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An Exploratory Analysis of Associations between Drought and Coccidioidomycosis Incidence in Arizona and California

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B.S. Environmental Sciences
Emory University
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Thesis Committee Chair: Jeremy Hess, MD, MPH, FACEP

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Abstract

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Coccidioidomycosis is an infectious disease caused by inhalation of the fungal pathogens *Coccidioides immitis* and *Coccidioides posadasii*, endemic to the southwestern United States. The past two decades have seen a striking increase in disease incidence, particularly in Arizona and California. This increase is hypothesized to have been impacted by climate and environmental conditions. Previous studies have analyzed the impact of climate conditions on coccidioidomycosis incidence in multiple counties in California and Arizona, establishing a link between sequences of wet and dry/warm climate conditions and coccidioidomycosis incidence in Arizona, although not in California. This study analyses the associations between coccidioidomycosis case counts and temperature, precipitation, and two drought indices in 3 counties in Arizona and 20 counties in California through bivariate and multivariate regression analyses. Patterns of alternating wet and dry climate conditions were associated with coccidioidomycosis case counts in both Arizona and California, captured through both precipitation and drought index variables. Conclusions from this study reveal a previously unidentified pattern of climate conditions impacting coccidioidomycosis in California; inclusion of drought indices is shown to have utility in elucidating this pattern. These results will contribute to our understanding of how disease patterns may change in light of expanding and intensifying drought in the region.

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Introduction

Coccidioidomycosis, or "Valley Fever," is an infectious disease caused by a soil-dwelling fungus, the incidence of which has been rapidly increasing in recent years.[1] In the past two decades, the incidence of coccidioidomycosis, typically a pulmonary infection but sometimes with other manifestations, has risen dramatically in the southwestern United States, from 5.3 cases per 100,000 in 1998 to 42.6 cases per 100,000 in 2011.[2] Coccidioidomycosis infection can induce lifelong morbidities, making it a serious burden to public health. This study attempts to characterize climate factors—specifically those relating to drought—associated with increased coccidioidomycosis incidence in California and Arizona.

Coccidioidomycosis

Coccidioidomycosis is a fungal infection, caused by the inhalation of *Coccidioides immitis* and *Coccidioides posadasii* spores, which produces a spectrum of disease. *Coccidioides* spp. are dimorphic fungi, meaning they go through two different phases—saprophytic and invasive—during their lifecycles. In the saprophytic phase, tubular hyphae (or mycelia) penetrate the soil. Arthroconidia are then formed by the segmentation of hyphae.[3] The arthroconidia are carried by the wind following a disturbance to the soil, and are either re-implanted in the soil or inhaled by a host.[4,5] If returned to the soil, arthroconidia can grow into more hyphae, repeating the cycle described above.[6]

The invasive phase is initiated when arthroconidia are inhaled by a host, such as a human, dog, horse, or other mammal; these hosts represent dead-ends to the transmission of coccidioidomycosis. The inhaled arthroconidia then deposit in the lungs and transform their cell walls into specialized structures called spherules.[7] The spherules are able to produce and release endospores, which propagate themselves by developing additional spherules within the host tissues.[8] Currently, there is no research suggesting differential pathogenicity between the two *Coccidioides* species.

Following exposure, coccidioidomycosis can manifest in multiple ways. It has been established that around 60% of exposed humans do not experience adverse health effects, while the remaining 40% experience a range of pulmonary manifestations.[9] Immunosuppression status, pregnancy, comorbidities including diabetes and cardiovascular disease, and ethnicity are all risk factors for developing symptomatic infection.[10] Pulmonary manifestations associated with coccidioidomycosis range from benign pulmonary infection—considered primary disease—to moderately severe respiratory disease.[11,12] Those with primary disease typically recover without treatment and maintain immunity to exogenous reinfection; however, endogenous reinfection and subsequent dissemination is possible.[12,4]

Of the aforementioned range of pulmonary manifestations, between 5% and 10% result in residual pulmonary nodules or thin-walled cavities, which may or may not be symptomatic, and may resolve spontaneously or require antifungal or surgical treatment.[7,11] Up to 1% of these manifestations result in extrapulmonary dissemination.[11] The most common sites of dissemination are the skin, bones, and meninges.[11]

Geographic Range

Coccidioides spp. is found in arid/semi-arid ecological zones in the Western Hemisphere, between the 40° latitudes, north and south.[13] These ecological zones are characterized by warm summers, mild winters, and precipitation ranging from 10 – 50 cm.[10,13] *Coccidioides* spp. thrive in sandy and alkaline soils.[14] In the United States, this translates to Arizona, California, Nevada, New Mexico, Texas, and Utah; however, soil samples from south central Washington were positive for *C. immitis* in 2010, suggesting that the hospitable range may be larger than previously considered.[15]

Interestingly, *C. posadasii* and *C. immitis* maintain discrete habitats; *C. immitis* is found in Central and Southern California. *C. posadasii* is found from Arizona to West Texas, as well as parts of California, Central and South America, and throughout Mexico.[13,16]

Attempts to isolate *Coccidioides* spp. from the soil have been largely unsuccessful as a result of the highly sporadic and localized distribution of the fungus; as a result, the geographic range described above has been extrapolated primarily from epidemiologic studies and population surveys utilizing dermal hypersensitivity mapping.[10] This represents a major challenge to the study of this pathogen; several barriers exist between climate impacts on fungal growth and epidemiological data.

Climate Pressures

Coccidioides spp*.* require a series of environmental mechanisms to survive and disseminate—described in the literature as the “grow and blow hypothesis.” The first hypothesized mechanism –grow – refers to the increased fungal growth facilitated by an increase in soil moisture that results from precipitation. Studies in Arizona have identified several positive associations relating coccidioidomycosis incidence to precedent precipitation—ranging from one-month lags to seasonal precipitation lagged one year.[6,17,18]

However, research in California has yielded no such associations.[19-21] This is potentially due to differential precipitation patterns; California precipitation occurs mainly in the winter, whereas Arizona experiences monsoon rains during late summer in addition to winter precipitation.[19,22] It has also been suggested that the regional difference in *Coccidioides* species plays a role in the heterogeneity of these results.[19]

The subsequent mechanism – blow—refers to dry conditions driving sporulation, desiccation and aerosolization of the pathogen, thus allowing for exposure via respiration. This mechanism has been corroborated in the literature through negative associations identified between precedent and concurrent precipitation and current coccidioidomycosis incidence, suggesting the suppression of spore-carrying dust by precipitation.[17,18]

It has also been hypothesized that, since *Coccidioides* spp. are poor competitors, an initial stage of soil heating and drying facilitates the "grow and blow" hypothesis by partially sterilizing competitors from the soil surface, as *Coccidioides* spp*.* remain viable 10-30 cm below the soil surface.[7] Following a period of precipitation, *Coccidioides* spp. surface soils regain hospitable conditions, resulting in *Coccidioides* spp. returning to the soil surface to continue growth.[23]

Drought

Given the climate conditions associated with coccidioidomycosis, drought stands out as an interesting potential driver of increased incidence. The southwestern United States is typically drier and hotter than the rest of the United States; however, future climate projections suggest this already parched region will become even hotter and drier.[22,24] In the southwestern US, the 2001-2010 decade was the warmest on instrumental record, with greatest warming occurring during the spring and summer seasons—when *Coccidioides* spp. are likely growing after winter precipitation.[22]

Since 2000, the southwestern United States has also experienced sustained episodes of drought. The 2001-2010 decade saw the second largest areal extent of drought in the southwest since 1901.[22] Drought can generally be characterized in four ways—meteorological, agricultural, hydrological, and socioeconomic.[25] This study pertains to hydrological drought—that is, drought associated with the effects of periods of precipitation shortfalls on surface and/or subsurface water supplies, such as soil moisture.[25] This is captured through a drought index, which is a proxy based on climatic information, maintained on the assumption that it will quantify the true degree of drought hazard exerted.[26]

Previous studies have assessed the relationship between coccidioidomycosis incidence and various climatic and environmental variables, including precipitation, temperature, wind speed, PM_{10} concentration, and drought.[6,17-19,27,28] Drought, in these studies, has been represented by two of the Palmer indices—Palmer Z and Palmer Drought Severity Index (PDSI).[6,27] These indices, representing short (meteorological)- and long (hydrological)-term drought, are calculated from precipitation, temperature, evapotranspiration, soil moisture loss and recharge, and runoff components.[27,29] Combined with the Palmer Hydrological Drought Index (PDHI), these three indices form the Palmer Index.[29]

There are currently many indices aimed at capturing the impact of drought, with varying strengths and weaknesses. The Palmer Index represents monumental developments in drought monitoring; it was created in 1965, and remains one of the most widely used indices today.[29,30] The index is based on a water balance model and measures both wet (positive) and dry (negative) conditions. However, the Palmer Index has shortcomings, including its inability to account for changes in vegetation in its water balance equations, inability to account for frozen precipitation/ground, and lack of comparability between locations and/or timescales.[31]

Additional indicators of drought have been validated and popularized in recent years; among them, the Standardized Precipitation Index (SPI) and the Standardized Precipitation Evapotranspiration Index (SPEI). In assessments of drought index performance in hydrologic, ecological and agricultural contexts, SPI and SPEI both met or outperformed Palmer Index and any offspring of Palmer Index.[26]

