REVIEW ARTICLE

mycoses
Diagnosis, Therapy and Prophylaxis of Fungal Diseases

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Let's talk about sex characteristics—As a risk factor for invasive fungal diseases

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Abstract

Biological sex, which comprises differences in host sex hormone homeostasis and immune responses, can have a substantial impact on the epidemiology of infectious diseases. Comprehensive data on sex distributions in invasive fungal diseases (IFDs) are lacking. In this review, we performed a literature search of in vitro/animal studies, clinical studies, systematic reviews and meta-analyses of invasive fungal infections. Females represented 51.2% of invasive candidiasis cases, mostly matching the proportions of females among the general population in the United States and Europe (>51%). In contrast, other IFDs were overrepresented in males, including invasive aspergillosis (51% males), mucormycosis (60%), cryptococcosis (74%), coccidioidomycosis (70%), histoplasmosis (61%) and blastomycosis (66%). Behavioural variations, as well as differences related to biological sex, may only in part explain these findings. Further investigations concerning the association between biological sex/gender and the pathogenesis of IFDs are warranted.

KEYWORDS
animal model, immunity, invasive fungal diseases, sex characteristics

1 | INTRODUCTION

Differences in sex have a determining influence on the prevalence and incidence of many infectious diseases, including infections caused by bacteria, viruses, parasites and fungi.[1-4] Sex-dependent host immune responses, hormone homeostasis and varying behavioural characteristics lead to distinct susceptibility and epidemiology of infectious diseases. Due to increased concern that the generalizability and reproducibility of research findings in animal models does not adequately address the standardisation of experimental set-ups, in 2017 the National Institutes of Health (NIH) announced policies that require applicants to report plans for balancing male/female ratios in animals in order to be considered for funding.[5]

In addition, sex distribution in the general population is often not considered when interpreting results on sex differences. Sex demographics for Europe in 2020 show percentages of 51.14% females/48.86% males, while in the United States 50.52% females/49.48% males for 2020, and global estimates report 49.58% females/50.42% males in 2021.[6-8] While a male predominance, in terms of the prevalence/incidence and severity, has been hypothesised for infections caused by *Aspergillus fumigatus* and *Cryptococcus neoformans*,[1] detailed analyses are lacking that more comprehensively investigate sex differences in fungal diseases, including in animal model studies. Here, we review the literature on sex differences in fungal diseases caused by moulds, yeast and selected endemic mycoses.

2 | METHODS

2.1 | Search strategy

A literature search in the PubMed database on in vitro/animal studies, clinical studies, meta-analyses and systematic reviews was performed between December 2021 and February 2022. Details on the search strategy and the MeSH terms utilised are depicted in the online supplement.

2.2 | Eligibility criteria and study selection

For in vitro/animal studies, observational studies published in English language were considered for analysis. Studies reporting on distinct sex differences in severity, susceptibility, exposure or sex hormone homeostasis were of particular interest. In adequate studies, the reference list was searched for additional studies.

For clinical studies, observational studies published in English were considered for inclusion. Clinical trials were specifically excluded as they reflect the demographics of which study participants consented for trial participation, not the underlying demographics of infection. Particular emphasis was placed on the largest epidemiological studies in terms of patient numbers so a minimum limit of ≥50 cases per study was set for inclusion. In adequate studies, the reference list was searched for additional studies. Overall sample size and sex distribution were calculated for included studies.

Between January 2022 and February 2022, a systematic PubMed literature search of meta-analyses and systematic reviews was performed on the pathogens of interest. Details of the search strategy are provided in the online supplement. All search results were considered for inclusion if overall sex distribution on the respective pathogen was reported. Relevant publications were manually selected. To avoid overlap, meta-analyses/systematic reviews were excluded if they were investigating the same disease entity, patient population, pathogen or geographical area. Flow diagrams displaying the selection process are provided for each fungus.

Information extracted from each clinical study, systematic review and meta-analysis is outlined in the online supplement.

3 | RESULTS

3.1 | Sex differences in immunity to fungal infection

Multiple studies have reported that, in general, females mount stronger immune responses than males (Figure 1).[9] The activity of innate immune cells, including macrophages and dendritic cells, as well as the associated inflammatory response, is enhanced in females compared with males.[10] Females also display increased CD3^{+} and CD4^{+} T-cell counts, whereas frequencies of CD8^{+} T-cells and natural killer (NK) cells are greater in males.[11] Because B cells are also more frequent in females than males,[11] basal and elicited antibody titres, particularly to viral infection and vaccination, are increased in females.[12] This results in an improved clearance of pathogens and a greater vaccine efficacy generally observed in females than males, but this instead contributes to their increased predisposition to inflammatory and autoimmune diseases.[13]

Multiple mechanisms have been described for how sex hormones influence immune function in females and males. For example, sex hormones regulate immune cell activation and function by binding to oestrogen and androgen receptors and interacting with nuclear hormone response elements (HREs)[10] and by modulating the epigenetic landscape directly.[14] Several genes coding for proteins involved in immunity, including gamma-interferon (*IFNG*) and interferon regulatory factor 5 (*IRF5*), possess HREs that, upon activation, drive the production of cytokines and chemokines.[15] IFN-γ is a pleotropic cytokine that is required for protection against a variety of fungal infections[16] and that has been proposed as a potential adjunctive immunotherapy for IFDs.[17] On the contrary, *IRF5* has been shown to relay signals from the dectin-1 receptor during fungal infection towards the production of type I interferons and protection from *C. albicans* infection.[18] Whether sex influences IFN-γ and other interferon-related signals in response to fungal infection remains, however, to be assessed.

