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RESEARCH

Sex differences in schizophrenia spectrum disorders: insights from the DiAPAson study using a data-driven approach

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Abstract

Purpose Schizophrenia Spectrum Disorders (SSD) display notable sex differences: males have an earlier onset and more severe negative symptoms, while females exhibit affective symptoms, better verbal abilities, and a more favourable prognosis. Despite extensive research, areas such as time perception and positivity remain underexplored, and machine learning has not yet been adequately utilised. This study aims to address these gaps by examining sex differences in a sample of Italian patients with SSD using a data-driven approach.

Methods As part of the DiAPAson project, 619 Italian patients with SSD (198 females; 421 males) were assessed using standardised clinical tools. Data on socio-demographics, clinical characteristics, symptom severity, functioning, positivity, quality of life (QoL), and time perspective were collected. Descriptive and regression analyses were conducted. Principal Component Analysis (PCA) and the Gaussian Mixture Model (GMM) was used to define data-driven clusters. A leave-one-group-out validation was performed.

Results Males were more likely to be single ($p < 0.001$) and less educated ($p = 0.006$), while females smoked more tobacco ($p = 0.011$). Males were more frequently prescribed antipsychotics ($p = 0.022$) and exhibited more severe psychiatric ($p = 0.004$) and negative symptoms ($p = 0.013$). They also had a less negative perception of past events ($p = 0.047$) and a better view of their psychological condition ($p = 0.004$). Females showed better interpersonal functioning ($p = 0.008$). PCA and GMM revealed two main clusters with significant sex differences ($p = 0.027$).

Conclusion This study identifies sex differences in SSD, suggesting tailored treatments such as enhancing interpersonal skills for females and maintaining positive self-assessment for males. Using machine learning, we highlight distinct SSD phenotypes, emphasising the need for sex-specific interventions to improve outcomes and QoL. Our findings stress the importance of a multifaceted, interdisciplinary approach to address sex-based disparities in SSD.

Trial registration ISRCTN registry ID ISRCTN21141466.

Keywords Schizophrenia spectrum disorder · Sex differences · Time perception · Positivity · Machine Learning

Introduction

The incidence, onset, and clinical course of several mental disorders differ by sex [1]. This is also the case for Schizophrenia Spectrum Disorders (SSD), which are chronic and debilitating mental disorders characterised by severe deficits in cognitive functions, emotional regulation, and perceptual experiences, often leading to highly compromised global functioning, physical health, and overall well-being [2–5].

While meta-analyses have found no significant differences between males and females in point prevalence of schizophrenia in the general population [6], significant sex differences have been observed in the incidence of the disorder [7].

In Italy, the last official mental health report released by the Ministry of Health [8] reports 28,738 residents in 2001 Residential Facilities (RFs) in the year 2022, equating

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to 5.7 residents per 10,000 inhabitants. Males were 34.4% more represented than females, with rates of 3.9 and 1.9 per 10,000, respectively. Among Day Centers, 22,196 users were reported (4.4 per 10,000), about half with SSD, and males (2.75 per 10,000) outnumbered females (1.35 per 10,000) by 34.1%. Community mental health services treat 30.6 individuals with schizophrenia per 10,000 inhabitants nationally, with a male rate 20.1% higher than the female rate (37.0 vs. 24.6 per 10,000).

The discrepancy between similar prevalence rates (equal in males and females) and higher incidence rates in males can be explained by a combination of biological, environmental, and social factors [9, 10]. Additionally, differences in the onset, symptom presentation, clinical course and functioning of people with this disorder are likely influenced by underlying sex differences [11–14]. Males with SSD experience earlier onset, more severe negative symptoms (e.g., apathy, social withdrawal), greater cognitive impairments (e.g., executive functioning, verbal memory), and a more severe course with frequent hospitalisations and poorer outcomes [15]. Females, however, are more prone to affective symptoms (e.g., depression, anxiety), have better verbal abilities, longer remission, superior functioning, and better response to treatment, though with higher risks of side effects like weight gain [10, 15–22]. Premorbidly, females show higher education, social functioning, and support [23], which persist post-onset, leading to better adaptation and greater life satisfaction [10, 21, 24, 25]. Males, clinging to unattainable goals, report more dissatisfaction [10], poorer global functioning, and higher disability [26–28]. Overall, females report better quality of life (QoL), well-being, and self-esteem [29, 30].