The Standardized Precipitation Index, as its name indicates, is based on precipitation alone. Using long-term monthly precipitation records (>30 years), a probability distribution function is fit to the data. Then, the cumulative distribution is transformed to a normal distribution with a mean of zero and standard deviation of one.[32] This calculation relies on the assumptions that the variability of precipitation is higher than that of other potential inputs, and that other potential inputs are stationary—in short, that any other variables are negligible.[33] SPI has many strengths—among them is the ability to calculate SPI for a variety of timescales, allowing both short-term and longer-term water resources to be monitored. Additionally, because SPI is, by its own calculation, normally distributed, the frequency of extremes according to this index are consistent at any location and/or timescale.[32,34]

The Standardized Precipitation Evapotranspiration Index is based on both precipitation and potential evapotranspiration (PET), which is the water that would be removed via evaporation and transpiration, assuming water amount is not a limiting factor.[35] Where the SPI is calculated using historic monthly precipitation in the calculation, SPEI utilizes the monthly difference between precipitation and PET, as a simplified representation of climatic water balance.[33,36] PET can be calculated using multiple methodologies. A probability distribution is then fit to the data, at which point the cumulative distribution is transformed to a log-normal distribution, with a mean of 0 and standard deviation of 1. Similar to SPI, this index is advantageous in that it standardized, and can thus be compared with other SPEI values at any location and/or timescale. Additionally, SPEI accounts for evapotranspiration processes that stand to be impacted based on future climate projections.[33]

Given the benefits and drawbacks of each of these drought indices, the SPI and SPEI appear to be superior to the Palmer Index within the context of the southwestern United States. Both the SPI and SPEI excel in their standardization across different climate zones, an important characteristic considering the differential climates of Arizona and California.

Purpose of Study

The purpose of this study is to add to the body of literature relating climate conditions to coccidioidomycosis incidence. Previous studies have assessed the impact of climate and the environment in coccidioidomycosis incidence, primarily focused on Kern County in California, and Pima and Maricopa Counties in Arizona. This overall objective of this retrospective observational study is to describe the temporal characteristics of coccidioidomycosis incidence in relation to drought-specific climate and environmental variables. This study is set in a broader geographic region than has been previously studies, encompassing 3 counties in Arizona and 20 counties in California. Further, this study attempts to apply additional drought characterization methods—SPI and SPEI—toward quantifying the association between drought and coccidioidomycosis. This study will improve our understanding of coccidioidomycosis and provide an opportunity to better understand temporal and geographic influences on factors controlling this pathogen.

Methods

Data Collection

Coccidioidomycosis has been a nationally notifiable disease since 1995; as such, confirmed cases are to be reported to the Nationally Notifiable Diseases Surveillance System (NNDSS). Cases from California and Arizona meeting the Council of State and Territorial Epidemiologists (CSTE) case definition of laboratory and clinical confirmation of infection were included in the dataset. Cases confirmed only by a single positive serological test in Arizona were included in the dataset starting in 2008, when the CSTE updated the case definition.[2]

Cases were tabulated by county. Aggregate case counts were calculated for Maricopa, Pima and Pinal counties in Arizona and Contra Costa, Fresno, Kern, Kings, Los Angeles, Madera, Merced, Monterey, Orange, Placer, Riverside, Sacramento, San Bernardino, San Diego, San Luis Obispo, San Joaquin, Solano, Stanislaus, Tulare, and Ventura counties in California for every month from 2000 – 2013 to form a case count Excel dataset, which was imported into SAS software v. 9.3 (Cary, NC).[37]

Censal and intercensal population estimates were obtained from the United States Census Bureau for each county in the study area from 2000-2013.[38] Population estimates were linearly interpolated to generate monthly population estimates for each county. The estimates for July of 2014 were unavailable during analysis, so interpolation lines from July of 2012 to July of 2013 were extended to December of 2013. Population estimates were added to the case count dataset in SAS. Demographic data for each county was collected for the 2000 geography as well as the 2010 geography.

State and county shapefiles were obtained from the 2013 TIGER/Line Shapefiles created by the United States Census Bureau.[39] These files were created using the North American Datum 1983 Geographic Coordinate System. Climate Division shapefiles were obtained from NOAA's National Climatic Data Center (NCDC).[40] Climate division boundaries were overlaid on county boundaries; using ArcGIS v. 10.2 (Redlands, CA), counties were assigned to climate divisions according to majority land area—that is to say, if a county was located in multiple climate divisions, it was assigned to the division in which the majority of the county's land area fell.[41]

SPI, SPEI, average precipitation, and average, minimum and maximum temperature values were collected for each month from 1998 to 2008. The data was downloaded as a 3 by 3 kilometer gridded product from NCDC, with each grid representing the average parameter value for a given month. SPI and SPEI both range from -3 to 3, with negative values indicating dry conditions and positive values indicating wet conditions. Precipitation is expressed in millimeters, while temperature is expressed as degrees Celsius. The gridded data was converted to match county and climate division health boundaries using ArcGIS. Detailed data processing methods can be found in appendix I. The converted data was then exported to SAS, where it was merged with the case count and population dataset.

Temperature and precipitation averages were detrended in SAS by subtracting a line of best fit from each variable's time series to create anomaly variables.

Descriptive Analysis

Initially, a series of descriptive statistics were generated from the data. A crude incidence rate per 100,000 people was calculated in SAS for each county and climate division, using the linearly interpolated population estimates.

Monthly and yearly crude incidence rates and cumulative case counts were then plotted graphically. Monthly and yearly climate and environmental variables were also plotted graphically. Graphs were compared, visually noting any patterns or trends.

Chloropleth maps of yearly averages for each variable were generated in ArcGIS as a method of visualizing the progression of coccidioidomycosis incidence and drought, and understanding changes in precipitation and temperature.

Finally, associations between coccidioidomycosis and relatively static demographic variables were assessed using Pearson Product-Moment Correlation Coefficients.

Bivariate Analysis

Preceding bivariate analysis, correlations between all climate variables were assessed using Pearson Product-Moment Correlation Coefficients (table 1). Of the 80 correlations, 73 were significant, suggesting similar variables may not contribute significantly or uniquely toward future modeling processes. Therefore, averages for precipitation, temperature, SPI and SPEI were retained for future analysis; all other climate variables were excluded.

To assess bivariate relationships, the remaining variables were lagged up to 24 months, as established in the literature, to better understand the temporal influence on climate-coccidioidomycosis associations.[6] Lagged variables were created by assigning a given month's value to the lagged month—for example, a 2-month lag assigns the January SPI value to March. The assignment of lagged values was conducted in SAS.

An initial exploration of bivariate relationships was conducted looking at the entire dataset, without stratifying for state or month. Multiple regression techniques equipped to handle case counts, including Poisson Regression, Zero-Inflated Poisson Regression, and Negative Binomial Regression were fit to the data; Negative

Binomial Regression was ultimately selected as the most appropriate technique for the data, as the count data are highly over-dispersed (mean=107.0; variance=44832.0). Case counts were set as the dependent variable, each climate parameter was set as the independent variable, and the natural log of the population served as the offset term. Regression coefficient estimates and their associated p-values were recorded.

Next, the exploration of bivariate relationships was expanded by stratifying by state, climate division and month, using the methods described above.

Multivariate Analysis

The bivariate analysis allowed for a simple assessment of precedent conditions on disease ecology; however, it did not capture the impact of both short-term and seasonal mechanisms. To get at this relationship, seasonal variables were created based on *a priori* knowledge drawn from the literature; six-month averages were created for each climate variable, averaging 2- to 7-month lags.[27] Proximal variables, which give some indication of conditions controlling exposure, were simply 1-month lagged climate variables. The 1-month lag was chosen over concurrent conditions as a means of accounting for the incubation period of the pathogen.

Next, multivariate negative binomial regression models were constructed. Each model adhered to the following equation:

$$\ln(\text{case count}) = ß_0 + ß_1(\text{proximal } X_1) + ß_2(\text{seasonal } X_1) + ß_3(\text{proximal } X_2) + ß_4(\text{seasonal } X_2) + \ln(\text{population})$$

where X_1 always represents temperature, as it diverged most often from the other variables (table 1). X_2 represents precipitation, SPI or SPEI. Models were constructed for the entire dataset, before stratifying by state, climate division, and month.

Results

Exploratory Analysis

Climate

Climate conditions in the study region varied both spatially and temporally. Temperatures ranged from -17.3°C to 46.5°C across the study region and period. Throughout the study period, yearly temperature values varied minimally (fig. 1). Looking at intra-annual temperature variability revealed an expected pattern of a gradual summer peak and winter trough across minimum, average and maximum values (fig. 2). This same pattern held when sub-setting for state, though Arizona experienced warmer values across the time series for minimum, average, and maximum temperature variables (fig. 3).

Precipitation patterns proved to be less uniform than temperature in this study region and period. Precipitation ranged from no precipitation to 1256.9 mm. Inter-annual variability in precipitation varied across the time series; notable peaks in precipitation were experienced by all variables in 1998, 2005 and 2010, captured most acutely by the maximum precipitation variable (fig. 4). Figure 5, characterizing intra-annual variation, shows a distinct winter peak in precipitation, with a very slight secondary peak in late summer. Sub-setting for state revealed distinct precipitation patterns; Arizona experienced both late summer and winter peaks in precipitation, whereas California experienced only winter peaks (fig. 6).

