International Journal of Rheumatic Diseases

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International Journal of Rheumatic Diseases

ORIGINAL ARTICLE OPEN ACCESS

Females With Axial Spondyloarthritis Have Longer Diagnostic Delay and Higher Burden of the Disease. Results From the International Map of Axial Spondyloarthritis (IMAS)

Victoria Navarro-Compán[1] | Marco Garrido-Cumbrera[2,3] | Denis Poddubnyy[4,5] | Christine Bundy[6] | Souzi Makri[7] | José Correa-Fernández[2] | Shashank Akerkar[8] | Jo Lowe[9] | Elie Karam[10] | Fernando Sommerfleck[11]

[1]Hospital Universitario La Paz, Madrid, Spain | [2]Health & Territory Research (HTR), Universidad de Sevilla, Seville, Spain | [3]Spanish Federation of Spondyloarthritis Patient Associations (CEADE), Madrid, Spain | [4]Charité-Universitätsmedizin Berlin, Berlin, Germany | [5]German Rheumatism Research Centre, Berlin, Germany | [6]Cardiff University, Cardiff, UK | [7]Cyprus League for People With Rheumatism (CYLPER), Nicosia, Cyprus | [8]Mumbai Arthritis Clinic, Mumbai, India | [9]Axial Spondyloarthritis International Federation (ASIF), London, UK | [10]Canadian Spondylitis Association (CSA), Toronto, Canada | [11]Sanatorio Julio Mendez, Buenos Aires, Argentina

Correspondence: Marco Garrido-Cumbrera (mcumbrera@us.es)

Received: 27 June 2024 | **Revised:** 13 November 2024 | **Accepted:** 18 November 2024

Funding: This work was supported by Novartis Pharma.

Keywords: axial spondyloarthritis | diagnostic | disease burden | gender

ABSTRACT

Background: To assess gender differences in a large sample of patients included in the International Map of Axial Spondyloarthritis (IMAS) study from around the globe.

Method: IMAS is a cross-sectional online survey (2017–2022) of 5557 unselected axSpA patients from 27 countries. The current analysis assessed differences between males and females for: sociodemographic, health behaviors, disease characteristics, patient-reported outcomes, mental comorbidities, and treatments. Univariable and multivariable logistic regression analysis was used to evaluate the relationship between gender and disease characteristics, patient-reported outcomes, comorbidities, and treatments.

Results: Data from 5555 patients reporting gender were analyzed: 3492 from Europe, 769 from North America, 600 from Asia, 548 from Latin America, and 146 from Africa. Globally, 55.4% were females, with higher proportions in South Africa (82.2%) and lower in Asia (20.8%). Compared to males, a lower percentage of females smoked and consumed alcohol. The diagnostic delay was significantly longer (+2.4 years) in females, while the frequency of HLA-B27 positivity of axSpA was lower in females. The use of axSpA pharmacological treatment was more common in females with a higher proportion having ever taken nonsteroidal anti-inflammatory drugs (NSAIDs), conventional synthetic DMARDs (csDMARDs), and biologic DMARDs (bDMARDS).

Conclusions: Identifying the specific disease characteristics associated with gender in patients with axSpA may help to improve the diagnosis and management of the disease, and thereby reduce the disease burden for patients around the world.

1 | Introduction

Axial spondyloarthritis (axSpA) is a chronic inflammatory condition affecting predominantly the spine and sacroiliac joints [1]. Although this condition can affect both males and females, there are differences in gender in terms of prevalence, clinical presentation, disease characteristics, and response to treatment.

Albeit axSpA has been recognized as a disease that predominantly affects males [2], recent studies, including early onset axSpA show a similar prevalence among gender [3]. Females often experience longer delayed diagnosis or an underestimation of their symptoms due to the erroneous historical assumption that the disease mainly affects males [4]. This can lead to poor disease management coupled with delay in initiating appropriate treatment [5].

Females with axSpA may be more likely to report peripheral symptoms, compared to males, who often show more axial impairment [4]. Furthermore, females with axSpA usually have higher disease activity and greater functional limitations [6–8]. In addition, females commonly experience greater extramusculoskeletal manifestations such as inflammatory bowel diseases or peripheral manifestations such as arthritis and enthesitis [5, 8, 9].