In contrast to oestrogen, which enhances immune responses by upregulating proinflammatory cytokines such as tumour
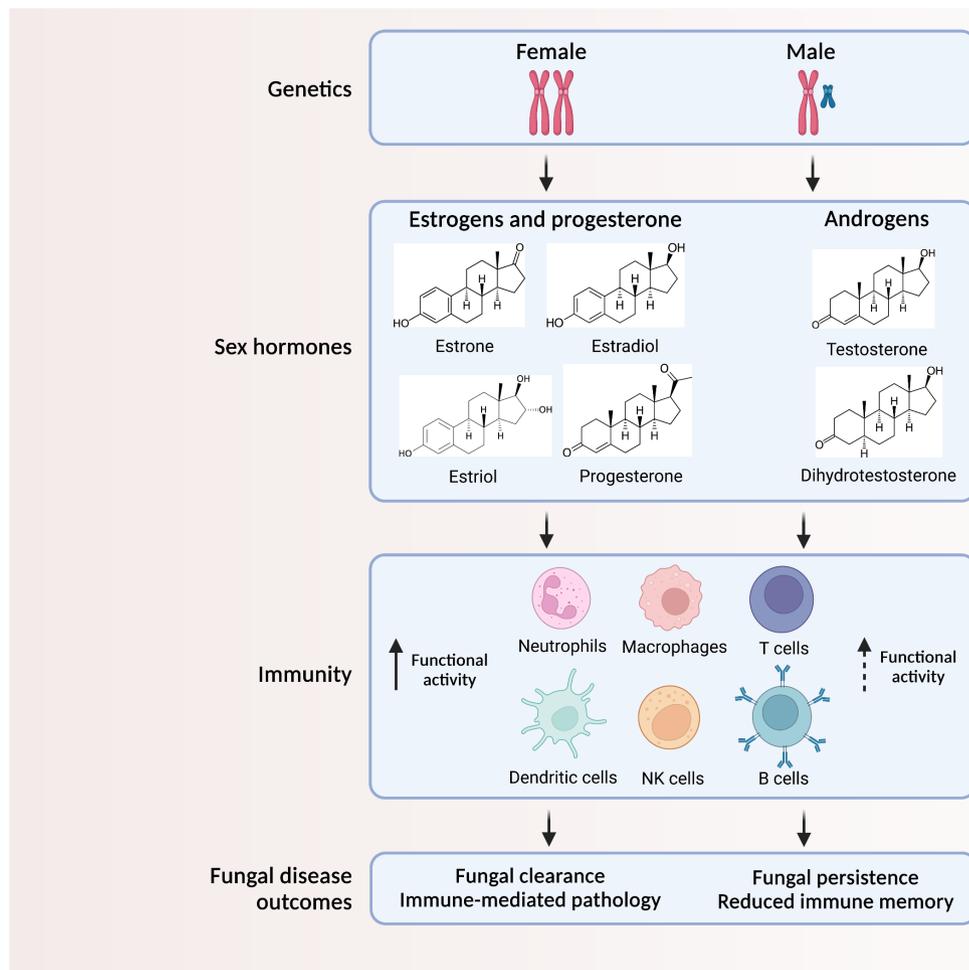
FIGURE 1 Sex differences in immunity to fungal infections

necrosis factor (TNF), androgens, in particular testosterone, are generally anti-inflammatory.[19] Testosterone has been shown to decrease NK cell, neutrophil and macrophage activity in vitro, resulting in reduced production of proinflammatory cytokines and reactive oxygen species.[20] Testosterone can also increase the production of anti-inflammatory cytokines, such as IL-10 and transforming growth factor (TGF)-β via androgen receptor signalling.[21] In fact, the genetic overexpression of IL-10 has been found to dampen the activation of protective proinflammatory responses to *Aspergillus* and increase the risk of invasive aspergillosis (IA).[22] The effects of sex hormones on immune function may, however, be cell specific. For instance, cytokine production following stimulation of monocytes with lipopolysaccharide was greater in cells from males than females, with the use of hormone-based contraceptive in females further decreasing cytokine levels, namely IFN-γ and TNF.[23]