SPI and SPEI exhibited similar trends. Both indices experienced maxima and minima to the fullest extent the scale would allow (-3.0 to 3.0). Across the study period, drought conditions fluctuated. The SPI and SPEI captured similar patterns of peaks and troughs; the study region experienced extremely dry conditions in 2002 and from 2006-2009, whereas more moist conditions were captured in 1998, 2005 and 2010 (fig. 7, 10). Intra-annual variation in drought revealed fluctuation from January to May for SPI and SPEI minima, averages and maxima (fig. 8, 11). The SPI and SPEI maxima gradually increased until July, before gradually decreasing into December. The SPI and SPEI minima gradually declined until September, before increasing into December. Sub-setting by state revealed similar patterns of fluctuation from January to May for SPI and SPEI minima, averages and maxima (fig. 9, 12). Maximum and average SPI variables captured periods of drier conditions in California than those captured Arizona, whereas all SPEI variables depicted generally drier conditions in Arizona. An exception to this occurred during the summer season—June through September. During this period, California superseded Arizona as the drier region, as captured by the SPEI, owing to the summer precipitation period in Arizona. Interestingly, this phenomenon was not captured by the SPI.

Assessing each of these climate components spatially revealed similar spatial trends. As determined in figures 3, 6, 9, and 11 and confirmed in figures 12-16, the warmest, driest conditions were found in the southeastern portion of the study area

(Arizona). The coolest, most damp conditions were found in the northwestern portion of the study area (N. California); the region in between served as a gradient between the two.

Coccidioidomycosis

Between 2000 and 2013, over 125,000 cases were reported in the study region. Of these cases, 86,250 (68.5%) occurred in Arizona and 39,580 (31.5%) occurred in California. Coccidioidomycosis incidence in this study area increased steadily from 2000 to 2006. From 2008 to 2011 incidence rose from 2.4 to just under 6 cases per 100,000, before falling to just above 2.5 cases per 100,000 in 2013 (fig. 17). Inter-annual variation remained low from January to November; in December, there was a striking increase in incidence (fig. 18). Sub-setting by state confirmed that far more cases occurred in Arizona than California (fig. 19). Additionally, while both states experienced a strong winter peak in incidence, Arizona showed a small secondary summer peak. Spatially, Arizona appears homogenous across the divisions and counties represented, while California showed highest incidence in the central, San Joaquin Valley area (fig. 20).

Bivariate Analysis

Negative binomial regression analysis of the entire dataset, without stratification, revealed many significant bivariate associations. Table 2 displays the results of each negative binomial regression, summarized as the sign of the regression coefficient for each variable at each lag; significant associations are displayed. Temperature was positively associated with coccidioidomycosis case counts at all lags, while precipitation was negatively associated with counts at all lags. SPI and SPEI were negatively associated with case counts up to 5- and 7-month lags, respectively; this means that as SPI/SPEI increased (i.e. conditions become less dry), case counts decreased. SPI and SPEI were intermittently negatively associated with case counts at later lags (SPI: 9-, 21- and 23-month lags; SPEI: 15-, 19-, 21-, 23- and 24-month lags).

Stratifying by state yielded dissimilar results to the previous analysis (table 3). In Arizona, temperature was positively associated with case counts at 3-, 4- and 15-month lags. Precipitation, SPI and SPEI were negatively associated with case counts from 1- to 3- month lags. Precipitation was also negatively associated from 6- to 9-month lags, while SPEI underwent a sign change and was positively associated with case counts at 11-, 12- and 16-month lags. Differing from Arizona, California temperature was exclusively negatively associated with case counts, at 1-, 7- through 13-, 16-, and 19- through 24-month lags. Precipitation underwent a dry/wet/dry pattern, with negative associations from 1- to 6-month lags, positive associations from 9- to 11-month lags, and negative associations again from 15- to 18-month lags. SPI and SPEI were positively associated with case counts intermittently from 1- to 17-month lags (SPI) and 7- to 14-month lags (SPEI).

Stratification by climate division (table 4) revealed alternating patterns of heating and cooling—shown by alternating positive and negative associations between temperature and case counts—for the Central Coast Drainage, San Joaquin Drainage and Southeast Desert Basin Divisions in California, as well as the Southeast Division in Arizona. Similarly, alternating positive and negative associations between precipitation and case counts were seen in these same California climate divisions, at similar lag periods. In the Southeast Division, periods of positively associated precipitation lined up with negatively associated temperature. SPI and SPEI in these four climate divisions appeared to generally line up with periods of positively associated precipitation. The remaining three climate divisions—Sacramento and South Coast Drainage Divisions in California, and South Central Division in Arizona—showed no discernable patterns of positive or negative associations for any climate variable.

Assessing monthly relationships (table 5) revealed a strong seasonal pattern to the associations between monthly case counts and precipitation. Alternating patterns of positive and negative associations between precipitation and case counts occurred from January to December, descending one lag as each month progressed. Interpreting this phenomenon revealed a repeating pattern of positive associations between precipitation from July to September and case counts, followed by negative associations between precipitation from October to May and case counts. Temperature was positively associated with case counts at all lags, across all months. SPI lags from around July through September appeared to be negatively associated with case counts from January to May, at which point the pattern disappeared.

Multivariate Analysis

Multivariate analysis of the entire dataset yielded three models, all with significant terms (table 6). All terms in model 1 were significant (seasonal and proximal temperature and precipitation). Seasonal temperature and SPI, as well as proximal temperature, were significant in model 2. Model 3 yielded only proximal and seasonal temperature as significant parameters. Regression coefficients for proximal and seasonal temperature remained positive regardless of model, while coefficients for proximal and seasonal precipitation, SPI and SPEI were all negative.

Stratification by state revealed differentiation in regression coefficient signs and levels of significance for each model (table 7). Proximal and seasonal precipitation were the only terms whose sign and significance remained unchanged by stratification. Overall, Arizona models more closely resembled the unstratified models.

Stratification by climate division revealed similar models among the Arizona climate divisions, with few differences in sign and significance (table 8). In California, the San Joaquin Drainage, South Coast Drainage and Southeast Desert Basin Divisions maintained similar models. The Central Coast Drainage model had some similarities to the previous four models, in that the seasonal temperature was consistently positive for all models, as well as some characteristics of the SPI and SPEI variables. The Sacramento Drainage Division model was highly dissimilar to other models.

Discussion

The differences between the SPI, SPEI and precipitation patterns in descriptive analyses suggested SPI and SPEI inclusion in climate-coccidioidomycosis analyses may have utility in capturing soil moisture conditions not fully captured by precipitation alone. In previous analyses, precipitation has been favored due to its predictive power as well as its purported ability to evaluate soil moisture conditions.[17,18] However, the differential inter- and intra-annual patterns between

SPI/SPEI and precipitation suggested that precipitation may not provide a complete picture of drought and soil moisture conditions impacting *Coccidioides* spp. The results of the bivariate analysis, however, did not testify to such an impact of SPI and SPEI. Consistent with the existing body of literature, precipitation is strongly associated with coccidioidomycosis in bivariate analyses.

Analyses of the entire dataset (both bivariate and multivariate) provide an ambiguous first look into climatic impacts on coccidioidomycosis. While highly significant, these results did not resemble a "grow and blow" pattern—none of the variables undergo changes in coefficient sign, and temperature and precipitation remain significant at all lags. Stratification by month in the bivariate analysis demonstrated a strong seasonal pattern, particularly with regard to precipitation. The consistency of the pattern indicates a strong seasonal effect on case counts, however, it is unclear why this pattern emerged; months associated with peaks in precipitation are captured in both the negative and positive regions of the lagged associations.

Stratification by state in both the bivariate and multivariate analyses showed tentative evidence of the "grow and blow" hypothesis. In Arizona, the bivariate analysis revealed precipitation was negatively associated with cases within the first three lagged months, suggesting that more immediate precipitation may suppress the "blow" component of the hypothesis, preventing fungal spores from aerosolizing; this same pattern was seen with SPI and SPEI. In California, a more pronounced pattern emerged—precipitation up to 6 months prior to the month of interest was negatively associated with case counts, again suggesting suppression of dust that, in otherwise dry conditions, may have facilitated spore exposure. This was preceded by positive associations between case counts and precipitation from 9- to 11-month lags. It is unclear whether this represents the “grow” component of the hypothesis, or rather some unknown ecological process acting upon the fungus.

Interestingly, patterns of alternating dry and wet conditions were more pronounced in California than Arizona—a phenomenon not previously seen in the literature. This novel pattern continued in the state stratified multivariate analysis. California models revealed that, taken together with proximal and seasonal temperature, proximal SPI and SPEI regression coefficients, though insignificant, were negative, while seasonal SPI and SPEI regression coefficients were significant and positive. This indicated that more intense proximal drought conditions (decreasing along the -3.0 to 3.0 scale) were associated with increased case counts, while more intense seasonal drought components were associated with decreased case counts. These results suggest that a sequence of dry and wet climate conditions is controlling some part of the *Coccidioides* spp. transmission process, potentially fungal growth—a pattern that has been established in Arizona. It is possible that these novel findings are a result of data processing and analysis; future studies should seek to confirm that these are not spurious results by adjusting for multiple comparisons. It is important to note that this pattern is captured in the multivariate analysis largely by the drought indices, rather than precipitation, suggesting climate conditions captured by these indices are not fully captured by precipitation.

