 30284073, https://doi.org/10.1007/s10393-018-1375-9.
35. Colson AJ, Vredenburgh L, Guevara RE, Rangel NP, Kloock CT, Lauer A. 2017. Large-scale land development, fugitive dust, and increased coccidioidomycosis incidence in the Antelope Valley of California, 1999–2014. Mycopathologia 182(5–6):439–458, PMID: 28084574, https://doi.org/10.1007/s11046-016-0105-5.
36. van Donkelaar A, Martin RV, Li C, Burnett RT. 2019. Regional estimates of chemical composition of fine particulate matter using a combined geoscience-statistical method with information from satellites, models, and monitors. Environ Sci Technol 53(5):2595–2611, PMID: 30698001, https://doi.org/10.1021/acs.est.8b06392.
37. Taylor JW, Barker BM. 2019. The endozoan, small-mammal reservoir hypothesis and the life cycle of *Coccidioides* species. Med Mycol 57(suppl 1):S16–S20, PMID: 30690603, https://doi.org/10.1093/mmy/myy039.
38. Comrie AC, Glueck MF. 2007. Assessment of climate coccidioidomycosis model: model sensitivity for assessing climatologic effects on the risk of acquiring coccidioidomycosis. Ann NY Acad Sci 1111(1):83–95, PMID: 17344540, https://doi.org/10.1196/annals.1406.024.
39. Tamerius JD, Comrie AC. 2011. Coccidioidomycosis incidence in Arizona predicted by seasonal precipitation. PLoS One 6(6):e21009, PMID: 21701590, https://doi.org/10.1371/journal.pone.0021009.
40. Head JR, Sondermeyer-Cooksey G, Heaney AK, Yu AT, Jones I, Bhattachan A, et al. 2022. Effects of precipitation, heat, and drought on incidence and expansion of coccidioidomycosis in western USA: a longitudinal surveillance study. Lancet Planet Health 6(10):e793–e803, PMID: 36208642, https://doi.org/10.1016/S2542-5196(22)00202-9.
41. CDC. 2011. Coccidioidomycosis/Valley Fever (*Coccidioides* spp.) 2011 Case Definition. https://ndc.services.cdc.gov/case-definitions/coccidioidomycosis-2011/ [accessed 1 May 2022].
42. CDPH (California Department of Public Health). 2018. Management & Reporting of Select Communicable Diseases Under Public Health Surveillance. CDPH IDB Guidance for Managing Select Communicable Diseases: Coccidioidomycosis (Valley Fever). https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/IDBGuidanceforManagingSelectCommunicableDiseases.aspx [accessed 1 August 2022].
43. Tsang CA, Anderson SM, Imholte SB, Erhart LM, Chen S, Park BJ, et al. 2010. Enhanced surveillance of coccidioidomycosis, Arizona, USA, 2007–2008. Emerg Infect Dis 16(11):1738–1744, PMID: 21029532, https://doi.org/10.3201/eid1611.100475.
44. Pappagianis D, Coccidioidomycosis Serology Laboratory. 2007. Coccidioidomycosis in California state correctional institutions. Ann N Y Acad Sci 1111(1):103–111, PMID: 17332089, https://doi.org/10.1196/annals.1406.011.
45. Sondermeyer G, Lee L, Gilliss D, Tabnak F, Vugia D. 2013. Coccidioidomycosis-associated hospitalizations, California, USA, 2000–2011. Emerg Infect Dis 19(10):1590–1597, PMID: 24050438, https://doi.org/10.3201/eid1910.130427.
46. Philip S, Martin RV, van Donkelaar A, Lo JW-H, Wang Y, Chen D, et al. 2014. Global chemical composition of ambient fine particulate matter for exposure assessment. Environ Sci Technol 48(22):13060–13068, PMID: 25343705, https://doi.org/10.1021/es502965b.