Besides the role of hormones, a significant contribution of sex chromosome complement on immunity has also been proposed.[24] The reasons for this are multiple: (i) one X chromosome is randomly inactivated in all cells in a female, providing an advantageous mosaicism compared with the XY complement, (ii) detrimental mutations in one X chromosome with possible effects on immune function will affect half of the cells in a female, but necessarily all cells in a male, (iii) and the XX chromosome complement endows females with additional allelic diversity with likely advantages upon immune challenge.
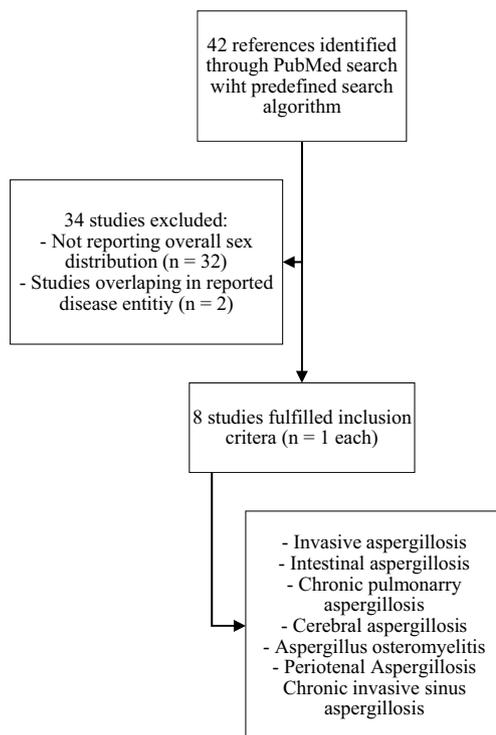
Multiple innate immune receptors, for example, Toll-like receptor (TLR)7 and TLR8, as well as IL-1 receptor-associated kinase 1 (IRAK1), a key regulatory molecule in TLR signalling, cytokine receptors, for example, IL12RG and IL13RA2, and transcription factors, for example, forkhead box P3 (FOXP3), are encoded on the X chromosome and show sex-specific induction following fungal or bacterial infection.[25] The relevance of TLRs to sex-biased immune responses is supported by the observation that the number of X chromosomes in healthy individuals and in Klinefelter's syndrome (i.e. XXY individuals) regulates cytokine production ex vivo after TLR stimulation.[26] Importantly, X-linked TLR7 has been found to participate in recognition of *Candida* spp. and subsequent production of type I interferons to modulate antifungal immune responses.[27,28] It is thus not surprising that TLR7 was reported to play an essential role in a mouse model of disseminated candidiasis.[29] Instead, TLR7 expression was found to aggravate experimental aspergillosis by dampening the antifungal effector functions of macrophages,[30] thus pointing to pathogen-specific signatures that may also be regulated by sex.

(A)

Cases N	Female	Male	Time frame	Disease entitiy
1,941	29.6%	51%	1995 - 2001	Invasive Aspergillosis
1,028	30%	70%	2000 - 2019	Aspergillus sensitization in COPD
891	37.5%	62.5%	Inception - 2021	Chronic pulmonary aspergillosis
235	42.6%	57.4%	2000 - 2020	Cerebral aspergillosis
76	29.5%	60.5%	1980 - 2009	Chronic invasive sinus aspergillosis
56	48.2%	51.8%	/	Intestinal aspergillosis
55	49%	51%	1968 - 2019	Aspergillus peritonitis
46	6.5%	93.5%	1965 - 2010	Aspergillus osteomyelits in chronic granulomatous disease

FIGURE 2 Invasive aspergillosis—sex distributions in meta-analyses and systematic reviews. Panel (A) Meta-analyses/systematic reviews on aspergillosis. Abbreviation: COPD, chronic obstructive pulmonary disease. Panel (B) Meta-analyses/systematic reviews selection process of patients with aspergillosis

(B)

3.2 | Sex differences in investigated pathogens

3.2.1 | Moulds

Aspergillosis

In total, 42 meta-analyses/systematic reviews on aspergillosis, which were conducted between 2001 and 2022, were analysed (Figure 2). Of 42 studies, 32 did not report on overall sex distributions and were excluded. Of the 10 studies remaining, eight reported on different disease entities and hence fulfilled inclusion criteria (Figure 2). Two of three studies investigating central nervous system (CNS)

aspergillosis were excluded due to overlap with the largest and most recent meta-analyses/systematic reviews that were included. In all of the included meta-analyses/systematic reviews, there was a male predominance ranging from 51% to 93.5%.[31–38]

In vitro/animal models. In vitro/animal models are fundamental in order to mimic the unavoidable and ubiquitous exposure of humans to *Aspergillus* spores. Such research furthers understanding of pathogenetic mechanisms, diagnostics and therapeutic strategies in *Aspergillus*-related diseases. To date, standardisation of animal models in *Aspergillus* studies is lacking, including variability in the
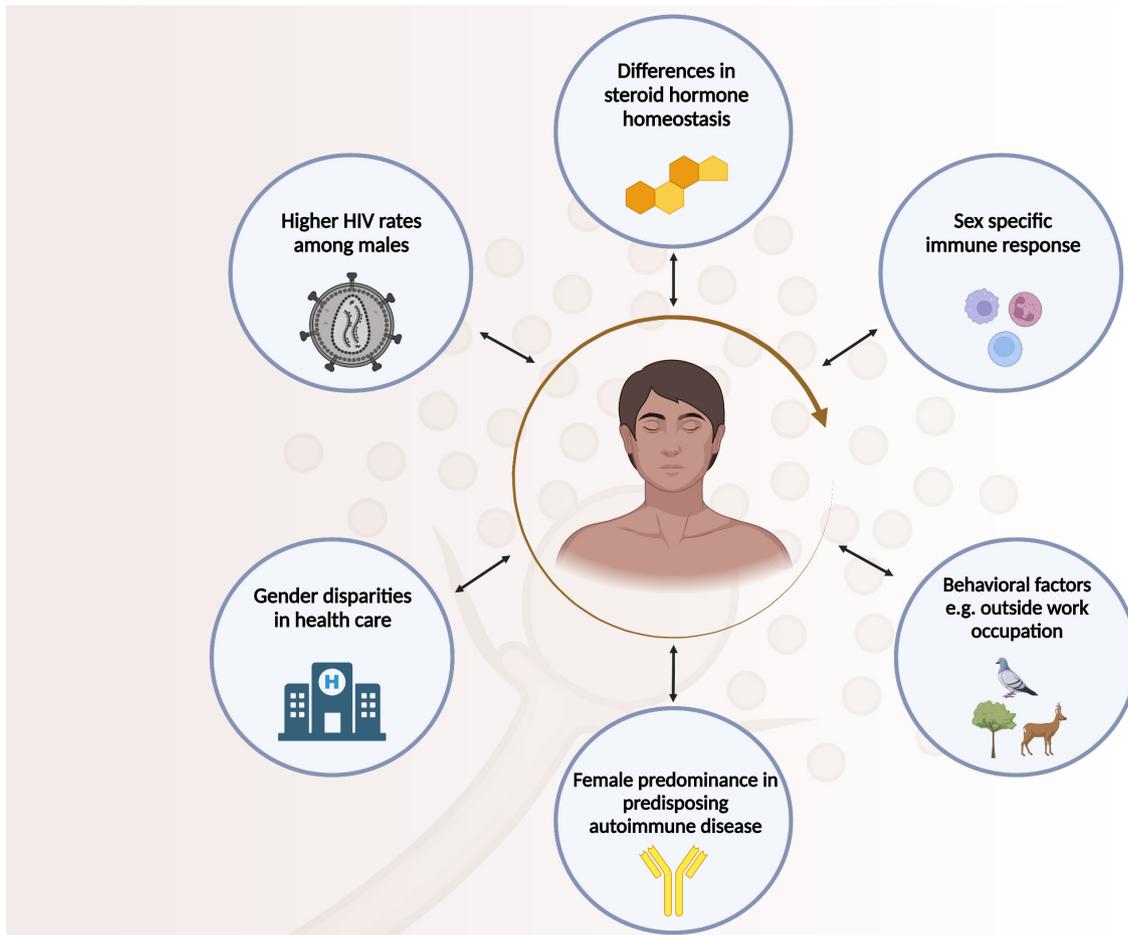
FIGURE 3 Factors that may explain differences in sex distribution in invasive fungal diseases