Limitations

A number of limitations emerged throughout the research process. One limitation inherent to this study is its emphasis on the relationship between climate and reported human cases as a proxy for the relationship between climate and *Coccidioides* spp. proliferation, due to fungal concentration data. Human cases are far removed from the climate and environmental mechanisms acting upon the fungi. Further, the resolution of the data available for this analysis proved to add another level of complexity and complication to disentangling the relationship between climate and coccidioidomycosis. The health data used in this analysis are very coarse—they represent only the month of reporting for cases, and do not include additional information concerning date of symptom onset or estimated date of exposure. As a result, the health data are further removed from influencing climate and environmental mechanisms. Though sensitivity analyses have established that explanatory power is retained using monthly reporting, models gain clarity and explanatory power when incorporating exposure adjustments.[28] This is because the exposure-to-report date lag is highly variable, introducing additional noise into the analysis.[42]

A number of uncertainties should be noted regarding the data used in this analysis. One such uncertainty pertains to the population estimates; migrant populations were likely not captured in the analysis. Two particular migrant populations come to mind, the first known as "snow birds," or retired/semi-retired residents who come to the region for the winter. The second migrant population underestimated in population estimates is undocumented immigrants. It is unknown how these two populations contribute to coccidioidomycosis case counts.

Finally, this study is limited in its consideration of the coccidioidomycosis exposure pathway. This study assessed how proximal dry conditions facilitate exposure; however, many steps of the exposure pathway remain between proximal dry conditions and infection. These steps include disturbance of the soil, suspension of spores in the air, and human activity that may put people at risk. In analysis, these missing steps may be incorporated through inclusion of land use datasets that give indication of novel soil disturbance (construction or agricultural activity), as well as particulate matter/dust datasets.

Recommendations for Future Study

As mentioned previously, many important environmental, demographic and climatologic variables were not able to be included in this analysis. Future studies should develop methods of adjusting population offsets to account from migrant groups in both states. Inclusion of additional environmental factors – particularly dust, land use and soil moisture parameters—may provide a more nuanced understanding of conditions impacting fungal growth and dispersion. These data, previously difficult to estimate, are newly available through innovative modeling processes.[43,44]

Additionally, future studies may incorporate a sensitivity analysis to better understand how the summarization of spatially variable climate data to health boundaries impacts findings. In this study, as previously mentioned, the unit of analysis was the climate division. One method of sensitivity analysis would be to replicate analyses using county as the unit of analysis. An additional method of sensitivity analysis would be to assign spatial weights to climate factors based on population—likely utilizing census tracts—to understand if summarization to such large spatial unit is masking important climate exposures at a smaller scale.

Conclusion

This study builds on the existing literature relating climate variables to coccidioidomycosis incidence data to gain a better understanding of the impact of climate and seasonality on the ecology of this disease. Various statistical approaches were employed to explore the complex role of drought on this pathogen. Resultant associations, achieved through both bivariate and multivariate regression techniques, corroborate the “grow and blow” hypothesis in Arizona, as well as provide evidence for a similar pattern in California. The discovery of this pattern was facilitated through inclusion of robust drought indices in analyses, indicating that further investigation into the role of drought on the ecology of and exposure to *Coccidioides* spp. is warranted.

Figures & Tables

TABLE 1. Pearson Product-Moment Correlation Matrix for all Climate Variables; insignificant associations bolded and italicized

	PRECIPITATION				TEMPERATURE				SPI			SPEI		
	MIN	AVG	MAX	ANOM	MIN	AVG	MAX	ANOM	MIN	AVG	MAX	MIN	AVG	MAX
PRECIPITATION - MIN														
PRECIPITATION - AVG	0.87154 <0.0001													
PRECIPITATION - MAX	0.63032 <0.0001	0.83831 <0.0001												
PRECIPITATION - ANOMALY	0.7869 <0.0001	0.94259 <0.0001	0.83075 <0.0001											
TEMPERATURE - MIN	-0.2038 <0.0001	-0.3105 <0.0001	-0.4673 <0.0001	-0.2738 <0.0001										
TEMPERATURE - AVG	-0.343 <0.0001	-0.4251 <0.0001	-0.4678 <0.0001	-0.3609 <0.0001	0.85419 <0.0001									
TEMPERATURE - MAX	-0.4392 <0.0001	-0.5527 <0.0001	-0.5124 <0.0001	-0.4437 <0.0001	0.7646 <0.0001	0.96238 <0.0001								
TEMPERATURE - ANOMALY	-0.2852 <0.0001	-0.3671 <0.0001	-0.4131 <0.0001	-0.3895 <0.0001	0.77088 <0.0001	0.92662 <0.0001	0.91543 <0.0001							
SPI - MIN	0.48852 <0.0001	0.557 <0.0001	0.51945 <0.0001	0.53909 <0.0001	-0.0832 0.0023	-0.2043 <0.0001	-0.2575 <0.0001	-0.189 <0.0001						
SPI - AVG	0.41986 <0.0001	0.52528 <0.0001	0.51752 <0.0001	0.5274 <0.0001	***0.01708*** ***0.5317***	***-0.0298*** ***0.2756***	-0.0628 0.0216	***0.00758*** ***0.7814***	0.85192 <0.0001					
SPI - MAX	0.26247 <0.0001	0.35242 <0.0001	0.40761 <0.0001	0.39935 <0.0001	0.14328 <0.0001	0.20224 <0.0001	0.19226 <0.0001	0.227 <0.0001	0.66848 <0.0001	0.86882 <0.0001				
SPEI - MIN	0.45007 <0.0001	0.50618 <0.0001	0.47299 <0.0001	0.47899 <0.0001	-0.2461 <0.0001	-0.3462 <0.0001	-0.3811 <0.0001	-0.3308 <0.0001	0.69965 <0.0001	0.63862 <0.0001	0.48942 <0.0001			
SPEI - AVG	0.4626 <0.0001	0.57877 <0.0001	0.56995 <0.0001	0.56789 <0.0001	-0.253 <0.0001	-0.3278 <0.0001	-0.3649 <0.0001	-0.3067 <0.0001	0.7369 <0.0001	0.76627 <0.0001	0.61337 <0.0001	0.87335 <0.0001		
SPEI - MAX	0.32705 <0.0001	0.44144 <0.0001	0.49773 <0.0001	0.47446 <0.0001	***-0.0161*** ***0.5548***	***0.00012*** ***0.9965***	***-0.023*** ***0.4018***	***0.02205*** ***0.4193***	0.6868 <0.0001	0.82429 <0.0001	0.87474 <0.0001	0.67112 <0.0001	0.80762 <0.0001	

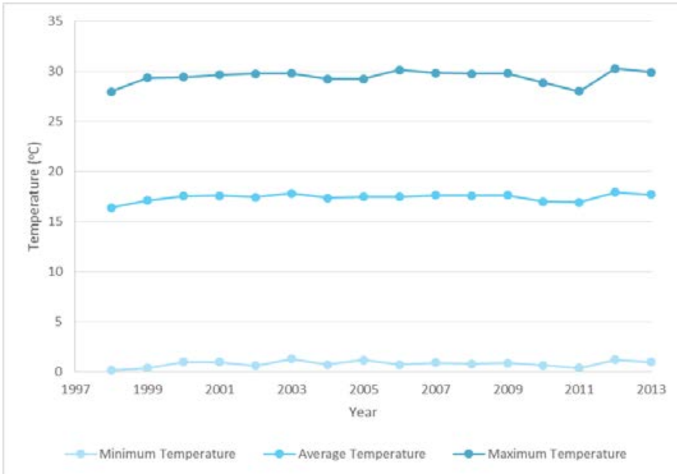

FIGURE 1: Inter-Annual Variation in Minimum/Average/Maximum Temperature (1998 – 2013); Entire Study Area

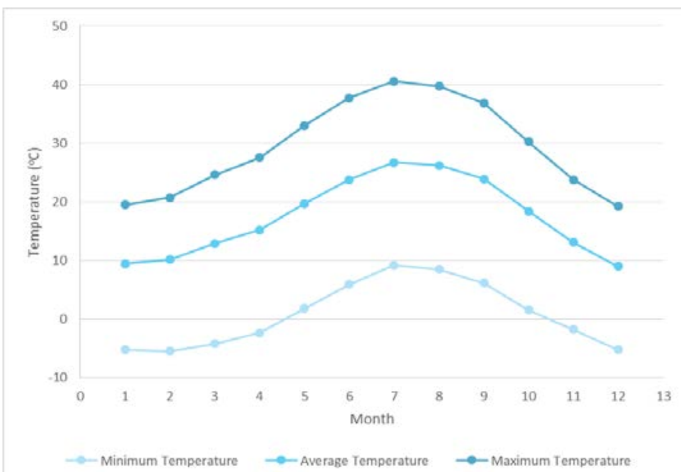

FIGURE 2. Intra-Annual Variation in Minimum/Average/Maximum Temperature; Entire Study Area

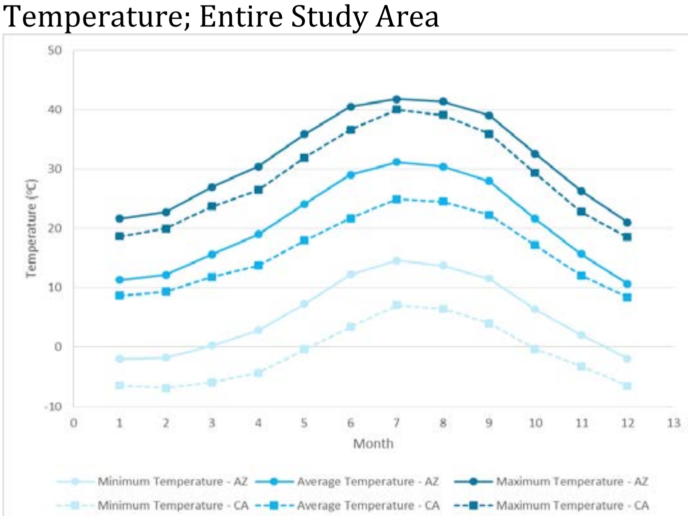

FIGURE 3. Intra-Annual Variation in Minimum/Average/Maximum Temperature; by State

