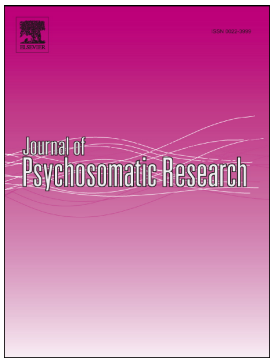

Social phobia in immune-mediated inflammatory diseases

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Social Phobia in Immune-Mediated Inflammatory Diseases

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Abstract

Objective: Immune-mediated inflammatory diseases (IMID) such as multiple sclerosis (MS), inflammatory bowel disease (IBD) and rheumatoid arthritis (RA) are associated with a high prevalence of psychiatric comorbidity but little is known about the prevalence of social phobia in IMID, or the factors associated with social phobia. We aimed to determine the prevalence of social phobia in MS, IBD and RA, and the factors associated with social phobia in these IMID.

Methods: We obtained data from the enrollment visit of a cohort study in IMID of whom 654 participants were eligible for this analysis (MS: 254, IBD: 247, RA: 153). Each participant underwent a semi-structured psychiatric interview which identified depression and anxiety disorders including social phobia (lifetime and current), an assessment of disease activity, and reported sociodemographic information.

Results: Overall, 12.8% of participants had a lifetime diagnosis of social phobia (MS: 10.2%, IBD: 13.0%, RA: 17.0%). Social phobia was associated with younger age (OR 0.98; 0.97-1.00), having a high school

education or less (OR 1.78; 1.08-2.91), comorbid major depressive disorder (OR 2.79; 1.63-4.78) and comorbid generalized anxiety disorder (OR 2.56; 1.30-5.05). Persons with RA had increased odds of having social phobia as compared to persons with MS (OR 2.26; 1.14-4.48) but not IBD.

Conclusion: Persons with IMIDs have a relatively high lifetime prevalence of social phobia, exceeding that reported for the Canadian general population. Strategies aimed at early detection, and effective clinical management of social phobia in IMID are warranted.

Keywords: social phobia, immune-mediated inflammatory disease, anxiety, multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis

1. Introduction

Immune-mediated inflammatory diseases (IMID) such as multiple sclerosis (MS), inflammatory bowel disease (IBD) and rheumatoid arthritis (RA), are common in Canada. The inflammatory processes of these diseases affect different organ systems, yet all are associated with a higher prevalence of anxiety disorders than in the general population.[1-3] In MS, for instance, comorbid anxiety disorders and other psychiatric disorders are associated with worsened fatigue, increased pain and lower adherence to disease-modifying medications.[4] Despite their adverse impacts, anxiety disorders typically remain underdiagnosed and undertreated in IMID,[5, 6] and are relatively understudied compare to depressive disorders.

Anxiety disorders include panic disorders, generalized anxiety disorder (GAD), social anxiety disorder and specific phobias. Social anxiety disorder, also known as social phobia, is characterized by a fear of social situations in which the individual may be subjected to perceived scrutiny or criticism by others.[7] Social phobia is one of the most prevalent anxiety disorders with a lifetime prevalence of 8% in Canada.[8] The prevalence of social phobia is higher among women, and among individuals who are younger, with less education and lower socioeconomic status, and limited social support.[9, 10] Social phobia is associated with an increased risk of comorbid psychiatric disorders including substance use

disorder, major depressive disorder, and other mood and anxiety disorders.[9-11] Social phobia is a burdensome condition that impairs social, occupational and recreational functioning, and can diminish participation in society.[10] Despite the substantial burden caused by social phobia, and the fact that it is highly treatable, many patients do not seek medical attention.[7]

Relatively little is known about the prevalence of social phobia in persons with IMID, but physical and cognitive impairments associated with these chronic diseases may increase concerns regarding performance in social settings. In a cohort of 245 persons with MS, one-third had clinically meaningful symptoms of social anxiety.[12] In another cohort of 140 persons with MS who underwent a semi-structured diagnostic interview the lifetime prevalence of social anxiety disorder was 7.8%.[6] In a cohort of 351 persons with IBD who participated in a fully structured interview, the lifetime prevalence of social anxiety disorder was 6%.[13] Factors associated with social phobia in IMID are not well understood. We aimed to determine: (i) the prevalence of social phobia in MS, IBD and RA; and (ii) the factors associated with social phobia in these conditions, thereby raising awareness about this understudied psychiatric comorbidity

2. Methods

This was an analysis of data collected at enrollment as part of a longitudinal cohort study conducted to evaluate the prevalence and impact of psychiatric comorbidity in IMID.[14]