usage of *Aspergillus* strains, immunocompromised status, antibiotic prophylaxis for bacterial infection and route for experimental inoculation infection.[39] Another crucial, yet understudied variable, is the difference in biological sex. Steroid hormones and sex-specific immune responses lead to different host-pathogen interactions in *Aspergillus* infections (Figure 3).[40] Until recently, these sex-specific distinctions in animals exposed to *Aspergillus* remained unknown. Schaefer et al. showed that female mice generally exhibit higher immune responses, including antibody titres and granulocyte and lymphocyte recruitment than male mice.[40] To date, sex differences are still rarely reported in animal models studying *Aspergillus* infections.[39] In order to generate reliable and reproducible data, sex needs to be addressed in future studies as an important step towards standardised protocols.

Clinical studies. Numerous studies found a male bias in IA prevalence, with a general trend of higher prevalence, and partly severity, of invasive fungal infections in males.[1,41–43] Taking a closer look at sex differences in IA prevalence, we analysed 23 studies (Table 1). The proportion of males among IA cases ranged between 51% and 87% in 21 of the 23 studies included. Only 2 out of 23 studies reported female predominance, with proportions of 53% and 62%. Adding up

the number of all IA cases from included studies shows an overall *N* of 158,107 (female = 77,378 [48.9%], male = 80,729 [51.1%]).

A recent prospective study between 2012 and 2019 in Taiwan investigated the seroprevalence of *Aspergillus* IgG and disease prevalence of chronic pulmonary aspergillosis (CPA) in healthy volunteers and tuberculosis patients. Interestingly, they found a higher prevalence of *Aspergillus* IgG in women, which is a cornerstone for CPA diagnosis. Nevertheless, there was a higher prevalence of CPA disease in men.[44] This discordance suggests that women were more likely to mount an antibody response to *Aspergillus*, while men were still more likely to develop disease.[45]

Mucormycosis

In total, 28 meta-analyses/systematic reviews on mucormycosis/zygomycosis, which were conducted between 2007 and 2022, were analysed (Figure S1). Of 28 studies, 14 did not report on overall sex distributions and were excluded. Of the 14 studies remaining, eleven reported on different disease entities, patient populations or geographical areas, and hence fulfilled inclusion criteria (Table S1). One study was excluded due to overlap in investigated patient population, and two studies were excluded due to overlap in investigated disease entity with larger/more recent analyses. In all of the included

TABLE 1 Sex distribution in invasive aspergillosis

| Cases (N) | Sex | | | Study period | Patient cohort | References |
	Female	Male	Others			
83	27 (33%)	56 (67%)	/	2009–2016	ICU	122
454	189 (42%)	265 (58%)	/	/	HM	123
60	21 (35%)	39 (65%)	/	2011–2014	ICU	124
179	73 (41%)	106 (59%)	/	2011–2013	HM	125
219	81 (37%)	138 (63%)	/	1998–2017	Mixed	126
53	7 (13%)	46 (87%)	/	2011–2016	Mixed	127
50	12 (24%)	38 (76%)	/	2006–2013	ICU	128
70	33 (47%)	37 (53%)	/	2008–2014	SOT	129
52	18 (35%)	34 (65%)	/	2000–2010	Mixed	130
342	139 (41%)	203 (59%)	/	1993–2016	HM	131
393	149 (38%)	244 (62%)	/	2005–2007	Mixed	132
75	34 (45%)	41 (55%)	/	2013–2019	Mixed	133
154,888	76,118 (49%)	78,770 (51%)	/	2009–2013	Mixed	41
405	165 (41%)	240 (59%)	/	1990–2003	HM	134
115	51 (44%)	64 (56%)	/	2006–2011	Mixed	135
67	23 (34%)	44 (66%)	/	1998–2011	ICU	136
112	42 (37%)	70 (63%)	/	2000–2013	SOT	137
240	105 (44%)	135 (56%)	/	/	Mixed	138
64	40 (62%)	24 (38%)	/	2003–2011	SOT	139
186	51 (27%)	135 (73%)	/	03/2020–08/2020	COVID	140