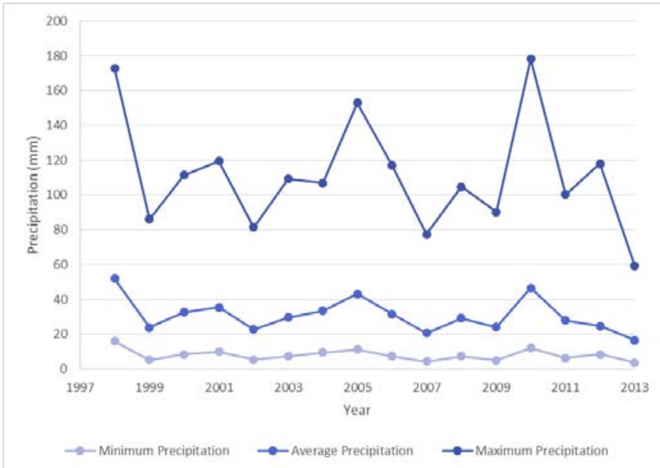

FIGURE 4: Inter-Annual Variation in Minimum/Average/Maximum Precipitation (1998 – 2013); Entire Study Area

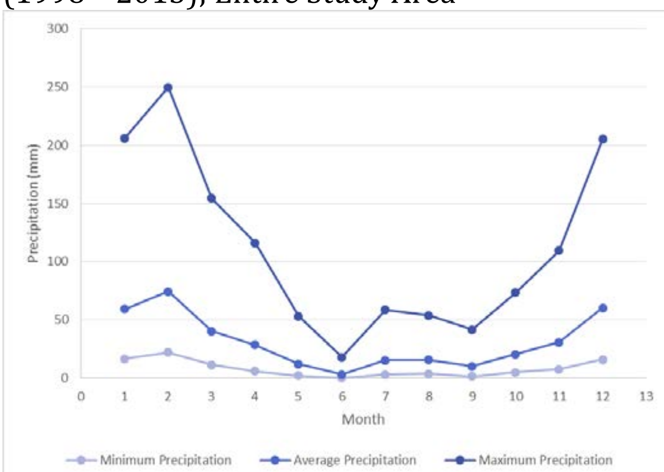

FIGURE 5. Intra-Annual Variation in Minimum/Average/Maximum Precipitation; Entire Study Area

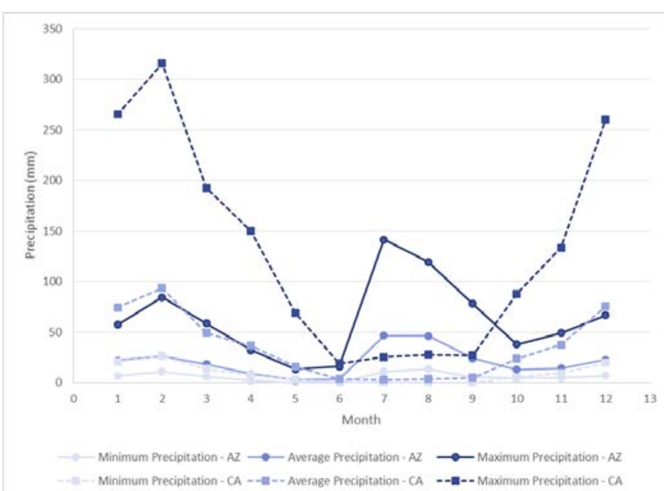

FIGURE 6. Intra-Annual Variation in Minimum/Average/Maximum Precipitation; by State

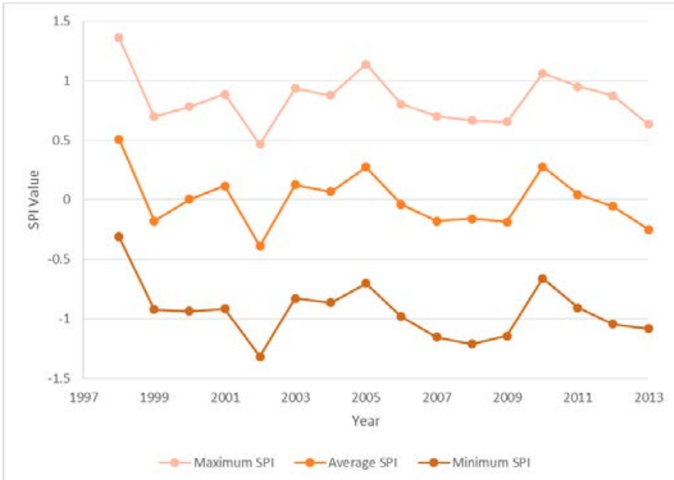

FIGURE 7: Inter-Annual Variation in Minimum/Average/Maximum SPI (1998 – 2013); Entire Study Area

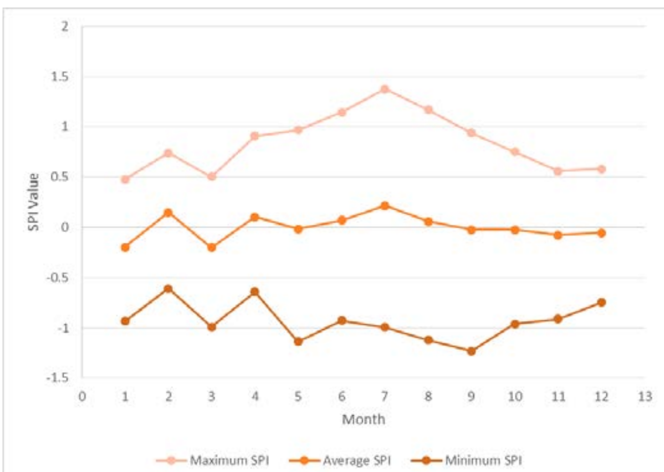

FIGURE 8. Intra-Annual Variation in Minimum/Average/Maximum SPI; Entire Study Area

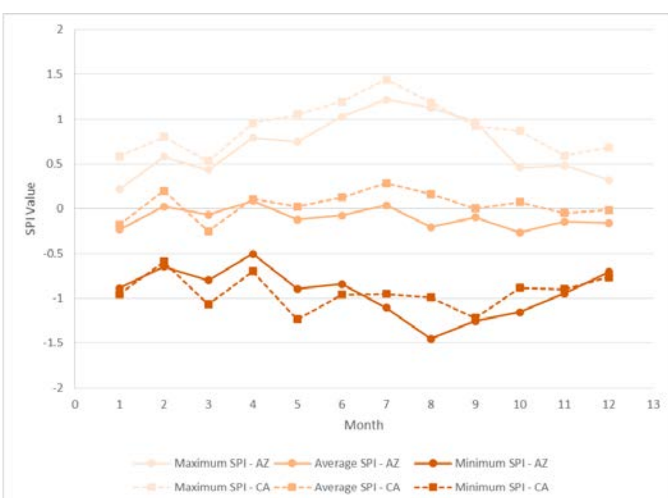

FIGURE 9. Intra-Annual Variation in Minimum/Average/Maximum SPI; by State

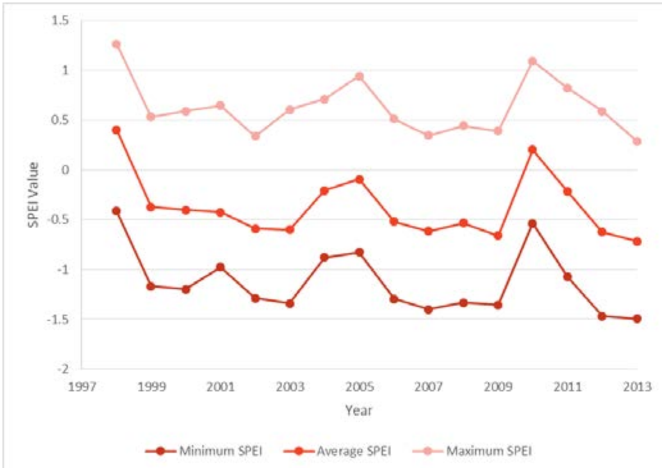

FIGURE 10: Inter-Annual Variation in Minimum/Average/Maximum SPEI (1998 – 2013); Entire Study Area

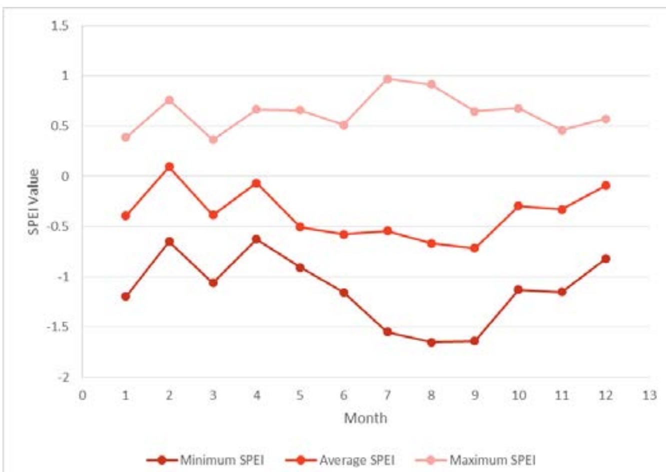

FIGURE 11. Intra-Annual Variation in Minimum/Average/Maximum SPEI; Entire Study Area