AxSpA can have a significant psychological and social impact on females, especially in areas related to self-esteem and quality of life. Compared to males, females have poorer levels of mental health including the presence of anxiety and depression [10].

There is some evidence to suggest that females may have a worse efficacy and response to treatments with biologic therapies than males [4], although this remains to be explored due to the scarcity of studies evaluating this.

As studies comparing gender differences of axSpA patients worldwide are scarce, the present report takes on special relevance. We assessed gender differences in a large sample of patients included in the International Map of Axial Spondyloarthritis (IMAS) study to understand the female experience of axSpA worldwide.

2 | Methods

2.1 | Survey Design and Development

The IMAS initiative is a research collaboration between the Axial Spondyloarthritis International Federation (ASIF), the Health and Territory Research (HTR) group of the University of Seville, and Novartis Pharma AG, together with a scientific committee composed of axSpA patient representatives, rheumatologists, psychologists, and health researchers. The study involves 27 countries worldwide: Argentina, Austria, Belgium, Brazil, Canada, Colombia, Costa Rica, France, Germany, India, Italy, Korea, Lithuania, Mexico, Netherlands, Norway, Philippines, Russia, Slovenia, South Africa, Spain, Sweden, Switzerland, Taiwan, Turkey, United Kingdom, and USA. The IMAS questionnaire was originally developed in Spanish and subsequently translated into the official language of each of the 27 participating IMAS countries. More information about design and dissemination of the survey has been already described in the seminal manuscripts on European [11] and International level [12, 13].

2.2 | Sample Selection and Recruitment

Ipsos and local patient organizations recruited unselected patients through an online survey between 2017 and 2022 (Figure 1). Eligibility criteria for IMAS participants included higher age than 18 years, residing in one of the selected countries, and self-reported diagnosis of axSpA (either ankylosing spondylitis—AS also referred to as radiographic (r-) axSpA or nonradiographic (nr-) axSpA).

2.3 | Collected Data

Sociodemographic characteristics, lifestyle, disease characteristics, mental comorbidities (self-reported prior anxiety, depression, and sleep disorders), and pharmacological treatments are described in Table S1.

Patient-reported outcomes were collected from the following scales:

- **Bath Ankylosing Spondylitis Disease Activity Index (BASDAI):** a self-administered instrument that evaluates disease activity in patients with axSpA. The overall BASDAI has a range from 0 to 10. Cut-off point at 4 indicates active disease (BASDAI $\geq$4) [14].
- **Spinal Stiffness Index:** an index developed by the University of Seville specifically for the IMAS survey to assess the degree of spinal stiffness experienced by patients in the spinal column, distinguishing between the cervical, dorsal, and lumbar areas. The index ranges between 3 and 12 points. Higher values of the index indicate greater spinal stiffness [15].
- **Functional Limitation Index:** an index developed by the University of Seville specifically for the IMAS survey to assess the degree of limitation in 18 activities of daily life. The index ranges between 0 and 54 points. Higher

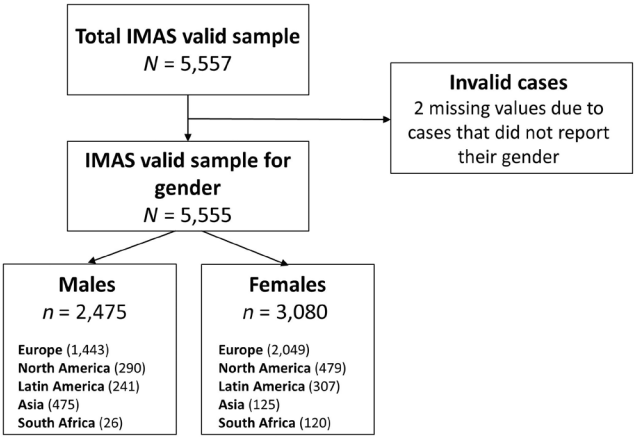

FIGURE 1 | Flowchart of the study sample selection.

values of the index indicate higher functional limitation [15].

- **12-item General Health Questionnaire (GHQ-12):** it is a screening measure of common mental health disorders in the general population, including symptoms of anxiety, depression, social dysfunction, and loss of confidence [16, 17]. The overall GHQ-12 has a range from 0 to 12. Cut-off point at 3 indicates risk of poor mental health (GHQ score ≥ 3).