47. Hand JL, White WH, Gebhart KA, Hyslop NP, Gill TE, Schichtel BA. 2016. Earlier onset of the spring fine dust season in the southwestern United States. Geophys Res Lett 43(8):4001–4009, https://doi.org/10.1002/2016GL068519.
48. Hyslop NP, Trzepla K, White WH. 2015. Assessing the suitability of historical $PM_{2.5}$ element measurements for trend analysis. Environ Sci Technol 49(15):9247–9255, PMID: 26125610, https://doi.org/10.1021/acs.est.5b01572.
49. Benedict K, Ireland M, Weinberg MP, Gruninger RJ, Weigand J, Chen L, et al. 2018. Enhanced surveillance for coccidioidomycosis, 14 US states, 2016. Emerg Infect Dis 24(8):1444–1452, PMID: 30014837, https://doi.org/10.3201/eid2408.171595.
50. Hector RF, Rutherford GW, Tsang CA, Erhart LM, McCotter O, Anderson SM, et al. 2011. The public health impact of coccidioidomycosis in Arizona and California. Int J Environ Res Public Health 8(4):1150–1173, PMID: 21695034, https://doi.org/10.3390/ijerph8041150.
51. PRISM Climate Group. 2014. PRISM Climate Data. https://prism.oregonstate.edu [accessed 16 December 2020].
52. California Department of Finance. 2024. Estimates. https://dof.ca.gov/forecasting/demographics/estimates/ [accessed 1 November 2024].
53. US Census Bureau. 2010. Try out our new way to explore data. https://www.census.gov/data.html [accessed 1 August 2022].
54. US Census Bureau. 2010. American Community Survey 1-Year Data (2005–2021). https://www.census.gov/data/developers/data-sets/acs-1year.html [accessed 1 August 2022].
55. Bhaskaran K, Gasparrini A, Hajat S, Smeeth L, Armstrong B. 2013. Time series regression studies in environmental epidemiology. Int J Epidemiol 42(4):1187–1195, PMID: 23760528, https://doi.org/10.1093/ije/dyt092.
56. Gasparrini A. 2011. Distributed lag linear and non-linear models in R: the package dlnm. J Stat Soft 43(8):1–20, PMID: 22003319, https://doi.org/10.18637/jss.v043.i08.
57. Flanders WD, Klein M, Darrow LA, Strickland MJ, Sarnat SE, Sarnat JA, et al. 2011. A method for detection of residual confounding in time-series and other observational studies. Epidemiology 22(1):59–67, PMID: 21068669, https://doi.org/10.1097/EDE.0b013e3181fdcabe.
58. Flanders WD, Strickland MJ, Klein M. 2017. A new method for partial correction of residual confounding in time-series and other observational studies. Am J Epidemiol 185(10):941–949, PMID: 28430842, https://doi.org/10.1093/aje/kwx013.
59. Greene DR, Koenig G, Fisher MC, Taylor JW. 2000. Soil isolation and molecular identification of *Coccidioides immitis*. Mycologia 92(3):406–410, https://doi.org/10.1080/00275514.2000.12061175.
60. Berman RJ, Friedman L, Pappagianis D, Smith CE. 1956. Survival of Coccidioides immitis under controlled conditions of temperature and humidity. Am J Public Health Nations Health 46(10):1317–1324, PMID: 13362665, https://doi.org/10.2105/ajph.46.10.1317.
61. Gasparrini A, Armstrong B. 2013. Reducing and meta-analysing estimates from distributed lag non-linear models. BMC Med Res Methodol 13(1):1, PMID: 23297754, https://doi.org/10.1186/1471-2288-13-1.
62. Gasparrini A, Armstrong B, Kenward MG. 2012. Multivariate meta-analysis for non-linear and other multi-parameter associations. Stat Med 31(29):3821–3839, PMID: 22807043, https://doi.org/10.1002/sim.5471.
63. Benedict K, Li Y, Molinari NAM, Jackson BR. 2021. Health care providers' testing practices for coccidioidomycosis and histoplasmosis in patients with community-acquired pneumonia—United States, 2020. Open Forum Infect Dis 8(2):ofab020, PMID: 33575429, https://doi.org/10.1093/ofid/ofab020.