Overall N = 158,107
Female = 77,378 (48.9%)
Male = 80,729 (51.1%)

	Female/male ratio/percentage only					
101	53%	47%	/	2004–2017	Mixed	141
232	1:1.4		/	2009–2011	Mixed	142
140	1:1.8		/	2004–2007	HM	143

Note: Included study cohorts were categorised by underlying risk factor (haematological malignancy, patients in the intensive care unit, patients with COVID-19 infection, single organ transplant (SOT) recipients and patients with mixed underlying diseases

Abbreviations: COVID-19, coronavirus-19; HM, haematological malignancy; ICU, intensive care unit; SOT, solid organ transplant.

meta-analyses/systematic reviews, there was a male sex distribution ranging from 31.8% to 80.3%.[46-55]

In vitro/animal models. To date, the potential influence of sex difference on findings in animal models of mucormycosis remains unclear. A recent study investigating sex differences in immunosuppressed mice with pulmonary mucormycosis analysed susceptibility to infection, host immune response and outcome of antifungal therapy. Results showed negligible differences in sex-specific susceptibility, but no difference in immune response or outcome of therapy. Based on these findings, it can be hypothesised that mucormycosis animal models might yield generalizable and reproducible biomedical research, regardless of animal sex used for experiments.[46]

Clinical studies. Mucormycosis is a rare, yet deadly invasive fungal infection that in some cases is difficult to diagnose. Between 2003 and 2010, <0.01% of hospitalizations in the United States accounted for mucormycosis, although infection is associated with mortality rates as high as 40%–90%.[56-58] Patients immunocompromised by cytotoxic chemotherapy resulting in neutropenia, patients with diabetic ketoacidosis or patients receiving other immunosuppressive therapies are primarily affected.[58] Recently, mucormycosis has come into the centre of attention as a devastating infection occurring in COVID-19 patients, particularly in India but also other parts of the world.[59]

In a large cohort of patients with mucormycosis, out of 5515 cases, 60.4% were male patients.[57] These findings correlate with findings of many other studies reporting a higher proportion of mucormycosis in males with rates between 65% and 81% (Table S2).[56,60-62] A male predominance was also observed among a large cohort of 2829 cases with COVID-associated mucormycosis (CAM) in India, where 71% were male.[63] While large cohorts of

CAM from outside India are lacking, a similar trend was observed also for other countries than India including Europe and the United States (78% of CAM cases were male).[59] This male predominance might partially be explained by the sexual differences in the immune response finding expression in more effective humoral and cell-mediated proinflammatory responses in women than in men (Figure 1). This comprises augmented Th1 responses, which are considered to enhance anti-Mucorales phagocytic activity and hence more sufficient protection against mucormycosis.[64] The protective effects of Th1 response were also found in other mould infections, particularly aspergillosis.[65]

3.3 | Fusariosis and other rare moulds

For fusariosis, 63% of 233 cases were reported to be male in one multicentre study[66] and similar trends have been observed in case series of other rare mould infections.[67,68]

3.3.1 | Yeasts

Invasive Candida infections
In total, 45 meta-analyses/systematic reviews on candidiasis, which were conducted between 2005 and 2022, were analysed (Figure S2). Of 45 studies, 42 did not report on overall sex distributions and were excluded. Of the three studies remaining, all fulfilled inclusion criteria (Table S3). In all of the included meta-analyses/systematic reviews, there was male predominance ranging from 52.5% to 64.7%.[69–71]

In vitro/animal models. In mouse models of systemic *C. albicans* infection, non-gonadectomized male mice were observed to be more susceptible to systemic candidiasis than female mice, while gonadectomized male mice were at similar risk to female mice. When supplemented with 5α-dihydrotestosterone, gonadectomized female and male mice were more susceptible to yeast infection, while gonadectomized male mice supplemented with 17-β-estradiol were protected, suggesting that testosterone plays an important role in decreasing resistance to systemic candidiasis (Figure 3).[72]

Clinical studies. Approximately, 150 million cases of severe fungal infections occur every year globally, resulting in 1.7 million deaths annually.[73] Of these, invasive candidiasis (IC) conservatively causes more than 250,000 of these infections, resulting in 50,000 deaths.[74]

In multiple studies, male sex has been shown to be a risk factor for invasive candidiasis (IC) with the proportion of males among cases of candidiasis between 52% and 60% in 7 of the 9 studies included (Table S4). Only 2 out of 9 studies reported female dominance with proportions of 51% and 53%, although the former study was the largest study found. In this survey of hospitalizations associated with IC in 33 states in the United States (U.S.) from 2002 to 2012, of over 138,000 cases of IC, rates overall tended to be higher in women (51% vs 49% in men), although rates were higher in men over

65 years of age.[43] In a study of patients with candidemia admitted to hospitals in France between 2001 and 2010, of over 15,000 cases of candidemia, 58.8% occurred in men at an incidence rate of 2.5, with 60% of deaths from candidemia occurred in males.[75] Adding up the number of all IC cases from included studies results in an overall *N* of 142,455 (female = 72,888 [51.2%], male = 69,567 [48.8%]).