2.4 | Statistical Analysis

The gender options included "female," "male," and "other", although only two participants responded "other", which has been excluded from the present analysis. IMAS cohort was divided into two categories: males and females. Mann–Whitney test was used to compare gender (males and females) with sociodemographic characteristics, health behaviors, disease characteristics, patient-reported outcomes, mental comorbidities, and treatments. SPSS 26.0 version was used to conduct the analysis.

3 | Results

Data from 5555 patients reporting gender were analyzed: 3492 from Europe, 769 from North America, 600 from Asia, 548 from Latin America, and 146 from South Africa. Globally, 55.4% were females, with higher proportions in South Africa (82.2%) and lower in Asia (20.8%; Figure 2).

With respect to sociodemographic characteristics and lifestyle factors, in comparison with males, females were younger, with higher educational level, less frequent members of patient organizations, and are less likely to smoke and consume alcohol (Table 1).

Regarding disease characteristics in Table 2, females had fewer years of symptom duration than males at the time where data were collected, experienced a longer diagnostic delay, had a lower proportion of HLA-B27 positive test results, and were less likely to report uveitis but more likely to report psoriasis than males. There was no difference between genders for reported inflammatory bowel disease. In addition, the use of NSAIDs, csDMARDS, and bDMARDs was higher in females (Table 2).

Compared to males, females with axSpA had higher disease activity (5.7 vs. 5.0), with especially high levels of fatigue (6.3 vs. 5.4) and neck, back, or hip pain (6.0 vs. 5.4, all $p < 0.001$). Females presented greater functional limitation (21.2 vs. 18.1 of males), with high limitation in 19.5% of females (16.3% of males, all $p < 0.001$). Although the spinal stiffness index was similar between males and females (7.5 and 7.6, respectively), males presented acute stiffness in cervical region (19.0% vs. 13.9%, $p < 0.001$) and in dorsal region (15.0% vs. 12.1%, $p = 0.041$), while acute stiffness in the lumbar region was found in females (30.2% vs. 25.0%, $p < 0.001$). Compared to males, females presented poorer mental health (5.1 vs. 4.2, $p < 0.001$), with greater stress, feelings of unhappiness or depression, less enjoyment of daily activities, and less concentration. In addition, females reported a higher proportion of mental comorbidities such as sleep disorders (41.4% vs. 30.3%), anxiety (39.2% vs. 27.0%), and depression (34.4% all $p < 0.001$; Table 3).

Results on sociodemographic, lifestyles, disease characteristics, patient-reported outcomes, mental comorbidities, and treatments by gender for each of the regions are shown in Table S2.