The limited number of Italian studies on sex differences in patients with SSD has consistently highlighted similar patterns of sex-based differences [31, 32].

As described, sex differences in SSD significantly influence onset, symptoms, prognosis, treatment response, and QoL [33]. Understanding these differences is essential to contribute to a more comprehensive understanding of the disorder and enable the development of more tailored and effective approaches to treatment and care. To deepen our understanding of critical sex differences in biological terms (distinct from gender identity or genetic variations), this study aimed to achieve two primary objectives.

The first objective was to examine sex differences in a large Italian sample of people with SSD, with a particular focus on exploring under-investigated areas such as time perception and positivity. Despite their potential to provide valuable insights, these domains have received limited attention in the literature.

The second objective was to apply machine learning (ML) techniques to identify subtle, specific patterns in sex differences associated with SSD.

According to the first outcome, time perception and its association with sex differences in patients with SSD have been very poorly studied, although timing and time perception are key issues for the psychopathology of schizophrenia [34, 35]. Patients with SSD typically have an unbalanced time perspective (defined as the *"nonconscious personal attitude that each of us holds towards time and the process whereby the continual flow of existence is bundled into time categories that help to give order, coherence, and meaning to our lives")* [36], a compromised automatic ability to expect and predict an event in time, and a psychological perception of time characterised by temporal fragmentation and disorganisation [37]. Time perception abnormalities in SSD are crucial to study, as they are associated with cognitive deficits, such as attention and memory impairments, which may impact daily functioning and QoL [38–40]. The internal clock hypothesis suggests a faster-running internal clock in these patients, though findings often point to increased variability in time perception instead [38, 41]. Furthermore, such time perception dysfunctions are linked to deficits in sustained attention, memory, and executive functioning, affecting social interactions and the sense of agency [42, 43]. Similarly, to date, no study has examined sex differences in positivity among SSD patients. Positivity, i.e. the tendency to view life and experiences positively [44], has been sparsely researched in patients with SSD. Existing studies suggest patients with SSD may have a reduced ability to anticipate and experience positive emotions and outcomes [45, 46]. Findings from our previous study showed that patients with SSD had similar positivity scores than a large sample of the general population, and higher positivity scores were associated with better QoL, fewer symptoms, and functioning [47], indicating that positivity might play a role in symptom management and reduction.

With regard to the second outcome, over the last few decades ML techniques have emerged as valuable tools in psychiatry, offering the ability to process complex, high-dimensional data and develop optimal models for classification. In particular, recent studies on schizophrenia have utilised ML clustering techniques (such as K-means or GMM) to better understand the diverse clinical profiles of individuals with this disorder, highlighting the potential for these methods to reveal nuanced patterns in symptom severity, functioning, and other key variables [50–54]. Thus, this paper aims to contribute to an improved phenotypic characterisation of people with SSD, highlighting latent and elusive sex differences. We tried to identify data-driven subgroups that may exhibit variations across sexes. By exploring potential differences across multiple interrelated dimensions, this cross-sectional study may help disentangle different traits and domains related to different sexes and contributes to the development of interventions which address both sex differences and subtypes

to enable personalised treatment strategies and ultimately improve the QoL of people with SSD.

Methods

Study setting: DiAPAson

In Italy, individuals with SSD receive treatment from 123 Departments of Mental Health (DMH). These DMHs offer various types of care, including outpatient care services, hospital care, and RFs. RFs are specifically designed to support and supervise individuals with significant psychosocial impairments who may struggle to manage their symptoms and daily activities independently [55–57].

DiAPAson procedure and participants

Between October 2020 and October 2021, a total of 619 patients, including 312 residents and 307 outpatients, who met the DSM-5 criteria required for an SSD diagnosis [58], were enrolled across 37 DMHs and 99 RFs throughout Italy as participants in the DiAPASon project [59]. Detailed information about the project can be found in the study protocol [59]. The DMHs enlisted both outpatients and residents, whereas RFs exclusively recruited residents. Inclusion and exclusion criteria can be found in Supplementary Fig. 1.

For residents, recruitment was conducted using an alphabetical list of individuals with SSD present on a designated day; patients from this list were consecutively invited to join the study.

