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BRIEF REPORT

Sex Differences in Susceptibility to Coccidioidomycosis

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To assess sex-specific differences in coccidioidomycosis, a retrospective analysis of human patients, nonhuman primates, and veterinary patients (including the neutered status of the animal) was performed. We found higher rates of infection and severity in males. This observed increased infection risk suggests deeper biological underpinnings than solely occupational/exposure risks.

Keywords. coccidioidomycosis; veterinary; sex; gender; neutered; risk factor.

Coccidioidomycosis, caused by *Coccidioides immitis* and *C. posadasii*, is transmitted by aerosolization of soil-dwelling arthroconidia (eg spores) inhaled following soil disruption. Primary infection often manifests as an acute respiratory illness, although the spectrum of disease ranges from asymptomatic exposure to severe and life-threatening disseminated disease [1].

The populations at greatest risk include those with heavy exposure to airborne soil [2], although residence in or travel to an endemic region may cause infection. Severe and/or disseminated infections are more common in those with underlying immunosuppression, cardiopulmonary disease, or in certain ethnicities [3]. Male sex has also been proposed as a risk factor both for the acquisition of coccidioidomycosis and as a risk factor for severe disease [4, 5]. Prior reports have proposed male sex as a potential risk factor; however, some have argued that human males are disproportionately represented in construction-related tasks, farm work, and other occupations with extensive soil exposure [6, 7]. Similarly, behavioral differences between sexes in nonhuman primates and canines (eg, digging behavior) have been postulated to convey additional risk in males.

We performed the largest survey to date, using existing databases of human patients, nonhuman primates, and veterinary patients to ascertain if a difference in male:female sex is seen in the acquisition of coccidioidomycosis.

METHODS

Patient Consent

This study was approved by the Institutional Review Board of the University of California – Davis with a waiver of patient consent given the retrospective nature of the study.

Data Collection and Analysis

Laboratory records from human coccidioidomycosis patients at the UC-Davis Coccidioidomycosis Serology Laboratory were reviewed for a new diagnosis of coccidioidomycosis (2009–2020), defined as the first positive result for a unique patient. Patient age, sex, and titer data were abstracted from the Orchard Harvest Laboratory Information System (Carmel, IN, USA) using laboratory reports.

To calculate incidence by sex and age at diagnosis, serologic data were first binned by unique patient/date (of sample blood draw)/age/gender for each uninfected and infected patient. Relative risk ratios were calculated by comparing ratios of infected:uninfected at each age for both males and females. The mean maximum titer by age and gender was calculated among infected patients by identifying the maximum $\log_2$-transformed titer for each infected patient in either serum or, when applicable, cerebrospinal fluid (CSF) and then calculating the mean maximum titer by each age and gender. To calculate the incidence of coccidioidal meningitis by age and gender, data were additionally binned by the age of initial CSF serology, with only positive results included.

To assess whether environmental differences might impact infection risk, data from outdoor nonhuman primate colonies were also accessed. This primate colony (Born Free USA Primate Sanctuary) includes numerous primate species on a 175-acre sanctuary. Populations tested were selected to exclude primates included in experimental/investigational studies. Cases were reviewed for the diagnosis of coccidioidomycosis, and primate sex was abstracted.

Additional assessment was performed using medical records from the UC-Davis Veterinary Hospital/Clinics. Electronic medical records (Veterinary Medical & Administrative Computer System [VMACS]) was queried for all dogs with

Received 26 July 2021; editorial decision 20 October 2021; accepted 22 October 2021; published online 16 February 2022.

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Open Forum Infectious Diseases®2022

https://doi.org/10.1093/ofid/ofab543

coccidioidomycosis serology performed, and these cases were reviewed for new coccidioidomycosis cases between 2000 and 2020. Sex and castration/spayed status were recorded for each patient.

The literature was also reviewed to determine the male:female ratio noted in past studies. Studies performed within veterans' hospitals or military bases were excluded given the male:female differences in these populations.

P values were calculated using the Fisher exact test or Student *t* test and, where appropriate, adjusted for multiple comparison using Bonferroni correction. All analyses were performed in R, version 3.6.1, using custom scripts (R Core Team).