2.1 Study Population

Between November 2014 and July 2016 participants from the central Canadian province of Manitoba were enrolled if they had any of physician-confirmed: IBD, which included ulcerative colitis and Crohn's disease,[15] MS according to the prevailing diagnostic criteria at the time of diagnosis,[16-19] RA based on the 2010 American College of Rheumatology/European League Against Rheumatism,[20] major depressive disorder satisfying criteria in the Diagnostic and Statistical Manual, 4th edition (DSM-IV) and

any anxiety disorder per the DSM-IV, including post-traumatic stress disorder and obsessive-compulsive disorder. As described in detail elsewhere, participants were recruited from tertiary care and community settings using a combination of strategies including posters, social media posts, mailed or emailed letters to persons attending primary care and specialty clinics, as well as direct contacts by study coordinators in tertiary care settings. All participants were aged ≥18 years, able to provide informed consent and willing to participate in the study for three years. Ethics approval was obtained from the University of Manitoba Health Research Ethics Board.

2.2 Data Collection and Measures

At enrollment, participants underwent a psychiatric interview and completed questionnaires. Psychiatric comorbidities were assessed using the semi-structured clinical interview for DSM-IV-TR Axis I Disorders – Research Edition (SCID).[21] In the present study, it was used to identify current and lifetime presence or absence of major depressive disorder, GAD and social phobia. The clinical interview regarding social phobia also captured the types of situations which triggered the anxiety including public speaking, eating in front of others, writing in front of others, "performance" based situations, and "non-performance based" situations (such as meeting new people, speaking up in meetings, and going to parties). All interviewers were trained to administer the SCID by a registered clinical health psychologist with an extensive history of this interviewing technique.[14]

Questionnaires captured sociodemographic characteristics, smoking status, psychiatric symptom levels and pain at enrollment. Sociodemographic information obtained included gender (male or female), date of birth, race/ethnicity (White or non-White), the highest education level obtained (categorized as ≤high school/GED or any post-secondary education), annual household income (<$50000, $50000-$100000, >$100000 and declined to answer), marital status (married/common law or

single/divorced/widowed/separated) and if they had children (yes or no). Current smoking status was categorized as current smoker (yes or no).

The Hospital Anxiety and Depression Scale (HADS) was used to measure the severity of anxiety and depression symptoms;[22] it has been validated for use in IBD, MS and RA. [23-25] The scores for anxiety (HADS-A) and depression (HADS-D) are graded from zero to twenty-one, where scores ≥11 indicate clinically meaningfully elevated symptoms of anxiety and depression.

Disease activity in MS was measured using the annualized relapse rate, where relapses were defined as neurologic symptoms consistent with MS that lasted >24 hours, in the absence of fever or infection. Disease activity in ulcerative colitis was measured using the Powell Tuck Index (PTI) and Crohn's disease activity was measured using the Harvey Bradshaw Disease Activity Index (HBDAI).[26, 27] For both indices, a score of ≥5 indicates active disease. Disease activity in RA was measured using the Clinical Disease Activity Index (CDAI) where a score >2.8 on the CDAI indicates active disease.[28]

2.3 Analysis

We limited the analysis to participants who completed the SCID. Categorical variables were summarized using frequency (percent) and continuous variables using their mean and standard deviation. For bivariate analyses we used chi-square tests, Fisher's exact tests, Student's t-tests, ANOVA and Kruskal-Wallis tests as appropriate. We estimated the lifetime prevalence of social phobia in each IMID (MS, IBD and RA) overall, and stratified by sex and age. We also summarized the characteristics of social phobia, including age at onset and phobic situations.

We used multivariable logistic regression models to assess the association between lifetime occurrence of social phobia and IMID type, sociodemographic factors and comorbid psychiatric disorders. In addition to IMID status (MS [reference], IBD or RA), covariates considered were age (continuous), gender (female [reference] versus male), education (≤high school education, or >high school

[reference]), race (White [reference] or non-White), lifetime history of GAD (yes versus no[reference]), lifetime history of major depressive disorder (yes versus no [reference]), pain (continuous) and disease activity (active or inactive [reference]). These covariates were chosen based on the literature and those that reached statistical significance on univariate analysis. Additional models tested for interactions between IMID status and covariates by including product terms (IMID status*covariate). Associations determined from logistic regression were reported as odds ratios (OR) with 95% confidence intervals (95%CI). We assessed predictive accuracy of the models using the c-statistic, and goodness of fit using the Hosmer Lemeshow Goodness of Fit test.

Statistical analyses were performed using IBM SPSS Statistics, Version 26 (Armonk, NY: IBM Corp). P-values ≤0.05 were considered to be statistically significant.