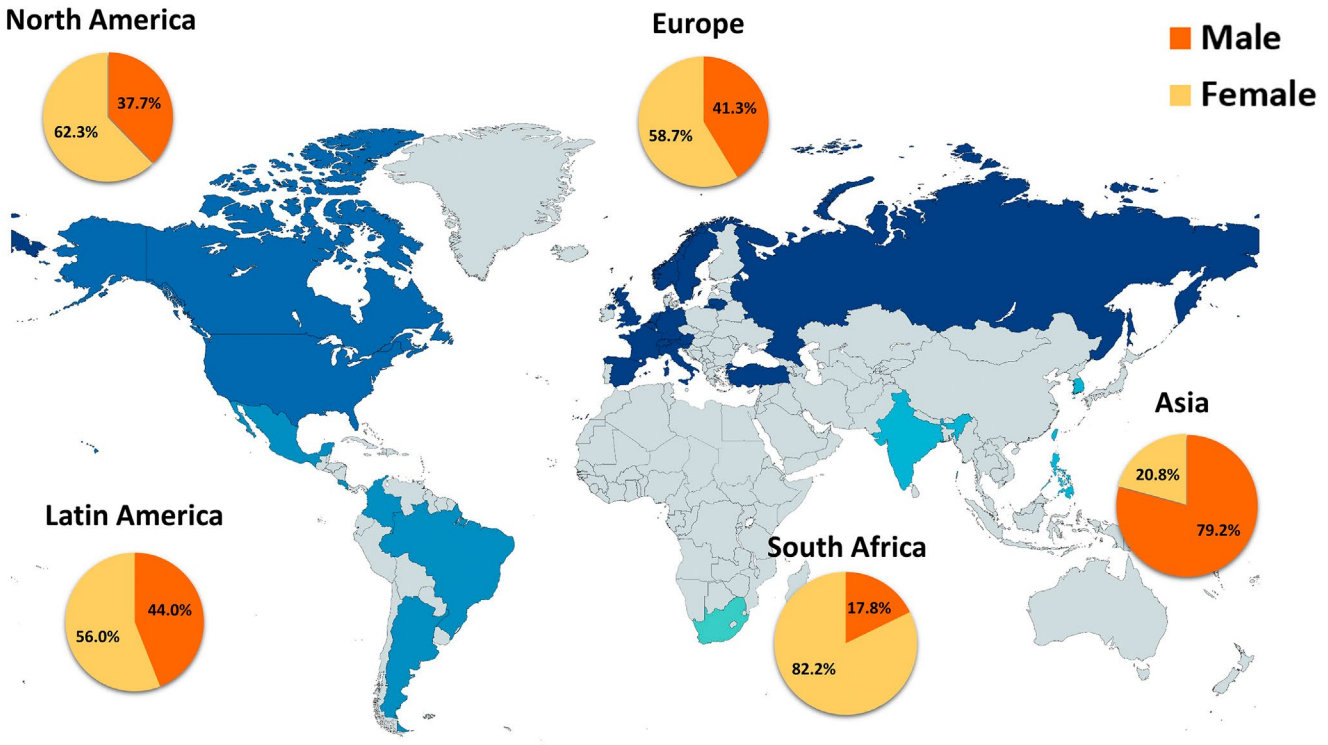

FIGURE 2 | Gender proportions by region.

TABLE 1 | Sociodemographic and lifestyle characteristics stratified by gender.

	Mean ± SD or *n* (%)		
	Male 2475 (44.6%)	**Female 3080 (55.4%)**	***p***
Sociodemographic			
Age	44.9 ± 13.6	43.2 ± 12.1	**< 0.001**
Educational level. University	1064 (43.0)	1505 (48.9)	**< 0.001**
Patient organization membership	1113 (45.0)	1293 (42.0)	**0.025**.
Lifestyle			
Smoking	548 (23.3)	580 (19.7)	**0.002**
Alcohol consumption	823 (33.8)	808 (26.7)	**< 0.001**
Physical activity. Yes	1993 (81.3)	2473 (81.8)	0.640

Note: Bold values represent statistical significance ($p < 0.05$).

TABLE 2 | Disease characteristics and pharmacological treatments stratified by gender.

	Mean ± SD or *n* (%)		
	Male 2475 (44.6%)	**Female 3080 (55.4%)**	***p***
Disease characteristics			
Age at symptom onset	26.7 ± 11.5	26.9 ± 11.2	0.188
Diagnostic delay	6.1 ± 7.8	8.5 ± 9.7	**< 0.001**
Symptom duration	18.1 ± 13.9	16.3 ± 12.7	**< 0.001**
HLA-B27 Positive	1115 (78.9)	1348 (65.8)	**< 0.001**
Inflammatory bowel disease	324 (14.2)	399 (13.9)	0.737
Uveitis	564 (25.3)	607 (21.5)	**0.002**
Psoriasis	172 (17.3)	289 (22.7)	**0.002**
Treatment			
NSAIDs	1729 (75.5)	2190 (81.2)	**< 0.001**
csDMARDs	933 (41.3)	1206 (45.5)	**0.003**
bDMARDs	1093 (47.1)	1362 (50.2)	**0.030**

Abbreviations: bDMARDs, biological disease–modifying antirheumatic drugs; csDMARDs, conventional synthetic disease–modifying antirheumatic drugs; NSAIDs, nonsteroidal anti-inflammatory drugs.
Note: Bold values represent statistical significance ($p < 0.05$).

4 | Discussion

The present study on axSpA patients from the IMAS global study showed how females had worse patient-reported outcomes, namely disease activity, functional limitations, and mental health, as well as longer time to diagnosis. Although the spinal stiffness index was similar between males and females, males presented higher stiffness in cervical and dorsal, while females had higher stiffness in the lumbar region.