64. Kollath DR, Morales MM, Itogawa AN, Mullaney D, Lee NR, Barker BM. 2023. Combating the dust devil: utilizing naturally occurring soil microbes in Arizona to inhibit the growth of *Coccidioides* spp., the causative agent of Valley fever. J Fungi (Basel) 9(3):345, PMID: 36983513, https://doi.org/10.3390/jof9030345.

65. Ramsey ML. 2023. *Locking Down the Dust: Exploring the Association Between Coccidioides Posadasii and Biological Soil Crusts* [master's thesis]. Flagstaff, AZ: Northern Arizona University.
66. Gorris ME, Treseder KK, Zender CS, Randerson JT. 2019. Expansion of coccidioidomycosis endemic regions in the United States in response to climate change. Geohealth 3(10):308–327, PMID: 32159021, https://doi.org/10.1029/2019GH000209.
67. Achakulwisut P, Anenberg SC, Neumann JE, Penn SL, Weiss N, Crimmins A, et al. 2019. Effects of increasing aridity on ambient dust and public health in the U. S. Southwest under climate change. Geohealth 3(5):127–144, PMID: 31276080, https://doi.org/10.1029/2019GH000187.
68. Achakulwisut P, Mickley LJ, Anenberg SC. 2018. Drought-sensitivity of fine dust in the US Southwest: implications for air quality and public health under future climate change. Environ Res Lett 13(5):054025, https://doi.org/10.1088/1748-9326/aabf20.
69. Ayres A, Kwon J, Collins J. 2022. *Land Transitions and Dust in the San Joaquin Valley*. https://www.ppic.org/publication/land-transitions-and-dust-in-the-san-joaquin-valley/ [accessed 1 May 2023].
70. Xia W, Wang Y, Chen S, Huang J, Wang B, Zhang GJ, et al. 2022. Double trouble of air pollution by anthropogenic dust. Environ Sci Technol 56(2):761–769, PMID: 34941248, https://doi.org/10.1021/acs.est.1c04779.
71. Ayres A, Hanak E, McCann H, Mitchell D, Sugg Z, Rugland E. 2021. *Groundwater and Urban Growth in the San Joaquin Valley*. https://www.ppic.org/publication/groundwater-and-urban-growth-in-the-san-joaquin-valley/ [accessed 1 May 2022].
72. Pu B, Ginoux P. 2017. Projection of American dustiness in the late 21st century due to climate change. Sci Rep 7(1):5553, PMID: 28717135, https://doi.org/10.1038/s41598-017-05431-9.
73. Johnson SM, Carlson EL, Fisher FS, Pappagianis D. 2014. Demonstration of *Coccidioides immitis* and *Coccidioides posadasii* DNA in soil samples collected from Dinosaur National Monument, Utah. Med Mycol 52(6):610–617, PMID: 24847036, https://doi.org/10.1093/mmy/myu004.
74. Chow NA, Kangiser D, Gade L, McCotter OZ, Hurst S, Salamone A, et al. 2021. Factors influencing distribution of *Coccidioides immitis* in soil, Washington State, 2016. mSphere 6(6):e00598-21, PMID: 34730378, https://doi.org/10.1128/mSphere.00598-21.
75. Marsden-Haug N, Goldoft M, Ralston C, Limaye AP, Chua J, Hill H, et al. 2013. Coccidioidomycosis acquired in Washington State. Clin Infect Dis 56(6):847–850, PMID: 23223598, https://doi.org/10.1093/cid/cis1028.
76. CDPH. n.d. Valley Fever Data and Publications. https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/ValleyFeverDataPublications.aspx [accessed 1 August 2022].
77. CDPH. 2024. Infectious Diseases Branch. Surveillance and Statistics Section. https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/SSS.aspx [accessed 18 April 2024].