3. Results

3.1 Study participants

We enrolled 656 participants with an IMID, of whom 654 completed the SCID, including 254 with MS, 247 with IBD and 153 with RA.[14] Most participants were female, White, had some post-secondary education, and were married with children (Table 1). On average, participants with RA were older than participants with MS and IBD. The IBD cohort had the largest proportion of male participants, while the RA cohort had the largest proportion of non-White participants. Income varied across IMID, being highest among those with IBD and lowest among those with RA.

3.2 Social phobia

Overall, 84 (12.8%) participants had a lifetime diagnosis of social phobia, including 26 (10%) with MS, 32 (13%) with IBD and 26 (17%) with RA (Table 2). The prevalence of social phobia was higher in participants with RA than in participants with MS ($\chi^2(1) = 3.9$, $p = 0.048$), but not than participants with IBD (RA vs. IBD, $\chi^2(1) = 1.2$, $p = 0.26$). Sixty-three (9.6%) participants had current social phobia including

19 (7.5%) with MS, 27 (10.9%) with IBD and 17 (11.1%) with RA (Table e1). The prevalence of lifetime social phobia was similar in women and men overall ($\chi^2(1) = 0.63$, $p = 0.43$, Table 2), and among the MS, IBD and RA participants. The prevalence of lifetime social phobia did not differ by age group in the IMID participants overall (Cochran-Armitage trend $Z = 1.6$, $p = 0.11$), or in the IBD (Cochran-Armitage trend $Z = 1.1$, $p = 0.26$) or RA (Cochran-Armitage trend $Z = -0.65$, $p = 0.51$) participants. However, the prevalence of social phobia was higher in the younger MS participants than in the older MS participants (Cochran-Armitage trend $Z = 2.9$, $p = 0.004$).

Among all participants who ever had social phobia, the situation which most commonly provoked fear was public speaking, while writing in public was least likely to provoke fear (Figure 1). Participants with MS were more likely to report a fear of public speaking and performance-related tasks than participants with IBD and RA, while participants with RA were most likely to report fear of non-performance-related tasks. The median (IQR) age at onset of social phobia was 15 (9.5-35) years in the IMID participants overall and did not differ across groups (Kruskal Wallis $H = 1.5$ (2), $p = 0.46$).

3.3 Factors associated with social phobia

As compared to participants without social phobia, participants with lifetime social phobia tended to be younger and were less likely to have a post-secondary education (Table 3). Participants with social phobia were more likely to have active IMID disease than those without social phobia. Participants with social phobia were more likely to have elevated symptoms of anxiety and depression based on the HADS and were also more likely to have a lifetime diagnosis of GAD or major depressive disorder. Findings were similar for current social phobia (Table e1).

On univariate analysis, the odds of lifetime social phobia were higher among participants with RA than MS, but did not differ for participants with IBD as compared to those with MS (Figure 1, Model 1). This finding persisted on multivariable analysis. Several demographic factors were associated with social phobia (Table 4, Model 2). As compared to having a high school education or less, having any post-secondary education was associated with reduced odds of social phobia. Gender and race were not associated with social phobia. Lifetime histories of GAD and major depressive disorder were associated with more than two-fold increased odds of social phobia. When we added disease activity to this multivariable model the findings were unchanged (Model 3). Disease activity was not associated with social phobia (OR 0.96; 95%CI: 0.52 – 1.76). We did not observe interactions between IMID status (IBD, MS or RA) and model covariates in Models 2 or 3 (data not shown).

4. Discussion

In this study of 654 persons, we found that 12.8% of persons with IMIDs had a lifetime prevalence of social phobia. The prevalence of social phobia was lowest in MS and highest in RA; this difference persisted even after adjusting for sociodemographic factors but could reflect biological or social factors. Sociodemographic factors associated with a lifetime history of social phobia among the IMIDs included lack of any post-secondary education. Consistent with the literature, the psychiatric comorbidities of a lifetime history of GAD and major depressive disorder were substantially more common than reported in the general population.[29-31] These comorbidities were more strongly associated with a lifetime history of social phobia than sociodemographic factors.