Although historically axSpA was considered a predominantly male disease [2], more recent studies have shown that axSpA affects both males and females, although with differences in clinical presentation and disease progression. Females tend to have fewer visible radiographic signs, which has led to delayed or misdiagnosis in the past [4, 5]. Therefore, it is now recognized internationally that the prevalence of axSpA is balanced between genders, with females experiencing nonradiographic forms of the disease in greater proportion [5].

One of the key points of gender differences in axSpA relates to the diagnostic delay, with females from IMAS having a longer diagnostic delay for more than 2 years compared to males. In this sense, females often face a later diagnosis or an underestimation of their symptoms due to the erroneous belief that the disease mainly affects males [2, 4]. This may be because females present with different early symptoms than males. In addition, it has been shown that females with axSpA need a higher number of visits to different specialists in order to have a diagnosis [18]. This may lead to a delay in initiating appropriate treatment,

TABLE 3 | Patient-reported outcomes and mental comorbidities.

	Mean ± SD or *n* (%)		
	Male 2475 (44.6%)	**Female 3080 (55.4%)**	***p***
Patient-reported outcomes			
BASDAI (0–10)	5.0 ± 2.2	5.7 ± 2.0	**< 0.001**
-Fatigue	5.4 ± 2.5	6.3 ± 2.4	**< 0.001**
-Neck, back, or hip pain	5.4 ± 2.6	6.0 ± 2.4	**< 0.001**
-Pain other than neck, back, or hip	4.3 ± 2.8	4.8 ± 2.7	**< 0.001**
-Discomfort to touch or pressure	4.2 ± 2.8	5.3 ± 2.7	**< 0.001**
-Morning stiffness level	5.0 ± 2.8	5.6 ± 2.7	**< 0.001**
-Morning stiffness duration	3.9 ± 2.9	4.4 ± 3.0	**< 0.001**
Functional limitation index (0–54)	18.1 ± 15.2	21.2 ± 15.3	**< 0.001**
-Low	1345 (55.0)	1374 (45.3)	**< 0.001**
-Medium	703 (28.7)	1068 (35.2)	
-High	398 (16.3)	592 (19.5)	
Spinal stiffness index (3–12)	7.5 ± 2.6	7.6 ± 2.4	0.279
-Cervical region. Acute stiffness	458 (19.0)	416 (13.9)	**< 0.001**
-Dorsal region. Acute stiffness	361 (15.0)	370 (12.1)	**0.041**
-Lumbar region. Acute stiffness	603 (25.0)	903 (30.2)	**< 0.001**
GHQ-12 (0–12)	4.2 ± 4.0	5.1 ± 4.1	**< 0.001**
-Concentration. Less than usual	781 (32.6)	1403 (47.5)	**< 0.001**
-Lost sleep worrying. Less than usual	911 (38.1)	1394 (47.2)	**< 0.001**
-Playing useful part in things. Less than usual	750 (31.3)	1217 (41.2)	**< 0.001**
-Capable of decision. Less than usual	531 (22.2)	815 (27.6)	**< 0.001**
-Under strain. Less than usual	1026 (42.9)	1577 (53.3)	**< 0.001**
-Feel cannot overcome difficulties. Less than usual	898 (37.5)	1353 (45.8)	**< 0.001**
-Enjoy daily activities. Less than usual	1009 (42.2)	1470 (49.7)	**< 0.001**
-Face up to problems. Less than usual	709 (29.6)	981 (33.2)	**< 0.001**
-Feel unhappy/depress. Less than usual	1005 (42.0)	1471 (49.8)	**< 0.001**
-Lost confidence. Less than usual	908 (37.9)	1311 (44.4)	**< 0.001**
-Feel worthless. Less than usual	677 (28.3)	1044 (35.3)	**< 0.001**
-Feel happy. Less than usual	755 (31.6)	1051 (35.6)	**0.002**
Mental comorbidities			
Anxiety	623 (27.0)	1149 (39.2)	**< 0.001**
Depression	620 (26.8)	1007 (34.4)	**< 0.001**
Sleep disorders	696 (30.3)	1206 (41.4)	**< 0.001**

Note: Bold values represent statistical significance ($p < 0.05$).

which could result in disease progression. Furthermore, in relation to this longer diagnostic delay, females in the IMAS cohort were also associated with lower HLA-27 test positivity, confirming previous studies [19]. Therefore, physicians could be advised to listen to females who present with different symptoms than males, as well as to continue research specifically on the female experience.