Outpatients were community-dwelling patients with SSD who were approached consecutively at the outpatient units for potential participation until the recruitment target was achieved. Residents were recruited using an alphabetical list of patients with SSD present on an index day; based on this list, residents were consecutively invited to participate in the study. Overall, the project enrolled a total of 98 RFs, each recruiting an average of 3.3 ($\pm$2.6) residents, which corresponds to approximately 27% of patients within each RF. All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration [60] of 1975, as revised in 2008. All participants provided informed consent to participate. They were provided with comprehensive details about the study and were encouraged to seek clarification if needed. While the treating clinician administered some of the assessment tools, research assistants supported patients in completing self-reported questionnaires.

DiAPAson assessments

Clinical records and interviews with healthcare professionals were used to collect socio-demographic information, including biological sex. It is important to note that no questions regarding gender identity were included in the study.

Participants included in the DiAPAson project underwent a comprehensive evaluation using various standardised tools. Detailed information regarding the assessment can be found in the study protocol [59]. The assessment process involved a combination of clinician-administered instruments, self-reported questionnaires, and socio-demographic data, as reported in Supplementary Table 1.

Clustering

To gain a deeper insight into sex differences in the DiAPAson dataset, the participants were further characterised using ML clustering approaches. First, clusters were defined based on clinical scores and sub-scores that showed statistically significant differences between females and males among all DiAPAson participants. Prior to clustering, all clinical ratings were normalised between 0 and 1, and missing values for each score were imputed as the corresponding median value. A leave-one-group-out cross-validation (LOGO-CV) strategy [61] was used, in which all subjects from one of the 37 recruiting sites were on turn excluded from training and used as test data. Only non-self-correlating variables that were common across all iterations were used for clustering.

To further reduce the dimensionality of the dataset and enable a clearer visualization of the clusters, a Principal Component Analysis (PCA) [62] was performed on the remaining variables. The two most significant components extracted from the PCA were then used to define clusters using a Gaussian Mixture Model (GMM) [63]. The number of clusters for the GMM was determined based on the Bayesian information criterion (BIC).

Cluster validation

As no suitable external dataset was available to validate clustering consistency, the cluster assignments of the individual patients of each excluded group were compared in the LOGO-CV with those of the PCA-GMM model trained on the entire dataset. The selection of clinical variables, their normalisation, and data imputation followed the same procedures as in the LOGO-CV approach. Only the features that survived the process of handling self-correlating variables from the previous step were considered.

Statistical analysis

Quantitative variables were described using mean and standard deviation (SD) or median and interquartile range, while qualitative variables were presented as counts and percentages.

To simplify the analyses and reduce the number of age groups, we categorised ages 20 to 55 into three broader groups. This approach balances efficiency with the established practice of using age bands to capture key developmental stages and life transitions relevant to mental health.

Sociodemographic and clinical variables were compared between female and male participants using the $\chi 2$ test or Fisher's exact test for categorical variables and the t-test or Mann–Whitney test for continuous variables, as appropriate. All tests were two-sided with a significance level of 5%. All analyses were conducted using R version 4.3.1.

The ML framework used was based on the sci-kit-learn library version 1.3.2 [64] and Python version 3.10.12. Variable comparisons between the clusters were conducted using the same tests as described above. Analysis of Covariance (ANCOVA) with age as a covariate was used to assess the intra- and inter-sex differences in the DiAPAson dataset. The Bonferroni correction for multiple testing was used.

Results

Sociodemographic and clinical characteristics of female and male participants with SSD

As indicated in Table 1, the majority of participants were aged between 43 and 55 years. Although most participants were single, males were significantly more likely to be *single* ($p < 0.001$) compared to females.

While females exhibited a significantly greater number of *education years* than males ($p = 0.006$), no significant differences between sexes were found in terms of employment status, living arrangements, and support network. Considering collaboration skills, no significant differences were found between females and males. Females reported higher rates of daily *cigarette consumption* than males ($p = 0.011$).

There were no significant differences between sexes in terms of disorder duration and lifetime years of psychiatric hospitalisation. The sample predominantly used first- and/or second-generation *antipsychotics,* with a significantly higher prescription rate of such medications in males compared to females ($p = 0.022$), and a higher prescription rate of non-antipsychotics in females compared to males ($p < 0.001$).