The prevalence of social phobia we observed in participants with IMID was higher than reported in the general population; the Canadian lifetime prevalence was reported as 8% in 2002 based on the Composite International Diagnostic Interview (CIDI).[8] Findings from prior studies regarding the prevalence of social phobia in IMID have been mixed, and generally have not compared the prevalence

of social phobia across IMID. A study in Nova Scotia, Canada found clinically meaningfully symptoms of social anxiety in 30.6% of MS patients. [12] This estimate is much higher than what we reported, likely due to methodological differences. Specifically, that study used the self-reported Social Phobia Inventory (SPIN) [32] which focuses on current self-reported fears, avoidance habits and physiologic responses and does not determine whether formal lifetime diagnostic criteria are met, while we used a semi-structured interview to identify diagnoses of social phobia according to DSM-IV criteria. The SPIN has been shown to over-estimate the prevalence of social phobia in adolescents with a positive predictive value of 17.9% and a negative predictive value of 99.6% when compared to a semi-structured clinical interview using a cut-off of 19, which was used in the study performed in Nova Scotia. [33] Another study with 140 MS participants, which used the SCID, reported a lifetime prevalence of social phobia of 7.8%, [6] which falls within the 95%CI for our estimate. A study of Manitoba participants with IBD reported a lifetime prevalence of social phobia of 8.0%, [13] which is lower than what we observed. That study used the CIDI which is known to under-diagnose social phobia, [34] having a positive predictive value of 91-100% but a negative predictive value of only 44-50% when compared to the SCID. [35] A study of 200 outpatients with RA in Hong Kong, which used the Chinese-bilingual SCID, found a lifetime prevalence of social phobia of 1.5%. [36] This estimate is substantially lower than what we observed, but the prevalence of anxiety is generally reported as being lower in East Asia compared to Canada, [37] and therefore it is difficult to directly compare to our results.

The social situations which provoked significant anxiety varied across IMID. Public speaking is a common anxiety-provoking situation, as demonstrated in a study of the general population in the US, which found that 21.2% of participants, regardless of social phobia status, had a fear of public speaking. [11] In the 2002 Canadian Community Health Survey, public speaking was the most common situation which provoked anxiety among participants with social phobia, while writing, eating or drinking while someone watches and using a public washroom were least likely to provoke fear. [8] Consistent with those

findings, we found that public speaking was the social situation which most often provoked fear, while writing in public was least likely to provoke fear. Fear of public speaking affected a greater proportion of participants with MS compared to the IBD or RA groups. This difference may reflect the higher prevalence of cognitive impairment, including slowed processing speed, in MS than IBD or RA,[38] or dysarthria, a less prevalent but potentially socially debilitating symptom in MS. Participants with RA were much less likely than MS or IBD participants to have a social fear of eating which again may also reflect clinical differences across conditions. In MS, tremor may interfere with feeding, swallowing is often impaired, and comorbid functional gastrointestinal disorders are common;[39] similarly, some foods may worsen symptoms of IBD. The more frequent occurrence of fear related to performance activities in MS than in the other IMID may reflect the greater physical impairments which occur in MS.

In the general population several demographic and clinical factors are associated with a higher risk of current and lifetime social phobia including female gender, lower income and education levels, white race, being unmarried and the presence of other psychiatric disorders.[9-11] We did not observe any associations between social phobia and marital status, income or race. Although we observed a greater proportion of women than men with social phobia, this association was not statistically significant, possibly due to the relatively small number of men enrolled. Lower education levels were associated with an increased likelihood of social phobia, consistent with findings in the general population and a prior study examining symptoms of social phobia in MS.[8, 12] As we observed, current social phobia is associated with GAD and major depressive disorder in the general population.[11] For example, a study examining 18,980 persons from the general population in six European countries found that 19.5% of persons with current social phobia had current comorbid major depressive disorder and 18.9% of persons had current comorbid GAD.[40] We did not observe any associations between current disease activity and lifetime social phobia. In the case of IBD we are reporting on symptoms and do not have information about true inflammatory activity as identified by endoscopy or radiology. Increased

symptoms of anxiety in general have been reported to be associated with disease activity in IBD and RA.[41, 42] Fear of the social consequences of anxiety is also associated with disease severity in RA. [43] However, other studies have shown no association between disease activity in IBD and diagnosed social phobia,[13] nor between the severity of MS and symptoms of social phobia.[12] The lack of association between current disease activity and lifetime social phobia that we observed may reflect the episodic nature of disease activity in IMIDs.

The median age of onset of social phobia in our cohort (15 years) was similar to the average age of onset of 13 years reported in the Canadian general population.[8] This suggests that social phobia does not arise as a consequence of IMID. Relatively little is known about the potential biological associations with IMID and social phobia, but this could reflect shared genetic or environmental factors,[44] or implicate a common role of inflammation,[45] as has been proposed similarly for major depressive disorder, which was even more common in this IMID cohort than social phobia. Potentially, the development of an IMID could exacerbate existing social phobia either psychologically or biologically. Persistent exposure to stimuli that induce fear and anxiety lead to central and peripheral release of pro-inflammatory cytokines. Persons with social phobia have been shown to have a heightened amygdala response when in fear-inducing situations and this amygdala response may be associated with increased peripheral levels of inflammatory cytokines.[45] Heart rate variability is reduced in social phobia, indicating reduced parasympathetic tone and increased sympathetic tone secondary to disruption of the hypothalamic pituitary axis,[45] which may also promote an inflammatory state.