IMAS results also showed that females reported higher disease activity—especially high levels of fatigue and neck, back, or hip

pain—and greater functional limitation compared to males. In particular, females reported fatigue, back pain, and longer morning stiffness in previous studies [5, 19]. Despite apparently suffering less structural spinal damage compared to males with axSpA, females experience greater limitations in physical function [20].

It is important to emphasize the result on the greater functional limitation in females as this index includes daily activities such as dressing, bathing, grooming, tying shoe laces, moving about the house, climbing stairs, getting into/out of bed, using the bathroom, shopping, preparing meals, eating, household cleaning, walking down the street, using public transportation, going to the doctor, driving, doing physical exercise, and having sexual intercourse. Most of these items of the functional limitation index refer to daily activities that females—being in most households the main housewives and caregivers—often have to combine, such as caring for children and family members, household activities, as well as carrying out their professional life [21, 22].

Females in the IMAS cohort showed poorer mental health compared to males, particularly greater stress, feeling of unhappinnes or depression, less enjoyment of daily activities, and less concentration. In addition, females with axSpA from IMAS had a higher prevalence of mental comorbidities such as anxiety, depression, and sleep disorders. In this vein, patients with rheumatic and musculoskeletal diseases are more likely to suffer from anxiety, depression, and insomnia due to low socioeconomic status, increased pain, or worsening of rheumatic disease [23], with worse outcomes such as disease activity, physical function, and quality of life in the case of females [24]. Special attention should be to females with autoimmune diseases and mental health issues who respond poorly to antidepressants and/or antipsychotic medication [25]. According to the IMAS study, females with axSpA, besides showing a poorer mental health—measured through the GHQ-12 scale—more frequently reported depression, anxiety, and sleep disorders. Mental health management is vital in patients with autoimmune rheumatic disease as psychological distress is consistently associated with poorer disease outcomes [26].

With respect to extra-musculoskeletal manifestations, females with axSpA in IMAS cohort are more likely to have psoriasis and less likely to have uveitis compared to males. In this vein, a recent study showed that, compared to males with axSpA, females were more likely to suffer from psoriasis, a common comorbidity in this group [5]. In addition, females with axSpA tend to be less likely to suffer from uveitis, a common ocular complication in this disease [27]. This gender difference in the clinical manifestation of axSpA highlights the importance of gender-specific management and treatment strategies.

Females with axSpA from IMAS showed a higher proportion of use of treatments such as NSAIDs, csDMARDs, and bDMARDs. This higher proportion of medication consumption may be due to the greater impact of the disease on females. However, compared to males, there is evidence of less efficacy of treatments in females, especially biologics [4]. Reduced efficacy to treatment could be due to misdiagnosis or the influence of comorbidities. In this regard, according to the latest ASAS-EULAR 2022 update, the first check that should be made after bDMARD failure is whether the diagnosis was correct or whether the symptoms are due to comorbidities [28]. Nevertheless, this topic should be treated with caution due to the lack of studies confirming gender differences in the efficacy of pharmacological treatments.

Significant disparities in gender differences were found for each of the IMAS regions. Specifically, in relation to diagnostic delay, disease activity, functional limitation, and mental health. In Europe and North America, females had to wait 2–4 years longer to be diagnosed than males. In contrast, in Asia, males had to wait a year longer to be diagnosed than females. In addition, Europe, Latin America, and Asia showed significantly higher disease activity in females compared to males. Functional limitation was higher in European and North American females compared to males, however, for Latin America, Asia, and South Africa this difference was not statistically significant. Compared to males, females in Europe, Latin America, and Asia presented poorer mental health, although the highest proportion of females diagnosed with anxiety and depression was found in South Africa. These gender differences may be determined by aspects such distinctions in disease manifestations, phenotypes and therapeutic response. However, cultural aspects such as the multiplicity of roles that females in certain regions endure, with additional responsibilities such as home and family care, could increase stress, reducing adherence to treatment and medical recommendations. Similarly, as in some countries, females may face barriers to access adequate diagnosis and treatment due to social and economic factors.