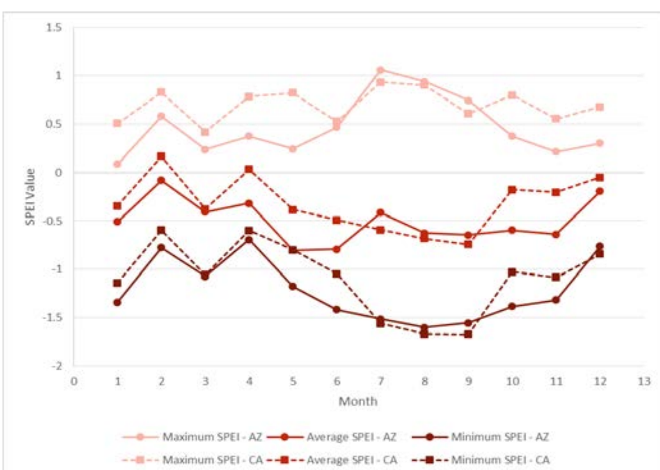

FIGURE 12. Intra-Annual Variation in Minimum/Average/Maximum SPEI; by State

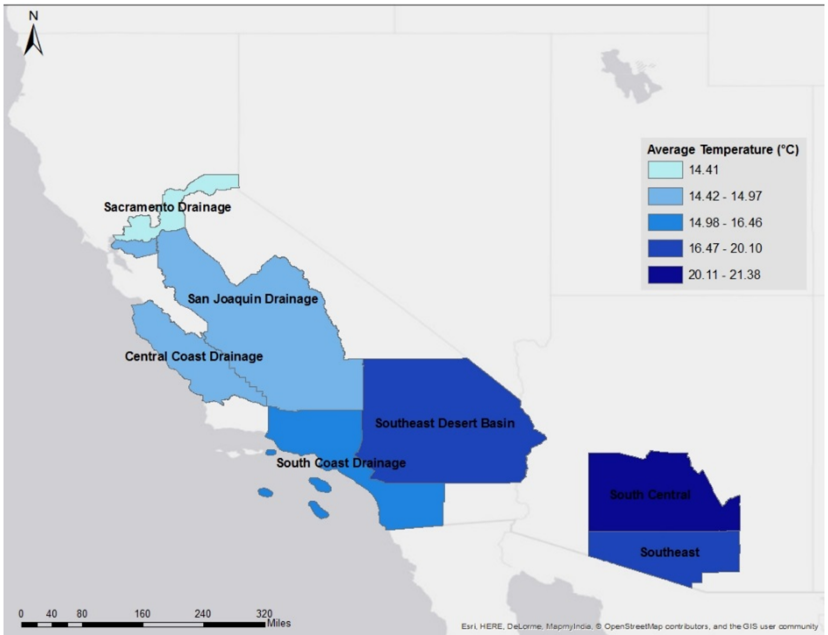

FIGURE 13. Average Temperature by Climate Division

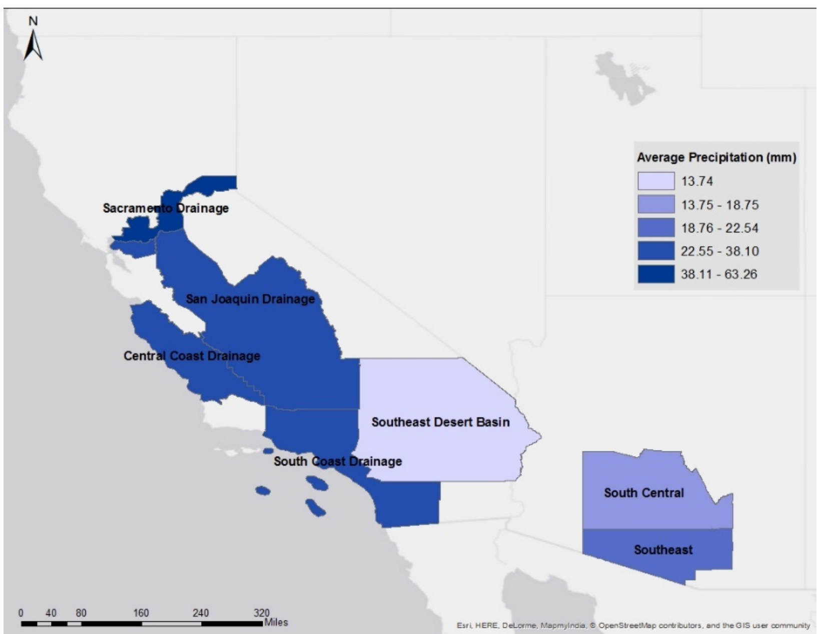

FIGURE 14. Average Precipitation by Climate Division

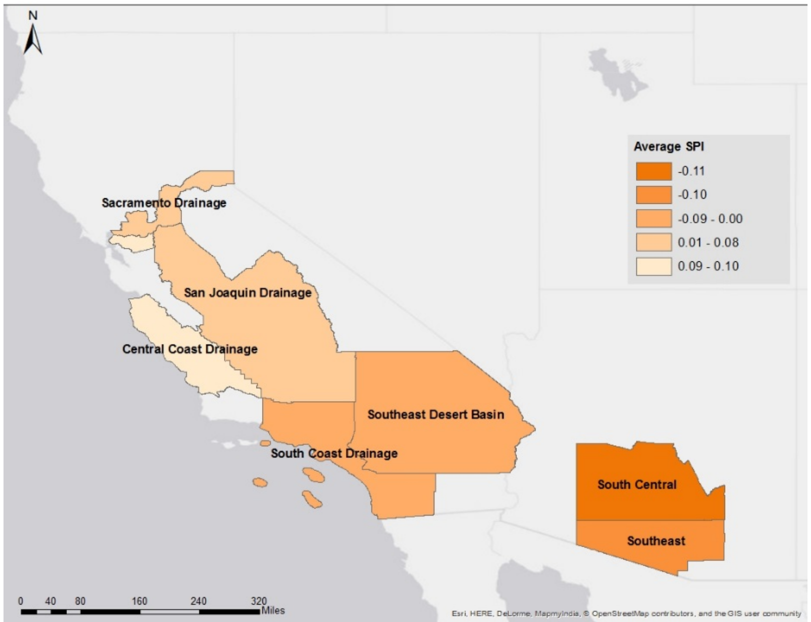

FIGURE 15. Average SPI by Climate Division

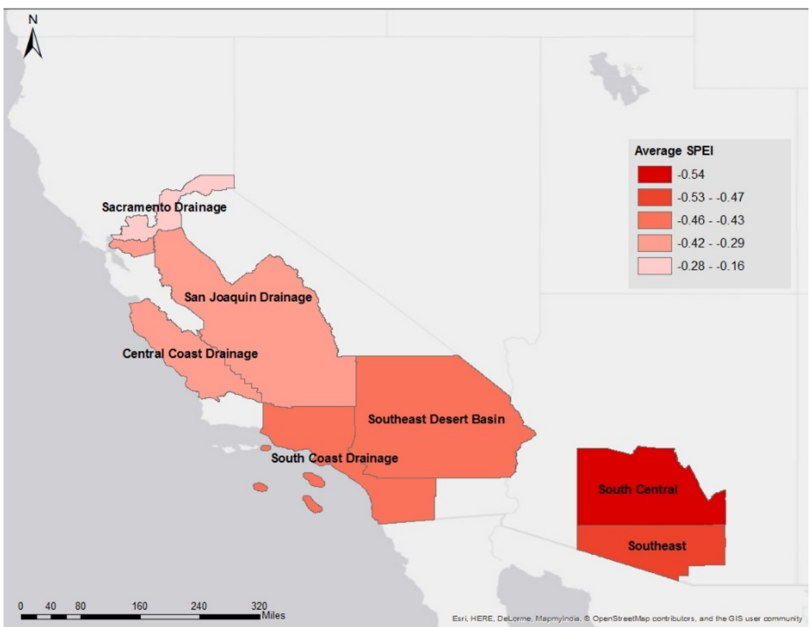

FIGURE 16. Average SPEI by Climate Division

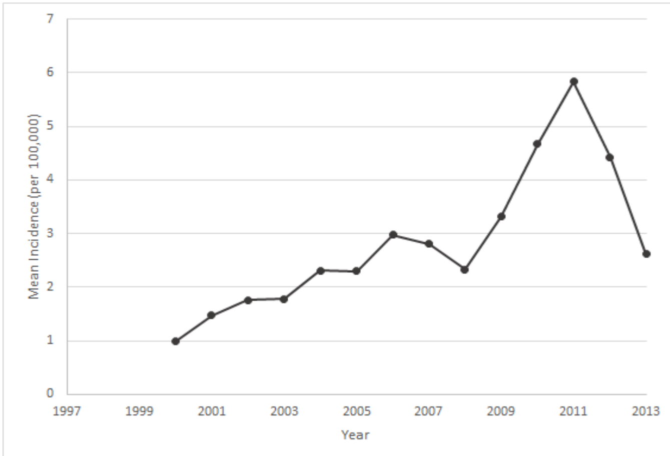

FIGURE 17. Inter-Annual Coccidioidomycosis Mean Incidence (per 100,000); Entire Study Area