A major strength of our study was the ability to compare findings across three IMIDs, unlike prior studies. The large sample size, and the recruitment of participants from the community and tertiary care centers were also strengths. We cannot exclude the possibility that some differences in the populations arose during the recruitment process given differences in the systems of care for these diseases in Manitoba. However, the observed differences between the three IMID with respect to gender ratios,

race, and age at diagnosis were consistent with expected differences in the epidemiology of these diseases. We were unable to examine the association between disease severity and social phobia due to the differences in the measures used for disease severity for each IMID, and the relatively small number of individuals affected by social phobia within each IMID. The only psychiatric comorbidities we evaluated were GAD and major depressive disorder but other psychiatric comorbidities are also likely to be relevant.

The prevalence of social phobia is high in persons with IMID, particularly among persons with comorbid depression or GAD, yet social phobia has received little attention despite its potential adverse impacts in these populations which already face functional limitations. Given the availability of effective treatments,[46] health care providers should focus on better ways to detect and manage this disorder in these populations.

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Declaration of interest

Charles Bernstein has consulted to Abbvie Canada, Janssen Canada, Pfizer Canada, Shire Canada, Takeda Canada, and has received unrestricted educational grants from Abbvie Canada, Janssen Canada, Shire Canada, and Takeda Canada. He has been on speaker's bureau of Abbvie Canada, Janssen Canada, Medtronic Canada and Takeda Canada

Jitender Sareen holds stock in Johnson and Johnson.

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Table 1. Characteristics of study participants.

Characteristics	**MS (n = 254)**	**BD (n = 247)**	**RA (n = 153)**	**Test Statistic (df), P-value**
Age (years), mean (SD)	51.1 (12.3)	47.4 (14.8)	59.6 (11.6)	H(2) = 67.8, <0.0001
Female, n (%)	207 (81.5)	155 (62.8)	129 (84.3)	$\chi^2(2) = 32.6$, <0.0001
White race, n (%)[a]	217 (85.8)	210 (85.4)	116 (75.8)	$\chi^2(2) = 32.6$, 0.018
Education, n (%)				$\chi^2(2) = 0.55$, 0.78
≤High school/ GED	94 (37.0)	84 (34.0)	55 (35.9)	
>High school	160 (63.0)	163 (66.0)	98 (64.1)	
Income, n (%)				$\chi^2(6) = 26.3$, <0.0001
<$50,000	81 (31.9)	58 (23.5)	69 (45.1)	
$50,000-100,000	99 (39.0)	104 (42.1)	48 (31.4)	
>$100,000	46 (18.1)	67 (27.1)	25 (16.3)	
Declined to answer	28 (11.0)	18 (7.3)	11 (7.2)	
Marital status, n (%)				$\chi^2(2) = 5.1$, 0.08
Single/Divorced/Widowed	73 (28.7)	87 (35.2)	60 (39.2)	

Married/common law	181 (71.3)	160 (64.8)	93 (60.8)	
Has children (%)	180 (70.9)	157 (63.6)	120 (78.4)	$\chi^2(2) = 10.1$, 0.006
Current smoker (%)	57 (22.4)	42 (17.0)	21 (13.7)	$\chi^2(2) = 5.3$, 0.07
HADS-A ≥ 8, n (%)[b]	86 (34.0)	90 36.6)	62 (40.8)	$\chi^2(2) = 1.9$, 0.39
HADS-A ≥ 11, n (%)[b]	40 (15.8)	41 (16.7)	20 (13.2)	$\chi^2(2) = 0.91$, 0.63
HADS-D ≥ 8, n (%)[c]	61 (24.2)	45 (18.2)	34 (22.2)	$\chi^2(2) = 2.7$, 0.26
HADS-D ≥ 11, n (%)[c]	20 (7.8)	16 (6.5)	14 (9.2)	$\chi^2(2) = 0.99$, 0.61
Age at diagnosis (years), mean (SD)[d]	36.3 (11.1)	30.4 (13.5)	41.5 (14.8)	H(2) = 68.7, <0.0001
Active disease, n (%)[e]	21 (8.3)	99 (41.3)	4[illegible] (33.1)	$\chi^2(2) = 72.9$, <0.0001
Lifetime history MDD, n (%)	105 (41.3)	98 (39.[illegible])	58 (37.9)	$\chi^2(2) = 0.48$, 0.79
Lifetime history GAD, n (%)	21 (8.3)	24 (9.7)	13 (8.5)	$\chi^2(2) = 0.36$, 0.83