Considering the individual differences in the experience of axSpA, physicians should assess each patient individually, providing a personalized and holistic management and treatment approach, focusing on their specific needs and symptoms, with special emphasis on the patient's gender, comorbidities, and contextual factors.

IMAS is not without limitations. First, the survey was based on self-reported data, with confirmation of the diagnosis by a physician. However, from comparison of the phenotypic characteristics of the IMAS patients with that of other cohorts of patients with axSpA in which physicians recruited axSpA patients, the risk of misdiagnosis in this group was not significantly higher than that in any other epidemiologic study of axSpA. Furthermore, several studies have investigated the validity of online surveys compared to traditional methods such as mail or face-to-face interviews, indicating comparable validity and reliability of data between the two methods [29–31]. In addition, online data collection could exclude some patients who are older or have lower Internet literacy. The use of invalidated scales or indices to assess functional limitations in daily activities and spinal stiffness is another limitation. In addition, not all countries have the same sample size, which gives greater weight to countries with a larger sample. Another limitation of the study is that no data were not collected from patients in China or Japan. Furthermore, in Africa, data were only collected from the South African region. Finally, the proportion of females is slightly higher than males, although we recognize that females are more likely to participate in online surveys [3].

Despite these limitations, the IMAS study is robust due to its large sample size and the consistency of its results with previous studies. In addition, IMAS encompasses the perspective of patients from countries around the world, along with the rigorous knowledge of an international and multidisciplinary panel of axSpA experts.

5 | Conclusion

Globally, although females with axSpA reported healthier behaviors and lower frequency of HLA-B27 positivity than males, they had greater diagnostic delay. Despite receiving medication more frequently, females in this IMAS study had higher disease activity, greater functional limitation, and poorer mental health. Although each patient is unique and may have a different experience of the disease, understanding gender-associated characteristics in axSpA is crucial for reducing the disease burden and diagnostic delay in females to improving axSpA care globally.

Author Contributions

V.N.-C., M.G.-C., D.P., F.S., C.B., S.M., J.C.-F., S.A., J.L., and E.K. contributed to the study conception and design. All authors contributed to the analysis and interpretation of data, made significant contributions to drafting and revising the article, provided intellectual content of critical importance to the work and approved the final version to be published.

Acknowledgments

We would like to thank all axial spondyloarthritis patients and patient organizations who participated in the IMAS study.

Ethics Statement

The present report does not contain any studies with animal subjects. All participants were asked to provide explicit opt-in consent prior to participating in the IMAS survey. Furthermore, the participants' data were anonymized and did not contain confidential, personal, or subject-identifying information. Ethical aspects related to data extracted from patients and their treatment were in accordance with the Declaration of Helsinki.

Conflicts of Interest

Victoria Navarro-Compán Speakers bureau: AbbVie, Eli Lilly, Janssen, MSD, Novartis, Pfizer, UCB Pharma, Consultant of: AbbVie, Eli Lilly, Galapagos, MoonLake, MSD, Novartis, Pfizer, UCB Pharma, Grant/research support from: AbbVie, Novartis, Marco Garrido-Cumbrera Grant/research support from: Novartis, Denis Poddubnyy Speakers bureau: AbbVie, BMS, Celgene, Janssen, Lilly, MSD, Novartis, Pfizer, Roche and UCB, Grant/research support from: AbbVie, MSD, Novartis, and Pfizer, Christine Bundy Speakers bureau: AbbVie, Celgene, Janssen, Lilly, Novartis and Pfizer, Souzi Makri Consultant of: Novartis, GSK and Bayer, José Correa-Fernández: None declared, Shashank Akerkar Speakers bureau: Pfizer, Novartis, Eli Lilly, Jansen, Jo Lowe Jo Lowe Grant/research support from: No personal funding, but ASIF has received funding from Novartis, UCB, Lilly, Abbvie, Boehringer Ingleheim, Pfizer, Janssen, Elie Karam: None declared, Fernando Sommerfleck Speakers bureau: Abbvie, Eli Lilly, Janssen, Novartis, Consultant of: Abbvie, Novartis, Janssen.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patient and Public Involvement

Not applicable.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.