RESULTS

We found 220 240 distinct human patients with coccidioidomycosis diagnostic data over the reviewed time period. In the cohort, 21 435/123 743 male patients (17.3%) and 9950/96 497 female patients (10.3%) were diagnosed with coccidioidomycosis (Supplementary Table 1). The proportion of infected males was significantly higher than for females (odds ratio [OR], 1.8; $P < 2.2^{*}10^{-16}$). Demographic information is available in Supplementary Table 1. The incidence of coccidioidomycosis by age and gender is shown in Figure 1A. While the incidence for females began to drop proportionally compared with males at around age 12–15, differences only became significant following Bonferroni correction at age 19 ($P = .02$). The odds ratio for infection among males relative to females maximized at age 35, with an odds ratio of 2.9 ($P = 2.9^{*}10^{-18}$), and continued throughout adulthood (Figure 1B). However, after age 80 the increased odds ratio for males became nonsignificant.

The average maximum serum complement fixation titers were found to be significantly (Student *t* test $P = 5.6^{*}10^{-59}$) higher among human males (1:3.3) than females (1:2.5). When comparing by age, significant differences between males and females were observed in few age brackets following Bonferroni adjustment due to higher titer variability (Figure 1C). The rate of coccidioidal meningitis was found to be significantly (OR, 1.35; $P = 5^{*}10^{-4}$) higher among infected males (2.4%) than infected females (1.8%). Similarly, the average maximum CSF complement fixation titer was higher ($P = .03$) in males (1:24.5) with coccidioidal meningitis compared with females (1:17.5).

In the evaluation of primate colony and canine data, at least 1 serum specimen was received for 57 nonhuman primates (male 40, female 17). Twenty-two males had been diagnosed with coccidioidomycosis (55%), while only 1 female had been diagnosed (5.9%; OR, 18.7; $P = .00042$). Similarly, data from the UC-Davis Veterinary Clinic included a total dog population of 163 351 (82 961 male, 80 390 female). A disproportionate number of male dogs were newly infected compared with females (99 vs 60; OR, 1.6; $P = .0041$). These results remained significant when comparing unaltered (noncastrated) males with unaltered (nonspayed) females (OR, 1.98; $P = .046$) and unaltered males with all females (OR, 2.2; $P = .00052$) (data not shown). Castration was protective when comparing castrated males with uncastrated males (OR, 1.56; $P = .043$) and led to a similar risk to that of females (castrated males vs all females: OR, 1.41; $P = .06$). Spaying of females did not have an effect on risk (OR, 1.14; $P = .617$).

DISCUSSION

The male sex has been recognized to have a significantly increased risk for coccidioidomycosis, and the estimated increased relative risk of infection has ranged from 1.1 to 5.6 in prior studies (Table 1) [8–10]. Some studies have conversely reported an increased relative risk for infection in females, although these were either geographically limited or did not capture all cases with coccidioidomycosis. For example, a manuscript by Smith et al. from 1940 revealed a M:F ratio of 0.44 [11]; however, this study only focused on patients presenting with erythema nodosum, which occurs more commonly in female patients [12].

Severity of disease has also been correlated with male sex. Among 128 cases of coccidioidomycosis that occurred in 1991, male sex was associated with a higher rate of hospitalization for severe disease [4]. Disseminated disease is also more frequent in male patients (3.5–5-fold increase) [8, 9]. In a longitudinal study conducted in the 1940s among military personnel, the frequency of dissemination in women was noted to be one-fifth of the rate found in men [13]. Others have subsequently noted this association with males disproportionally represented among cases of disseminated coccidioidomycosis [14, 15]. In our study, more males (human patients) were tested for coccidioidomycosis than females. This difference in testing practice may have potentially introduced bias to the study results.

Sex differences in outdoor activity and employment have been postulated to underly coccidioidomycosis risk differences, though no study to our knowledge has quantified exposure differences in an attempt to explain observed variance. The difference in sex as an independent risk factor for coccidioidomycosis is furthered by the nonhuman primate and veterinary data we present and is additionally correlated with the neutered status of the veterinary patients. Nonhuman primate behavior such as digging might explain increase in exposure to soil-dwelling pathogens, although differences in this behavior have not been noted in nonhuman primates. And similarly, activities are not likely to differ between male and female dogs [16]. Therefore, the overrepresentation of males, castrated and intact, is not likely to be explained by behavioral or environmental differences.