MS = multiple sclerosis, IBD = inflammatory bowel disease, RA = rheumatoid arthritis, MDD = major depressive disorder, GAD = generalized anxiety disorder, H = test statistic for Kruskal Wallis test, df = degrees of freedom, a-Missing for 1 person with MS, and 1 with IBD. b-Incomplete for 1 person with MS, 1 with IBD and 1 with RA. c-Incomplete for 2 persons with MS. d-Missing for 3 persons with IBD and 2 with RA. e-Missing for 2 persons with MS, 7 with IBD and 11 with RA.

Table 2. Prevalence (95% confidence interval) of lifetime social phobia according to gender, age and immune-mediated inflammatory disease (IMID)

	IMID	**MS**	**IBD**	**RA**	**Test statistic (df), P-value**
Overall	12.8 (10.4, 15.6)	10.2 (6.8, 14.6)	13.0 (9.0, 17.8)	17.0 (11.4, 23.9)	$\chi^2(2) = 3.9$, 0.14[a]
Gender					
Female	13.4 (10.5, 16.8)	11.6 (7.6, 16.8)	13.5 (8.6, 20.0)	16.3 (10.4, 23.8)	$\chi^2(2) = 1.5$, 0.47[b]
Male	11.0 (6.7, 16.9)	4.3 (0.52, 14.5)	12.0 (6.1, 20.4)	20.8 (7.1, 42.1)	$\chi^2(2) = 4.6$, 0.10[c]
Age group					
18-34	15.7 (8.9, 25.0)	22.2 (8.6, 42.3)	14.3 (6.4, 26.2)	0	$\chi^2(2) = 0.35$, 0.50[d]

35-54	14.6 (10.5, 19.5)	12.4 (7.1, 19.6)	16.0 (9.4, 24.7)	17.9 (7.5, 33.5)	$\chi^2(2) = 0.98,\ 0.61$[e]
≥55	10.5 (7.3, 14.5)	4.7 (1.5, 10.7)	8.8 (3.9, 16.6)	17.6 (10.9, 26.1)	$\chi^2(2) = 9.8,\ 0.0073$[f]

MS = multiple sclerosis, IBD = inflammatory bowel disease, RA = rheumatoid arthritis, df = degrees of freedom

a- P-values MS vs. IBD: $\chi^2(1) = 0.90,\ 0.34$, MS vs. RA: $\chi^2(1) = 3.9,\ 0.048$, IBD vs. RA: $\chi^2(1) = 1.2,\ 0.26$

b- P- values MS vs. IBD: $\chi^2(1) = 0.31,\ 0.58$, MS vs. RA: $\chi^2(1) = 1.5,\ 0.22$, IBD vs. RA: $\chi^2(1) = 0.42,\ 0.52$

c- P-values MS vs. IBD: Fisher's exact test, 0.12, MS vs. RA: Fisher's exact test, 0.04 IBD vs. RA: Fisher's exact test, 0.32

d- P-values MS vs. IBD: Fisher's exact test, 0.36, MS vs. RA: Fisher's exact test, 0.56 IBD vs. RA: Fisher's exact test, 1.0

e- P-values MS vs. IBD: $\chi^2(1) = 0.59,\ 0.44$, MS vs. RA: $\chi^2(1) = 0.77,\ 0.38$, IBD vs. RA: Fisher's exact test, 0.80

f- P-values MS vs. IBD: $\chi^2(1) = 1.32,\ 0.25$, MS vs. RA: $\chi^2(1) = 8.9,\ 0.0028$, IBD vs. RA: $\chi^2(1) = 3.3,\ 0.07$

Table 3. Characteristics of participants according to lifetime social phobia status

Characteristics	**Social Phobia (n = 84)**	**No Social Phobia (n = 570)**	**Test Statistic (df), P-value**
IMID, n (%)			$\chi^2(2) = 3.9,\ 0.14$
MS	26 (31.0)	228 (40.0)	
IBD	32 (38.0)	215 (37.7)	
RA	26 (31.0)	127 (22.3)	
Age (years), mean (SD)	48.7 (13.9)	52.1 (13.7)	$H(1) = 4.2,\ 0.04$
Female, n (%)	66 (78.6)	425 (74.6)	$\chi^2(1) = 0.63,\ 0.43$
White race, n (%)[a]	67 (79.8)	476 (83.8)	$\chi^2(1) = 0.86,\ 0.35$
Education, n (%)			$\chi^2(1) = 5.9,\ 0.01$
≤High school education/GED	40 (47.6)	193 (33.9)	
College or trade education	44 (52.4)	377 (66.1)	
Income, n (%)			$\chi^2(3) = 1.1,\ 0.78$
< $50,000	28 (33.3)	180 (31.6)	
$50,000-100,000	35 (41.7)	216 (37.9)	