Lastly, in neonates, male sex was a risk factor for IC on day three of life in one multicentre study of the Neonatal Research Network.[76] Another study in paediatric patients (mean age 4.5 years) from Brazil found that while invasive candidiasis occurred more often in females (53% vs 47%), male sex was a risk factor for death in patients with IC.[77,78]

Cryptococcosis
Out of 44 meta-analyses/systematic reviews on cryptococcosis, four met inclusion criteria and showed a male sex distribution ranging from 9.3% to 80%.[79–83] Details on selection process as well as results can be found in the online supplement.

In vitro/animal model. It is possible that sex hormones are involved in the increased incidence of cryptococcosis in males. Animal models have shown that testosterone can suppress the immune response to mice exposed to *C. albicans*,[84] and the same effect may occur with other yeasts. In contrast, oestrogen is thought to contribute to immune upregulation, including T-cell and B-cell stimulation[85] and phagocytosis.[86] Other studies showed increased phagocytosis of *C. neoformans* in the presence of a synthetic oestrogen, diethylstillbesterol[87] and growth inhibition of *C. neoformans* isolates incubated with oestrogen or diethylstillbesterol.[88] Thus, exposure and epidemiologic factors may not explain why males are predisposed to cryptococcosis, and biologic factors such as sex hormones may play a role—similar to IC—although future research is needed to further elucidate the pathogenesis of this relationship.

Clinical studies. Cryptococcosis has a well-known predilection for males, ranging from 72 to 80% in 4 out of 5 studies included in this review (Table S6). Only one study found higher rates of infection in females at 59%, and this study had the smallest sample size of those analysed. In one longitudinal study from Colombia, almost 80% of cases occurred in males, occurring at a 5.4:1 male–female ratio in persons with HIV infection and 3.9:1 male–female ratio in persons without HIV infection.[42] An aforementioned study in France found that of 1859 people hospitalised with cryptococcosis over a 10-year period, 72% were men.[75]

There are some possible explanations for the observed imbalance of sex. One theory is that males had increased exposure to pigeon droppings that contain *C. neoformans*,[89] although subsequent studies found that males and females are equally exposed.[90] Another theory is that since more males have HIV (Figure 3), they are at increased risk of dying given that HIV infection remains a strong risk factor for cryptococcosis (as noted in the aforementioned study from Colombia), although conflicting studies show that females either have a similar or increased risk of dying from HIV compared

with males,[91] arguing against this theory. Lastly, there are likely inherent differences in the immunologic response to *Cryptococcus* between males and females. In one study, peripheral blood mononuclear cells (PBMCs) from healthy donors were isolated and infected with *C. neoformans* and exogenous testosterone or 17-β-estradiol. *C. neoformans* proliferated to a higher degree in male PBMCs and male PBMCs had lower CD3+, CD4+ and CD8+ T-cell percentages during infection compared with females, suggesting that males may have an inherent deficit in T-cell response during infection.[92]

3.3.2 | Endemic Mycoses of the United States and beyond

Coccidioidomycosis
Two meta-analyses met inclusion criteria and showed predominance of male sex representing 70% and 81% of cases, respectively.[93,94] Details on selection process as well as results can be found in the online supplement.

In vitro/animal models. The effects of sex hormones on *Coccidioides* in vivo are not yet fully examined although clear effects have been demonstrated in vitro.[95–97] In a large dog population, 163,351 (82,961 males and 80,390 females) new *Coccidioides* spp. infections were observed in 99 male dogs versus 60 female dogs. Castration showed protective effects in male dogs [(odds ratio [OR] 1.6)], while spaying in female dogs had no influence on the OR.[98]

Clinical studies. Coccidioidomycosis is caused by dimorphic fungi of the genus *Coccidioides*, which consists of two species (*Coccidioides immitis* and *Coccidioides posadasii*). Approximately, 150,000 infections are noted in the U.S. per year with clinical manifestations ranging from asymptomatic exposure over acute self-limiting pneumonia to life-threatening disseminated disease.[99]

Debate about male sex potentially acting as an independent risk factor for increased susceptibility to infection, as well as more severe clinical courses, has already emerged in the literature.[100] Overall, in two studies with a combined case size of 62,364, there were much higher rates of infection in males compared with females (female = 20,727 [33.2%], male = 41,557 [66.8%]) (**Table S8**).

McHardy et al. reviewed coccidioidomycosis diagnostic data of 220,240 distinct humans between 2009 and 2020. Besides incidence rates by age and gender, they also analysed complement fixation titres in serum and cerebrospinal fluid (CSF) and gender differences in occurrence of coccidioidal meningitis. Overall, 21,435 male patients (17.3%) and 9950 female patients (10.3%) were diagnosed with coccidioidomycosis. Males and females were equally affected until the age of 19, when incidence of infection dropped in females with an increase in males. At the age of 35, the OR for infection peaked at a significant value of 2.9. Both serum and CSF complement fixation titres were significantly higher in male than in female patients, as well as the incidence of coccidioidal meningitis (2.4% for males vs 1.8% for females).[98]

As coccidioidomycosis is transmitted by soil disruption and subsequent inhalation of aerosolized spores, one argued that observed

differences arise from behavioural and/or occupational variances between sexes (Figure 3). However, no study quantified postulated exposure differences and, more importantly, data in animal models present similar findings, although impact of distinct exposure as well as behaviour associated with increased risk for infection, is virtually excluded in these studies.