The findings of the current study expand our understanding of gender differences in coccidioidomycosis incidence/severity and hint at deeper biological underpinnings of risk. For example,

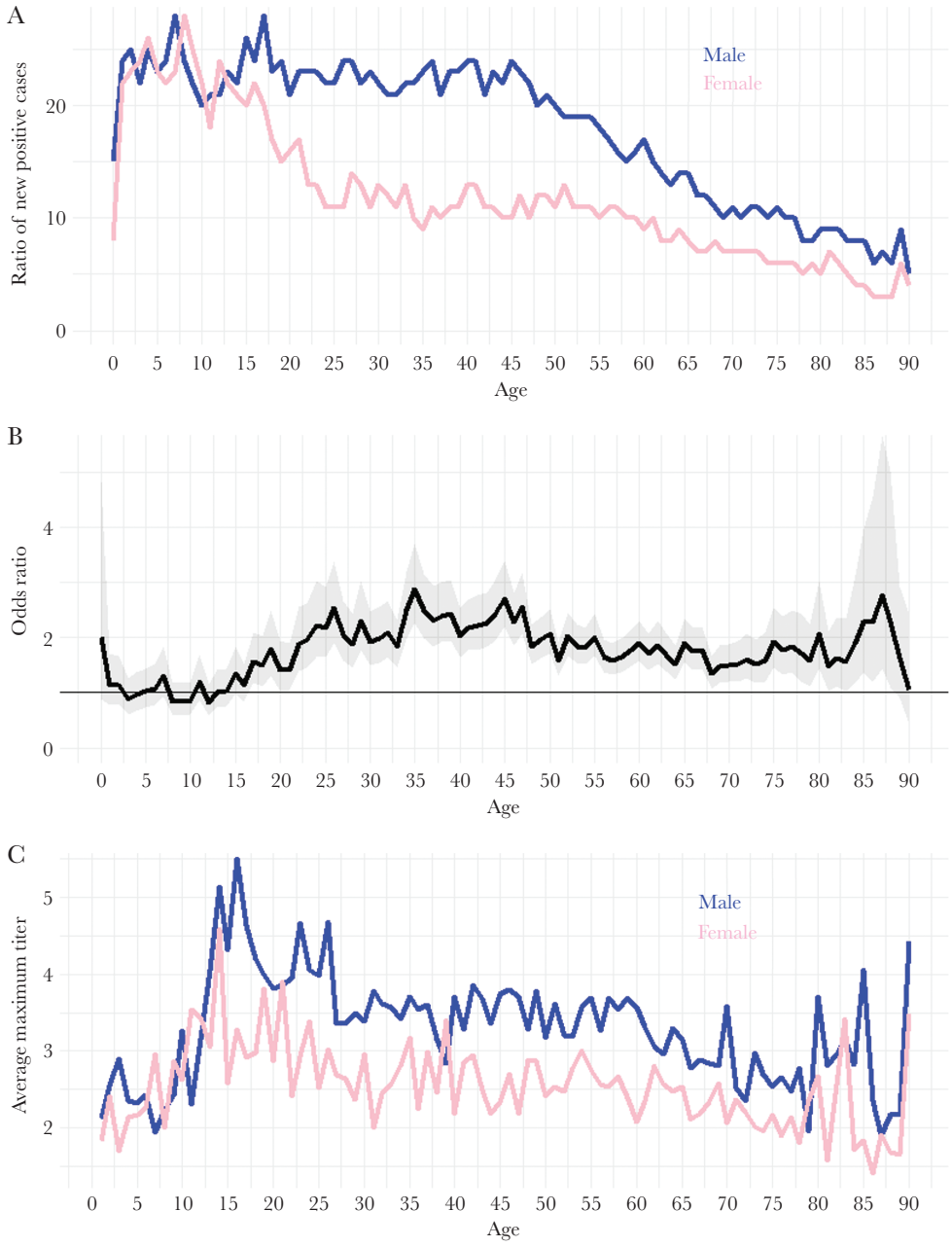

Figure 1. A, Human observations: incidence of coccidioidomycosis by age and gender. B, Odds ratios for coccidioidomycosis acquisition in human males compared with females. C, coccidioidal complement fixation titers by gender (human). Disease incidence and average maximum titers are similar across genders until early adulthood. A, Incidence of disease between age 0 and age 90. B, Odds ratios for infection among males. Numbers >1 indicate increased risk of males relative to females. Shaded areas represent 95% confidence CIs. C, Maximum serum complement fixation titers plotted by age of disease onset for males and females.