>$100,000	15 (17.9)	123 (21.6)	
Declined to answer	6 (7.1)	51 (8.9)	
Marital status, n (%)			$\chi^2(1) = 0.004,\ 0.95$
Single/Divorced/Widowed	28 (33.3)	192 (33.7)	
Married/common law	56 (66.7)	378 (66.3)	
Has children (%)	52 (61.9)	405 (71.1)	$\chi^2(1) = 2.9,\ 0.088$
Current smoker (%)	14 (16.7)	106 (18.6)	$\chi^2(1) = 0.16,\ 0.69$
HADS-A ≥8, n (%)[b]	54 (65.1)	184 (32.4)	$\chi^2(1)$ 33.3, <0.0001
HADS-A ≥11, n (%)[b]	32 (38.6)	69 (12.1)	$\chi^2(1) = 38.5$, <0.0001
HADS-D ≥8, n (%)[c]	34 (40.5)	106 (18.7)	$\chi^2(1) = 20.6$, <0.0001
HADS-D ≥11, n (%)[c]	14 (16.7)	36 (6.3)	$\chi^2(1) = 11.0$, <0.001
Lifetime history MDD, n (%)	56 (66.7)	205 (36.0)	$\chi^2(1) = 28.8$, <0.0001
Lifetime history GAD, n (%)	18 (21.4)	40 (7.0)	$\chi^2(1) = 18.8,\ 0.0001$
Age at IMID diagnosis (years), mean (SD)[d]	33.2 (13.7)	35.6 (13.6)	H(1) = 2.8, 0.14
Active disease, n (%)[e]	29 (35.8)	138 (25.0)	$\chi^2(1) = 4.3,\ 0.038$

IMID = immune-mediated inflammatory disease, MS = multiple sclerosis, IBD = inflammatory bowel disease, RA = rheumatoid arthritis, MDD = major depressive disorder, GAD = generalized anxiety disorder, H = test statistic for Kruskal Wallis test, a-Missing for 2 persons without social phobia; b-Incomplete for 1 person with social phobia and 2 without social phobia; c-Incomplete for 2 persons without social phobia; d-Missing for 5 persons without social phobia; e-Missing for 3 persons with social phobia and 17 persons without social phobia

Table 4. Odds ratios (95% confidence intervals) for association of sociodemographic and clinical factors with lifetime social phobia

Variable	**Model 1**	**Model 2[a]**	**Model 3[b]**
IMID			
MS	1.00	1.00	1.00
IBD	1.31	1.32	1.33
	(0.75 – 2.62)	(0.74 – 2.36)	(0.71 – 2.48)
RA	1.80	**2.26**	**2.38**
	(1.00 – 3.22)	**(1.19 – 4.31)**	**(1.20 – 4.69)**

Age		0.98	0.98
		(0.97 – 1.00)	(0.97 – 1.00)
Gender			
Female		1.00	1.00
Male		0.92	0.89
		(0.51 – 1.65)	(0.49 – 1.63)
Education			
≤High school		**1.74**	**1.93**
		(1.[illegible] – 2.85)	**(1.17 – 3.18)**
>High school		1.00	1.00
Race			
White		1.00	1.00
Non-white		0.92	0.96
		(0.479 – 1.71)	(0.51 – 1.82)
Lifetime major depressive disorder			
Absent		1.00	1.00
Present		**3.17**	**3.06**
		(1.92 – 5.25)	**(1.83 – 5.13)**
Lifetime generalized anxiety disorder			
Absent		1.00	1.00
Present		**2.44**	**2.39**
		(1.26 – 4.67)	**(1.22 – 4.66)**
Active disease			
Absent			
Present			1.0
			1.09
			(0.62 – 1.91)
c-statistic	0.56	0.73	0.73
HLGOF (X^2) [p-value]		6.88 [0.55]	4.10 [0.85]

IMID = immune-mediated inflammatory disease, MS = multiple sclerosis, IBD = inflammatory bowel disease, RA = rheumatoid arthritis, HLGOF = Hosmer Lemeshow Goodness of Fit

a- IBD vs. RA OR 0.58; 95%CI: 0.31-1.12; b- IBD vs. RA OR 0.56; 95%CI: 0.29-1.08

Figure 1. Fear-provoking situations among participants with lifetime social phobia.