Male participants exhibited a more severe clinical profile in terms of *psychiatric symptoms* ($p = 0.004$), as assessed by the BPRS, and *negative symptoms* assessed with the BNSS ($p = 0.013$). Specifically, males showed significantly higher levels of (i) *excitement* ($p < 0.001$) and severity of *positive* ($p = 0.050$), *negative* ($p < 0.001$), and *cognitive symptoms* ($p = 0.007$) according to the BPRS; and (ii) *anhedonia* ($p = 0.039$), *asociality* ($p = 0.008$), *avolition* ($p = 0.034$), and *blunted affect* ($p = 0.028$) according to the BNSS.

In contrast, females demonstrated better functioning in *interpersonal relationships* compared to males (SLOF; $p = 0.008$), with no significantly difference found in *self-reported functioning* (WHODAS 2.0; $p = 0.596$). They also tended to have a more negative or painful *perception of past experiences*, as indicated by ZTPI ($p = 0.047$). Male participants reported a more positive perception of their *psychological health* compared to females (WHOQOL-Bref; $p = 0.004$). There was no significant difference in *positivity* between the two sexes (P-Scale; $p = 0.590$).

Clustering of the DiAPAson group

Twelve clinical variables were initially selected to determine the clusters: BPRS Total Rating and Sub-rating for Negative symptoms, Cognitive symptoms and Excitement; BNSS Total Rating and Sub-rating for Anhedonia, Asociality, Avolition, Blunted affect; SLOF Sub-rating for Interpersonal relationships; WHOQOL Sub-rating for psychological domain; and ZTPI Sub-score for Past negative. After excluding the self-correlating variables, the BNSS Sub-rating for Anhedonia, Avolition, and Blunted affect were removed due to their correlation with the BNSS Total Score.

As shown in Table 2, which presents the demographic and clinical characteristics of the participants from the clusters defined in the LOGO-CV setting, the two clusters, named Cluster 0 and Cluster 1, comprised 359 (58.0%) and 260 (42.0%) subjects, respectively. The clusters differed significantly in terms of sex distribution ($p = 0.027$), as the number of female participants was 128 (35.5%) for Cluster 0 and 70 (26.6%) for Cluster 1. This cluster assignment matched the assignment in the model trained on the entire list of DiAPAson participants: 358 of 359 assignments (99.7%) matched for Cluster 0 and 258 of 260 assignments (99.2%) matched for Cluster 1. The results of the PCA-GMM model trained on the complete list of DiAPAson participants are illustrated in Supplementary Fig. 2.

As shown in Fig. 1 and detailed in Table 2, both the few clinical scores used for training (Fig. 1A) and many others that were not used for training (Fig. 1B) showed significant differences between the two clusters. Compared to participants in Cluster 1, those in Cluster 0 reported higher rates of residency in private accommodation ($p < 0.001$), support from family and friends ($p < 0.001$), collaboration skills ($p < 0.001$), and shorter duration of psychiatric hospitalisation ($p = 0.009$). Conversely, participants in Cluster 1 demonstrated significantly more severe psychopathology (BPRS; $p < 0.001$), negative symptoms (BNSS;