Histoplasmosis
Out of 25 meta-analyses/systematic reviews on histoplasmosis, four met inclusion criteria and showed a male predominance ranging from 68% to 100%.[101–104] Details on selection process as well as results can be found in the online supplement.

In vitro/animal models. There is a paucity of in vitro or animal model studies looking at histoplasmosis and sexual characteristics. Epidemiologically, histoplasmosis is the second most common systemic fungal disease in cats, who may be more susceptible to infection than dogs. In dogs, histoplasmosis is the most commonly diagnosed endemic fungal infection, with infection occurring more commonly in male dogs.[105] Infection may be subclinical or cause overt pulmonary or disseminated disease in dogs and cats.[106]

Clinical studies. There are less published data on the sex predilection of *Histoplasma* spp. than with some of the previously discussed fungi. One study in the U.S. and Puerto Rico evaluated 105 outbreaks involving 2850 people from 1938 to 2013. Of 1318 cases with complete data about patient sex, 60% of cases occurred in males.[107] Another multistate study in the U.S. of 3409 cases found that 61% of cases occurred in men. Overall, histoplasmosis is more common in males. Of six studies analysed, infection rates in males ranged from 50 to 80% with no studies showing higher infection rates in females (Table S10). Overall, of the total sample size of 4049 across these studies, there was a higher proportion of infections in males (female = 1577 [38.9%], male = 2472 [61.1%]).

Blastomycosis
One meta-analysis met inclusion criteria and reported 56% of cases among males.[108] Details on selection process as well as results can be found in the online supplement.

In vitro/animal models. As with histoplasmosis, there are a paucity of in vitro or animal model studies evaluating blastomycosis and sexual characteristics. Epidemiologically, *Blastomyces dermatitidis* can cause both respiratory and disseminated disease in dogs and cats, with dogs more commonly affected and infection occurring more frequently in male dogs.[105,109] In one study of 971 cases of blastomycosis in dogs from 22 veterinary hospitals in North America, dogs at the highest risk for infection were sexually intact male dogs who were 2–4 years old. This predilection is thought to be associated with roaming behaviour or selective use for hunting.[110]

Clinical studies. In a previously mentioned study from Ontario, Canada, from 1990 to 2015, 1092 cases of blastomycosis were reported. Of 963 cases in which patient sex was recorded, 65% of cases occurred

in men.[111] Similar findings were found in other studies in the U.S and Canada.[112–119] In a study looking at blastomycosis-related deaths in the U.S. from 1990 to 2010, there was a strong predilection for males with over 66% of deaths occurring in males.[120] Overall, like the other endemic fungi blastomycosis has a strong male predilection with rates ranging from 57 to 75% in 15 of 15 studies analysed (Table S12). No studies showed higher infection rates in females. Overall, the sample size of studies with blastomycosis cases was 7159 with a strong preponderance in males (female = 2448 [34.2%], male = 4711 [65.8%]).

As with other invasive fungal infections, the predilection for blastomycosis in males is unclear. One theory is that men participate in activities where they may be more likely exposed to *B. dermatitidis*, including from hunting, fishing or forestry work.[121] Further investigation into underlying biological or immunological causes is warranted.

4 | CONCLUSION

Differences in sex are known factors that influence the risk of acquiring a number of infectious diseases. Here, we evaluated sex differences and rates of invasive fungal infections including IA, mucormycosis, candidiasis, cryptococcosis and infections caused by endemic fungi (coccidioidomycosis, blastomycosis and histoplasmosis). Overall, there was a male predilection for invasive fungal infection seen with nearly all the fungal diseases in this review, except for invasive candidiasis (Figure 4). For the other fungal infections with male predominance, this was least pronounced with IA and most pronounced with cryptococcosis and the endemic fungi.

Potential explanations and theories for these findings include behaviours that may influence risk of infection, particularly from cryptococcosis and the endemic fungi, where traditionally men may have been at a higher risk of environmental exposure. This theory has been postulated for why male dogs, who may exhibit more roaming behaviour, are selectively used for hunting may be at higher risk. While possibly a contributing factor, this has not proven to be generalizable in all studies, and this theory seems less plausible contemporarily given that males and females currently do a lot of the same work tasks and have similar hobbies.