IMID = immune-mediated inflammatory disease, MS = multiple sclerosis, IBD = inflammatory bowel disease, RA = rheumatoid arthritis

Highlights

- Social phobia is common in persons with immune-mediated inflammatory diseases
- Rheumatoid arthritis was associated with social phobia more often than MS
- The most common fear-provoking situations differed across immune diseases

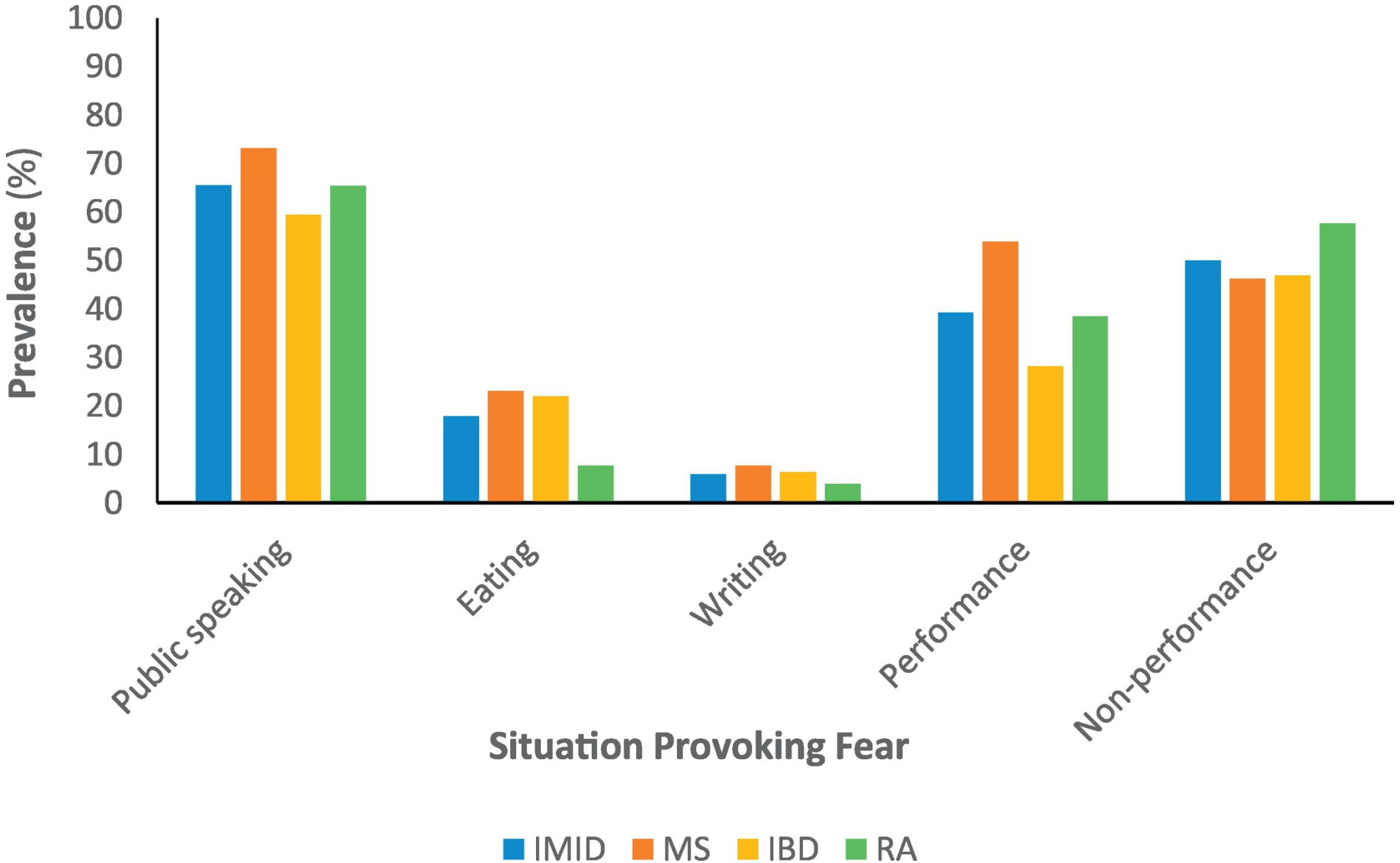
100
90
80
70
60
50
40
30
20
10
0
Prevalence (%)
Public speaking
Eating
Writing
Performance
Non-performance
Situation Provoking Fear
IMID
MS
IBD
RA

Figure 1