Table 1 Sociodemographic And Clinical Characteristics Of Patients With SSD

	FEMALE N = 198 (32.0%)	MALE N = 421 (68.0%)	p-value*
Age, n (%)			
20–30	25 (12.6%)	77 (18.3%)	0.108
31–42	60 (30.3%)	137 (32.5%)	
43–55	113 (57.1%)	207 (49.2%)	
Marital status, n (%)			
Single	150 (75.8%)	384 (91.2%)	**< .001**
Married or cohabiting	23 (11.6%)	20 (4.8%)	
Divorced or widowed	25 (12.6%)	17 (4.0%)	
Education (years)			
Mean (SD)	12.2 (3.2)	11.5 (3.0)	**0.006**
Median (Minimum; Maximum)	13 (1–23)	12 (2–21)	
Working status, n (%)			
Working	42 (21.2%)	86 (20.4%)	0.974
Studying	11 (5.6%)	24 (5.7%)	
Not working	145 (73.2%)	311 (73.9%)	
Living, n (%)			
Residential facility	93 (47.0%)	219 (52.0%)	0.278
Private accommodation (outcare)	105 (53.0%)	202 (48.0%)	0.278
Support network			
Family/friends highly collaborative	78 (39.4%)	166 (39.4%)	0.534
Family/Friends interested but not supportive	68 (34.3%)	157 (37.3%)	
Family/friends potentially available	29 (14.7%)	45 (10.7%)	
Absence of social support	23 (11.6%)	53 (12.6%)	
Collaboration skills			
Actively seeks treatment, willing to collaborate	107 (54.0%)	218 (51.8%)	0.073
Wants to be helped, but lacks motivation	67 (33.8%)	118 (28.0%)	
Passively accepts the treatment/intervention	18 (9.1%)	51 (12.1%)	
Does not show attention or compreh. for treatment efforts	5 (2.5%)	32 (7.6%)	
Actively refuses the treatment/intervention	1 (0.6%)	2 (0.5%)	
Smoking (cigarettes per day)			
Mean (SD)	14.8 (8.9)	10.6 (8.6)	**0.011**
Median (Minimum; Maximum)	15 (0–40)	20 (0–60)	
*Missing***	110	178	
Disorder duration (years)			
Mean (SD)	18.1 (9.1)	18.3 (9.7)	0.745
Median (Minimum; Maximum)	19 (2–40)	20 (0–49)	
Lifetime duration of psychiatric hospitalisation (years), n (%)			
< 1 years	99 (50.0%)	194 (46.1%)	0.495
1–5 years	53 (26.8%)	111 (26.4%)	
> 5 years	46 (23.2%)	116 (27.5%)	
Aps drugs			
Yes	190 (96.0%)	417 (99.0%)	**0.022**
No	8 (4.0%)	4 (1.0%)	
Non-Aps drugs			
Yes	141 (71.2%)	287 (68.2%)	**< .001**
No	57 (29.8%)	134 (32.8%)	
BPRS total rating, Mean (SD)	44.4 (13.9)	48 (15.2)	**0.004**
Depression/anxiety	15.0 (5.4)	15.1 (5.7)	0.939
Excitement	9.2 (4.0)	10.4 (4.8)	**< .001**

Table 1 (continued)

	FEMALE N = 198 (32.0%)	MALE N = 421 (68.0%)	p-value*
Positive symptoms	8.1 (3.9)	8.8 (3.9)	**0.050**
Negative symptoms	7.6 (3.8)	8.8 (3.9)	**< .001**
Cognitive symptoms	4.5 (1.9)	5.0 (2.4)	**0.007**
BNSS total rating, Mean (SD)	20.6 (15.5)	23.9 (15.7)	**0.013**
Anhedonia	4.9 (4.3)	5.7 (4.7)	**0.039**
Distress	1.8 (1.7)	1.8 (1.7)	0.817
Asociality	3.6 (2.9)	4.3 (3.1)	**0.008**
Avolition	3.5 (3.1)	4.0 (3.1)	**0.034**
Blunted affect	4.2 (4.4)	5.0 (4.6)	**0.028**
Alogia	2.5 (2.9)	3.0 (3.1)	0.057
SLOF total rating, Mean (SD)	181 (22)	178 (21)	0.065
Interpersonal Relationships	25.4 (5.9)	24.1 (5.6)	**0.008**
Activities	46.8 (8.1)	45.6 (7.6)	0.076
Work	21.4 (6.4)	20.7 (6.1)	0.264
WHODAS 2.0 total score, Mean (SD)	13.3 (9.2)	12.8 (9.3)	0.596
Missings	1	4	
WHOQOL-Bref total rating, Mean (SD)	87.7 (14.2)	89.3 (14.7)	0.216
Missings	6	7	
Physical domain	24.9 (4.5)	25.6 (4.8)	0.084
Psychological domain	18.7 (4.1)	19.7 (4.4)	**0.004**
Social relationship domain	9.8 (2.4)	9.5 (2.5)	0.072
Environment domain	27.6 (4.7)	27.8 (5.1)	0.494
ZTPI total score, Mean (SD)	184 (20.0)	182 (19.0)	0.392
Missings	6	9	
Past-Negative	35.5 (6.9)	34.3 (7.3)	**0.047**
Past-Positive	30.1 (5.3)	29.7 (5.4)	0.361
Present-Hedonistic	47.3 (8.6)	47.6 (8.4)	0.604
Present-Fatalistic	26.6 (6.0)	26.0 (6.1)	0.306
Future	44.1 (6.2)	44.6 (6.7)	0.428
POS, total score, Mean (SD)	27.4 (7.1)	27.7 (6.9)	0.590
Missings	1	3	