Another theory is that sex hormones may interact differently in males and females with IFDs, as has been postulated in IA and IC. In general, the available data suggest the existence of favourable immune responses in females that may confer increased resistance to infection compared to males. Sex hormone homeostasis might be influenced by various underlying mechanisms, which are not explicitly taken into account in investigated studies. Among others,
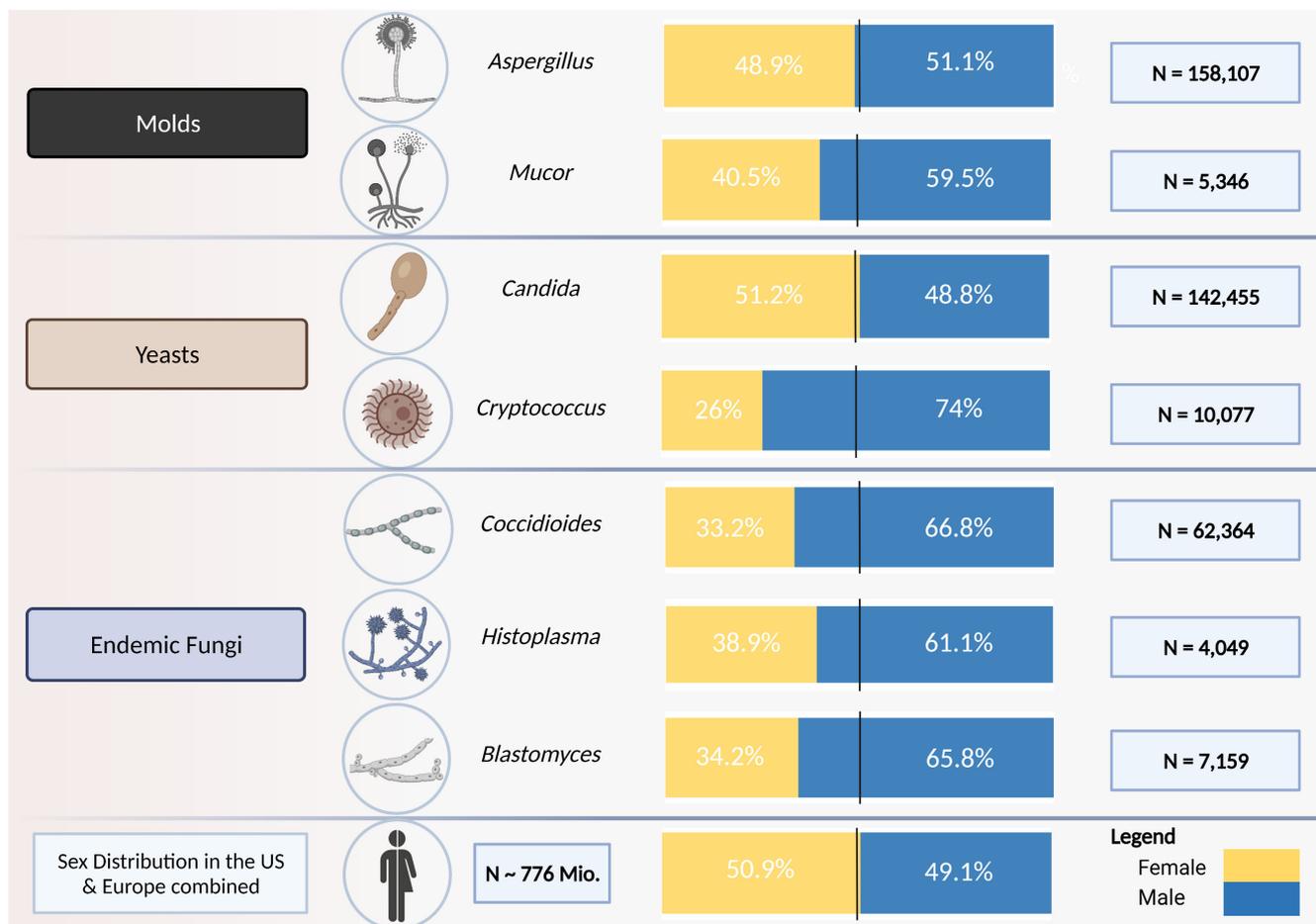

FIGURE 4 Overall sex distributions for a variety of invasive fungal diseases

these include (1) variances in oestrogen levels in adipose males/females (2) underlying conditions like hepatic cirrhosis influencing oestrogen levels (3) oral contraceptives as well as other drugs modifying hormone levels (4) hormonal changes until sexual maturity (5) decrease in oestrogen levels in menopausal females. Influence of the latter can be hypothesised as the quoted large study on IC (only fungal pathogen where a marginal female predominance was found) found higher infection rates in males over 65 years of age.

The issue of gender as risk factor for any disease process is highly complex and may be influenced by many factors which are difficult to be adequately assessed. For instance, in many parts of the world, cultural factors as well as general access to care play a role in who gets included in studies after all.

To date, the authors are not aware of any studies looking at rates of IFDs in transgender persons where the hormonal effects may further elucidate the observed sex predilection for infection with fungal pathogens.

Generally speaking, our observations support the consideration of sex as a biological variable in future studies, from fundamental research to preclinical drug development, clinical trials and epidemiological analyses. This will likely contribute to uncover novel features of the host immune response to fungi and ultimately support more equitable health outcomes.

The apparent overall predilection for IFDs in males warrants further investigation into this association, as many more, to date unstudied, nuances might refine the understanding of observed sex differences. Given that so many of these fungi are commonly found or even ubiquitous in the environment, reducing the risk of exposure to these pathogens can be challenging and further understanding risk factors for infection—and even ways to possibly modify risk—may help decrease the prevalence and incidence of these fungal infections that cause such morbidity and mortality.

In conclusion, we found male predominance in all fungal infections except IC. Meta-analyses on fungal infections rarely mentioned sex and gender distributions, which needs to improve in the future as sex may also be a driver of poor outcomes.

AUTHORS' CONTRIBUTIONS

GRT and MH contributed to conceptualisation and supervision; ME and MH contributed to methodology; ME, AC and JDJ contributed to writing—original draft preparation; MH, GRT, JDJ and AC contributed to writing—review and editing; ME and AC contributed to visualisation.

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CONFLICT OF INTEREST

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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