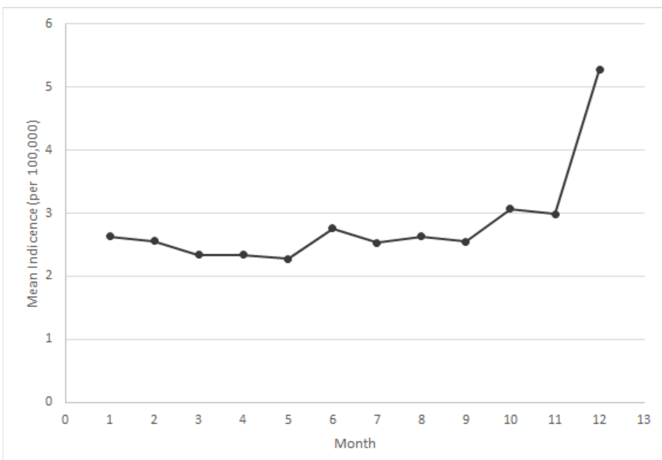

FIGURE 18. Intra-Annual Coccidioidomycosis Mean Incidence (per 100,000); Entire Study Area

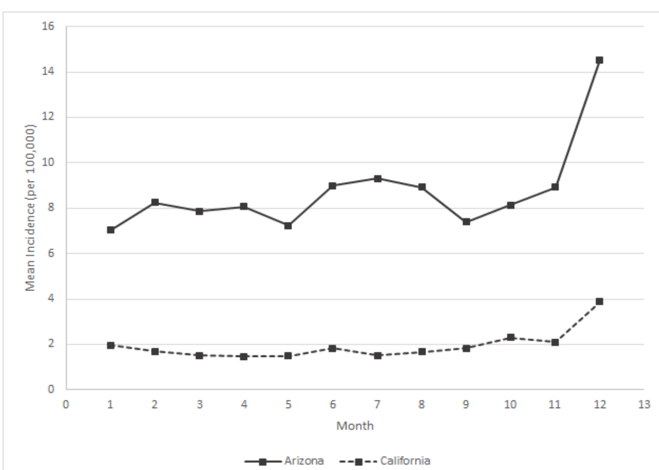

FIGURE 19. Intra-Annual Coccidioidomycosis Mean Incidence (per 100,000); by State

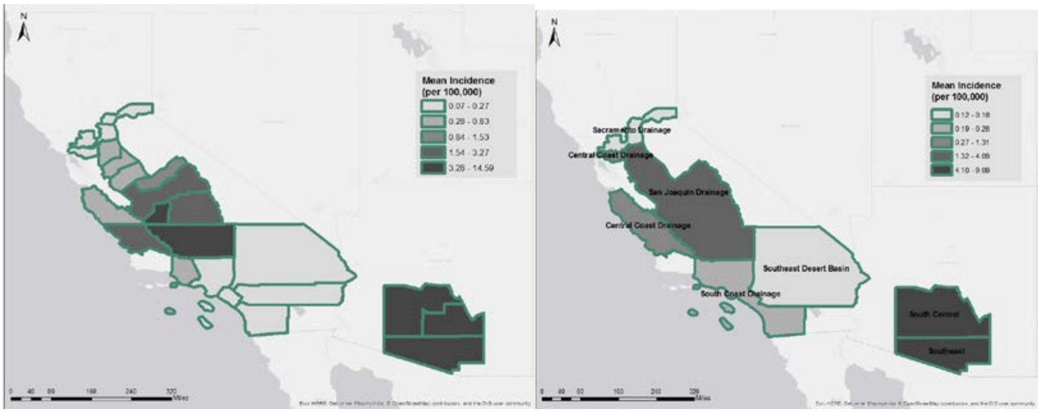

FIGURE 20. Mean Coccidioidomycosis by County (left) and Climate Division (right)

TABLE 2. Bivariate Negative Binomial Regression; Entire Study Area, Entire Study Period

Lag	Temp	Prcp	SPI	SPEI
1	(+)	(-)	(-)	(-)
2	(+)	(-)	(-)	(-)
3	(+)	(-)	(-)	(-)
4	(+)	(-)	(-)	(-)
5	(+)	(-)	(-)	(-)
6	(+)	(-)		(-)
7	(+)	(-)		(-)
8	(+)	(-)		
9	(+)	(-)	(-)	
10	(+)	(-)		
11	(+)	(-)		
12	(+)	(-)		
13	(+)	(-)		
14	(+)	(-)		
15	(+)	(-)		(-)
16	(+)	(-)		
17	(+)	(-)		
18	(+)	(-)		
19	(+)	(-)		(-)
20	(+)	(-)		
21	(+)	(-)	(-)	(-)
22	(+)	(-)		
23	(+)	(-)	(-)	(-)
24	(+)	(-)		(-)

TABLE 3. Bivariate Negative Binomial Regression; by State, Entire Study Period

	Arizona				California			
Lag	Temp	Prcp	SPI	SPEI	Temp	Prcp	SPI	SPEI
1		(-)	(-)	(-)	(-)	(-)		
2		(-)	(-)			(-)		
3	(+)	(-)	(-)	(-)		(-)		
4	(+)					(-)	(+)	
5						(-)	(+)	
6		(-)				(-)		
7		(-)			(-)		(+)	(+)
8		(-)			(-)		(+)	(+)
9					(-)	(+)		
10					(-)	(+)	(+)	(+)
11				(+)	(-)	(+)	(+)	(+)
12				(+)	(-)		(+)	(+)
13					(-)		(+)	
14							(+)	(+)
15	(+)					(-)	(+)	
16				(+)	(-)	(-)	(+)	
17						(-)	(+)	
18						(-)		
19					(-)			
20					(-)			
21					(-)			
22					(-)			
23					(-)			
24					(-)			

TABLE 4. Bivariate Negative Binomial Regression; by Climate Division, Entire Study Period

	Central Coast				Sacramento				San Joaquin				South Coast				Southeast Desert				South Central				Southeast			
Lag	**Temp**	**Prcp**	**SPI**	**SPEI**	**Temp**	**Prcp**	**SPI**	**SPEI**	**Temp**	**Prcp**	**SPI**	**SPEI**	**Temp**	**Prcp**	**SPI**	**SPEI**	**Temp**	**Prcp**	**SPI**	**SPEI**	**Temp**	**Prcp**	**SPI**	**SPEI**	**Temp**	**Prcp**	**SPI**	**SPEI**
1	(-)																							(-)				
2									(+)	(-)				(-)					(+)			(-)						
3		(-)							(+)	(-)							(+)	(-)							(+)			
4	(+)		(+)						(+)	(-)	(+)						(+)	(-)							(+)			
5	(+)		(+)						(+)	(-)							(+)	(-)							(+)			
6	(+)	(-)																(-)										(+)
7			(+)	(+)								(+)		(-)								(-)						
8			(+)	(+)					(-)	(+)		(+)					(-)		(+)	(+)								
9									(-)	(+)							(-)								(-)			
10	(-)	(+)	(+)	(+)					(-)	(+)		(+)					(-)	(+)	(+)	(+)					(-)	(+)		(+)
11	(-)	(+)		(+)					(-)	(+)		(+)					(-)	(+)						(+)	(-)	(+)		
12	(-)	(+)	(+)	(+)				(+)	(-)	(+)	(+)	(+)					(-)	(+)	(+)	(+)					(-)	(+)	(+)	(+)
13	(-)	(+)	(+)	(+)																								
14				(+)			(+)	(+)	(+)		(+)	(+)																
15								(+)	(+)	(-)							(+)								(+)			
16	(+)						(+)	(+)	(+)	(-)	(+)						(+)								(+)			
17	(+)	(-)							(+)								(+)								(+)			
18	(+)							(+)																				
19	(+)																											
20									(-)	(+)							(-)											
21								(+)	(-)	(+)							(-)											
22	(-)	(+)							(-)	(+)							(-)	(+)							(-)	(+)		
23	(-)	(+)							(-)								(-)								(-)			
24	(-)	(+)		(+)													(-)	(+)		(+)					(-)			