if gender disparity of disease risk were fully explained by differences in exposure, then no significant differences would be expected for maximum serum titers, meningitis risk, or maximum CSF titer, as observed here. The impact of repeated exposure (which theoretically may be more common in men) on coccidioidomycosis severity or serology results is currently unknown. Instead, the gender ratio observed in the present study is similar to that of *Paracoccidioides*, a pathogenic dimorphic fungus found primarily in South America and a close phylogenetic relative of *Coccidioides* with a similar though more pronounced predilection for causing disease in males compared with females [17–19]. Evaluation of *Paracoccidioides* isolates has found that estrogen inhibits the transition of *Paracoccidioides mycelium* to the yeast form; the authors of this study hypothesized that these in vitro findings would explain the reduced frequency of disease in adult women [20]. Mouse models have confirmed these in vitro findings, with fewer foci of *Paracoccidioides* infection in female mice compared with their male counterparts and castrated male mice exhibiting fewer colony-forming units than mice in control groups [17].

Table 1. Distribution of Coccidioidomycosis by Patient Sex in Past Reports

Author	Location; Year of Report	Total No. of Patients		Ratio of Males to Females
Reference		Males	Females	
CDPH [21]	CA Dept of Public Health; 1936	326	58	5.62[a]
Durry [4]	Tulare County, CA; 1991	74	54	1.37
CDC [22]	ADHS; 1990–1995	1731	1031	1.68
Leake[23]	Arizona; 1996–1997	66	23	2.87
Rosenstein [24]	Kern County, CA; 1996	507	398	1.27
Tsang [25]	ADHS; 2007–2008	3003	2661	1.13
Sondemeyer [7]	CA Dept of Public Health; 2000–2011	10 876	4870	2.23
Benedict [11]	CDC, 2011–2017	49 823	45 059	1.11

Abbreviations: ADHS, Arizona Department of Health Services; CDPH, California Department of Public Health.

[a]This report may have included a disproportionate number of males due to military involvement.

The effects of sex hormones on *Coccidioides* are less well defined [19]. Although 17β-estradiol, progesterone, and testosterone are highly stimulatory for the growth of *Coccidioides* in vitro, the most striking effects of estrogen occur only at concentrations present during advanced pregnancy. Theses differences in sex hormone concentrations and their effects on *Coccidioides* growth in vivo have yet to be fully examined.

We observed no differences in coccidioidomycosis incidence in humans until the age of 19. After this age, disease incidence for males does not appear to increase. Instead, incidence for females appears to decrease, findings consistent with the protective effects of estrogen as noted in paracoccidioidomycosis [17]. These effects may be amplified by differences in occupational exposure; however, it is difficult to explain a decrease in the risk to women if work-related factors are the sole factor responsible. This confounder led us to focus on nonhuman primate colonies and veterinary animals in order to further strengthen our hypothesis of sex as an independent risk factor.

In summary, we observed an increase in rates of coccidioidomycosis in all male mammalian species examined. Future studies focused on host hormonal differences and their direct effects on *Coccidioides* growth, the potential for blockade of these targets, and the specific immunologic effects should be performed.

Acknowledgments

Financial support. This work was supported by existing departmental funding and the Burden Family Gift Fund for Coccidioidomycosis Research.