TABLE 5. Bivariate Negative Binomial Regression; Entire Study Area, by Month

	January				February				March				April				May				June			
Lag	Temp	Prcp	SPI	SPEI	Temp	Prcp	SPI	SPEI	Temp	Prcp	SPI	SPEI	Temp	Prcp	SPI	SPEI	Temp	Prcp	SPI	SPEI	Temp	Prcp	SPI	SPEI
1	(+)	(-)			(+)	(-)			(+)	(-)	(-)		(+)	(-)			(+)	(-)		(-)	(+)	(-)		
2	(+)	(-)		(-)	(+)	(-)			(+)	(-)			(+)	(-)	(-)		(+)	(-)			(+)	(-)		(-)
3	(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)		
4	(+)	(+)			(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)	(-)	
5	(+)	(+)	(-)		(+)	(+)			(+)	(-)	(-)	(-)	(+)	(-)			(+)	(-)			(+)	(-)		
6	(+)	(+)			(+)	(+)	(-)		(+)	(+)			(+)	(-)		(-)	(+)	(-)		(-)	(+)	(-)		
7	(+)				(+)	(+)			(+)	(+)	(-)		(+)	(+)			(+)	(-)	(-)	(-)	(+)	(-)		
8	(+)	(-)			(+)				(+)	(+)			(+)	(+)			(+)	(+)			(+)	(-)	(-)	(-)
9	(+)	(-)		(-)	(+)	(-)			(+)				(+)	(+)			(+)	(+)	(-)		(+)	(+)		
10	(+)	(-)			(+)	(-)			(+)	(-)			(+)		(-)		(+)	(+)			(+)	(+)		
11	(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)			(+)		(-)		(+)	(+)		
12	(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)			(+)			
13	(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)		
14	(+)	(-)		(-)	(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)		
15	(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)		
16	(+)	(+)	(-)		(+)				(+)	(-)		(-)	(+)	(-)			(+)	(-)			(+)	(-)		
17	(+)	(+)			(+)	(+)			(+)				(+)	(-)		(-)	(+)	(-)			(+)	(-)		
18	(+)	(+)			(+)	(+)	(-)		(+)	(+)	(-)		(+)				(+)	(-)			(+)	(-)		
19	(+)				(+)	(+)			(+)	(+)	(-)		(+)	(+)	(-)		(+)				(+)	(-)		
20	(+)	(-)			(+)				(+)	(+)			(+)	(+)	(-)		(+)	(+)	(-)		(+)			
21	(+)	(-)			(+)	(-)			(+)				(+)	(+)	(-)		(+)	(+)			(+)	(+)		
22	(+)	(-)			(+)	(-)			(+)	(-)			(+)		(-)		(+)	(+)			(+)	(+)	(-)	
23	(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)			(+)				(+)	(+)		
24	(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)			(+)			

	July				August				September				October				November				December			
Lag	Temp	Prcp	SPI	SPEI	Temp	Prcp	SPI	SPEI	Temp	Prcp	SPI	SPEI	Temp	Prcp	SPI	SPEI	Temp	Prcp	SPI	SPEI	Temp	Prcp	SPI	SPEI
1	(+)				(+)	(+)			(+)	(+)	(-)		(+)	(+)			(+)	(-)	(-)	(-)	(+)	(-)		(-)
2	(+)	(-)			(+)				(+)	(+)			(+)	(+)	(-)		(+)	(+)			(+)	(-)		
3	(+)	(-)			(+)	(-)			(+)				(+)	(+)			(+)	(+)			(+)	(+)		
4	(+)	(-)			(+)	(-)			(+)	(-)			(+)				(+)	(+)			(+)	(+)		
5	(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)			(+)				(+)	(+)		
6	(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)			(+)			
7	(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)			(+)			
8	(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)		
9	(+)	(-)	(-)		(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)		
10	(+)	(+)			(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)		
11	(+)	(+)			(+)	(+)			(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)		
12	(+)	(+)			(+)	(+)			(+)	(+)			(+)	(-)			(+)	(-)			(+)	(-)		
13	(+)				(+)	(+)			(+)	(+)			(+)	(+)			(+)	(-)			(+)	(-)		
14	(+)	(-)			(+)				(+)	(+)			(+)	(+)			(+)	(+)			(+)			
15	(+)	(-)			(+)	(-)			(+)				(+)	(+)			(+)	(+)			(+)	(+)		
16	(+)	(-)			(+)	(-)			(+)	(-)			(+)				(+)	(+)			(+)	(+)		
17	(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)	(+)		(+)				(+)	(+)		
18	(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)			(+)			
19	(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)		(-)	(+)	(-)		
20	(+)	(-)		(-)	(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)		(-)
21	(+)				(+)	(-)		(-)	(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)		
22	(+)	(+)	(-)		(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)			(+)	(-)		
23	(+)	(+)	(-)		(+)	(+)			(+)				(+)	(-)		(-)	(+)	(-)			(+)	(-)		
24	(+)	(+)			(+)	(+)	(-)		(+)	(+)	(-)		(+)	(-)	(-)		(+)	(-)		(-)	(+)	(-)		

TABLE 6. Multivariate Negative Binomial Regression; Entire Study Area, Entire Study Period

		Model		
Model Parameter		1	2	3
Temperature	Proximal	(+)*	(+)*	(+)*
	Seasonal	(+)*	(+)*	(+)*
Precipitation	Proximal	(-)*		
	Seasonal	(-)*		
SPI	Proximal		(-)	
	Seasonal		(-)*	
SPEI	Proximal			(-)
	Seasonal			(-)

1: ln(count) = β_0 + β_1(Proximal Temperature) + β_2(Seasonal Temperature) + β_3(Proximal Precipitation) + β_4(Seasonal Precipitation) + ln(population)

2: ln(count) = β_0 + β_1(Proximal Temperature) + β_2(Seasonal Temperature) + β_3(Proximal SPI) + β_4(Seasonal SPI) + ln(population)

3: ln(count) = β_0 + β_1(Proximal Temperature) + β_2(Seasonal Temperature) + β_3(Proximal SPEI) + β_4(Seasonal SPEI) + ln(population)

***Significant at α=0.05**

TABLE 7. Multivariate Negative Binomial Regression; by State, Entire Study Period

		Model					
		Arizona			California		
Model Parameter		1	2	3	1	2	3
Temperature	Proximal	(-)	(+)	(+)	(-)*	(-)*	(-)*
	Seasonal	(+)*	(+)*	(+)	(-)*	(-)	(-)
Precipitation	Proximal	(-)*			(-)*		
	Seasonal	(-)*			(-)*		
SPI	Proximal		(-)*			(-)	
	Seasonal		(-)*			(+)*	
SPEI	Proximal			(-)*			(-)
	Seasonal			(-)*			(+)*

1: ln(count) = β_0 + β_1(Proximal Temperature) + β_2(Seasonal Temperature) + β_3(Proximal Precipitation) + β_4(Seasonal Precipitation) + ln(population)

2: ln(count) = β_0 + β_1(Proximal Temperature) + β_2(Seasonal Temperature) + β_3(Proximal SPI) + β_4(Seasonal SPI) + ln(population)

3: ln(count) = β_0 + β_1(Proximal Temperature) + β_2(Seasonal Temperature) + β_3(Proximal SPEI) + β_4(Seasonal SPEI) + ln(population)

***Significant at α=0.05**

TABLE 8. Multivariate Negative Binomial Regression; by Climate Division, Entire Study Period

		Model																				
		Central Coast			Sacramento			San Joaquin			South Coast			Southeast Desert			South Central			Southeast		
Model Parameter		1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
Temperature	Proximal	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(+)*	(+)	(-)	(+)	(+)	(+)	(+)	(+)	(-)	(+)	(-)	(+)	(+)	(+)
	Seasonal	(+)	(+)*	(+)*	(-)	(-)	(-)	(+)*	(+)*	(+)*	(+)*	(+)*	(+)*	(+)*	(+)*	(+)*	(+)	(+)	(+)	(+)*	(+)	(+)
Precipitation	Proximal	(-)			(-)			(-)			(-)			(-)			(-)*			(-)*		
	Seasonal	(+)			(-)			(-)			(-)			(+)			(-)*			(-)*		
SPI	Proximal		(+)			(-)			(-)			(-)			(-)			(-)*			(-)	
	Seasonal		(+)			(-)			(+)			(+)			(+)			(-)*			(-)	
SPEI	Proximal			(-)			(+)			(-)			(-)			(-)			(-)*			(-)
	Seasonal			(+)*			(+)*			(+)*			(+)			(+)*			(-)			(-)

1: $\ln(\text{count}) = \beta_0 + \beta_1(\text{Proximal Temperature}) + \beta_2(\text{Seasonal Temperature}) + \beta_3(\text{Proximal Precipitation}) + \beta_4(\text{Seasonal Precipitation}) + \ln(\text{population})$

2: $\ln(\text{count}) = \beta_0 + \beta_1(\text{Proximal Temperature}) + \beta_2(\text{Seasonal Temperature}) + \beta_3(\text{Proximal SPI}) + \beta_4(\text{Seasonal SPI}) + \ln(\text{population})$

3: $\ln(\text{count}) = \beta_0 + \beta_1(\text{Proximal Temperature}) + \beta_2(\text{Seasonal Temperature}) + \beta_3(\text{Proximal SPEI}) + \beta_4(\text{Seasonal SPEI}) + \ln(\text{population})$

***Significant at α=0.05**

Appendix I. *Converting NetCDF files*

1. Import NetCDF files to ArcGIS by selecting the *Make NetCDF Feature Layer* tool from the Multidimension Toolset in ArcToolbox. Though *Make NetCDF Raster Layer* is the more commonly used tool, the climate data pulled from the National Climatic Data Center has variable spacing between coordinate values, yielding errors in this method.

    Note: If processing multiple dimensions at once (months, years, etc.) batch processing the import step may save time. To batch process, right click on the *Make NetCDF Feature Layer* tool and select *Batch…*
2. Enter field values as prompted by the *Make NetCDF Feature Layer* window as prompted. Though *Row Dimensions* is presented as an optional field, fill with latitude and longitude variables; this will prevent error. Additionally, fill the *Dimension Values* field with the desired dimension (months, years, etc.).
3. Run the tool once fields have been appropriately filled.
4. Import a shapefile of desired health boundaries (counties, states, etc.).
5. Spatially join each imported NetCDF dimension to the health boundary shapefile by right clicking the shapefile and selecting *Join* from *Joins and Relates*.
6. Elect to "Join data from another layer based on spatial location." Select the desired NetCDF feature layer as the layer to join. Select appropriate summary statistics.
7. Run the tool once fields have been appropriately filled.
8. Export output shapefiles to SAS to be sorted, concatenated, and merged with health dataset.

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