Potential conflicts of interest. All authors: no conflicts of interest to declare. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Nguyen C, Barker BM, Hoover S, et al. Recent advances in our understanding of the environmental, epidemiological, immunological, and clinical dimensions of coccidioidomycosis. Clin Microbiol Rev **2013**; 26:505–25.
2. Brown J, Benedict K, Park BJ, Thompson GR 3rd. Coccidioidomycosis: epidemiology. Clin Epidemiol **2013**; 5:185–97.
3. Galgiani JN, Ampel NM, Blair JE, et al. 2016 Infectious Diseases Society of America (IDSA) clinical practice guideline for the treatment of coccidioidomycosis. Clin Infect Dis **2016**; 63:e112–46.
4. Durry E, Pappagianis D, Werner SB, et al. Coccidioidomycosis in Tulare County, California, 1991: reemergence of an endemic disease. J Med Vet Mycol **1997**; 35:321–6.
5. Einstein HE, Johnson RH. Coccidioidomycosis: new aspects of epidemiology and therapy. Clin Infect Dis **1993**; 16:349–54.
6. Diaz JH. Travel-related risk factors for coccidioidomycosis. J Travel Med **2018**; 25:1–8.
7. Sondermeyer G, Lee L, Gilliss D, Tabnak F, Vugia D. Coccidioidomycosis-associated hospitalizations, California, USA, 2000-2011. Emerg Infect Dis **2013**; 19:1590–7.
8. Cox RA, Magee DM. Coccidioidomycosis: host response and vaccine development. Clin Microbiol Rev **2004**; 17:804–39, table of contents.
9. Drutz DJ, Catanzaro A. Coccidioidomycosis. Part II. Am Rev Respir Dis **1978**; 117:727–71.
10. Benedict K, McCotter OZ, Brady S, et al. Surveillance for coccidioidomycosis - United States, 2011-2017. MMWR Surveill Summ **2019**; 68:1–15.
11. Smith CE. Epidemiology of acute coccidioidomycosis with *Erythema nodosum* ("San Joaquin" or "Valley Fever"). Am J Public Health Nations Health **1940**; 30:600–11.
12. Chowaniec M, Starba A, Wiland P. *Erythema nodosum* - review of the literature. Reumatologia **2016**; 54:79–82.
13. Smith CE, Beard RR. Varieties of coccidioidal infection in relation to the epidemiology and control of the diseases. Am J Public Health Nations Health **1946**; 36:1394–402.
14. Arsura EL, Kilgore WB, Caldwell JW, et al. Association between facial cutaneous coccidioidomycosis and meningitis. West J Med **1998**; 169:13–6.
15. Wheat LJ, Wass J, Norton J, et al. Cavitary histoplasmosis occurring during two large urban outbreaks. Analysis of clinical, epidemiologic, roentgenographic, and laboratory features. Medicine (Baltimore) **1984**; 63:201–9.
16. Grayzel SE, Martinez-Lopez B, Sykes JE. Risk factors and spatial distribution of canine coccidioidomycosis in California, 2005-2013. Transbound Emerg Dis **2017**; 64:1110–9.
17. Shankar J, Restrepo A, Clemons KV, Stevens DA. Hormones and the resistance of women to paracoccidioidomycosis. Clin Microbiol Rev **2011**; 24:296–313.
18. Sharpton TJ, Stajich JE, Rounsley SD, et al. Comparative genomic analyses of the human fungal pathogens *Coccidioides* and their relatives. Genome Res **2009**; 19:1722–31.
19. Drutz DJ, Huppert M, Sun SH, McGuire WL. Human sex hormones stimulate the growth and maturation of *Coccidioides immitis*. Infect Immun **1981**; 32:897–907.
20. Restrepo A, Salazar ME, Cano LE, et al. Estrogens inhibit mycelium-to-yeast transformation in the fungus *Paracoccidioides brasiliensis*: implications for resistance of females to paracoccidioidomycosis. Infect Immun **1984**; 46:346–53.
21. Public Health Reports by the United States Public Health Service: Containing Information on the current Prevalence of Disease, the Prevention and Control of Disease, and Related Subjects. **1937**.
22. Centers for Disease Control and Prevention. Coccidioidomycosis—Arizona, 1990-1995. MMWR Morb Mortal Wkly Rep **1996**; 45:1069–73.
23. Leake JA, Mosley DG, England B, et al. Risk factors for acute symptomatic coccidioidomycosis among elderly persons in Arizona, 1996-1997. J Infect Dis **2000**; 181:1435–40.
24. Rosenstein NE, Emery KW, Werner SB, et al. Risk factors for severe pulmonary and disseminated coccidioidomycosis: Kern County, California, 1995-1996. Clin Infect Dis **2001**; 32:708–15.
25. Tsang CA, Anderson SM, Imholte SB, et al. Enhanced surveillance of coccidioidomycosis, Arizona, USA, 2007-2008. Emerg Infect Dis **2010**; 16:1738–44.