Aps = antipsychotics; Pts = patients

*Bold values indicate statistical significance at the $p < 0.05$ level

**The missing data include both non-smokers and unanswered responses

BPRS Brief Psychiatric Rating Scale, *BNSS* Brief Negative Symptom Scale, *SLOF* Specific Level of Functioning Scale, *WHODAS* World Health Organization Disability Assessment Schedule, *WHOQOL-Bref* World Health Organization Quality of Life-BREF, *ZTPI* Zimbardo Time Perspective Inventory, *POS* Positivity Scale

$p < 0.001$), poorer functioning (SLOF; $p < 0.001$) except for physical functioning ($p = 0.281$), higher self-reported disability/functioning (WHODAS; $p = 0.001$), and lower QoL (WHOQOL-Bref; $p = 0.001$), positivity (P-Scale; $p < 0.001$), and time perception (ZTPI; $p < 0.001$). Specifically, they scored lower in past-positive ($p = 0.003$), present-hedonistic ($p < 0.001$) and future time perspectives ($p < 0.001$) compared to participants in Cluster 0.

Intra- and Inter-sex differences between the clusters in the DiAPAson group

Figure 2 summarises intra- and inter-sex differences between the clusters, with hotter colours indicating lower p-values and thus higher statistical differences. As shown in the first two rows of the Fig. 2, there were few inter-sex (M vs F) differences in the clinical variables within Cluster 0 and Cluster 1, with the main differences observed

Table 2 Sociodemographic Characteristics Of Patients With Ssd For Each Cluster

	CLUSTER 0 N = 359 (58.0%)	CLUSTER 1 N = 260 (42.0%)	p-value*
Sex, n (%)			
Male	231 (64.3%)	190 (73.1%)	**0.027**
Female	128 (35.7%)	70 (26.9%)	
Age, n (%)			
20–30	50 (13.9%)	52 (20.0%)	0.298
31–42	127 (35.4%)	70 (26.9%)	
43–55	182 (50.7%)	138 (53.1%)	
Marital status, n (%)			
Single	303 (84.4%)	231 (88.9%)	0.263
Married or cohabiting	32 (8.9%)	11 (4.2%)	
Divorced or widowed	24 (6.7%)	18 (6.9%)	
Education (years)			
Mean (SD)	11.8 (3.0)	11.5 (3.1)	0.165
Median (Minimum; Maximum)	13 (2–23)	12 (1–21)	
Working status, n (%)			
Working	84 (23.4%)	44 (16.9%)	0.225
Studying	21 (5.8%)	14 (5.4%)	
Not working	254 (70.8%)	202 (77.7%)	
Living, n (%)			
Residential facility	157 (43.7%)	155 (59.6%)	**< 0.001**
Private accommodation (outcare)	202 (56.3%)	105 (40.4%)	
Support network, n (%)			
Family/friends highly collaborative	165 (46.1%)	79 (30.4%)	**< 0.001**
Family/Friends interested but not supportive	130 (36.3%)	95 (36.5%)	
Family/friends potentially available	34 (9.5%)	40 (15.4%)	
Absence of social support	29 (8.1%)	46 (17.7%)	
Collaboration skills, n (%)			
Actively seeks treatment, willing to collaborate	227 (63.2%)	98 (37.7%)	**< 0.001**
Wants to be helped, but lacks motivation	97 (27.0%)	88 (33.8%)	
Passively accepts the treatment/intervention	20 (5.6%)	49 (18.9%)	
Does not show attention or compreh. for treatment efforts	14 (3.9%)	23 (8.8%)	
Actively refuses the treatment/intervention	1 (0.3%)	2 (0.8%)	
Smoking (cigarettes per day)			
Mean (SD)	16.2 (7.3)	17.6 (10.3)	0.157
Median (Minimum; Maximum)	17 (0–40)	20 (0–60)	
*Missing***	173	115	
Disorder duration (years)			
Mean (SD)	18.1 (9.5)	18.3 (9.5)	0.829
Median (Minimum; Maximum)	18 (0–49)	20 (1–41)	
Lifetime duration of psychiatric hospitalisation (years), n (%)			
< 1 years	187 (52.1%)	106 (40.8%)	**0.009**
1–5 years	96 (26.8%)	68 (26.1%)	
> 5 years	76 (21.1%)	86 (33.1%)	
Aps drugs, n (%)			
Yes	350 (97.5%)	257 (98.9%)	0.363
No	9 (2.5%)	3 (1.1%)	
Non-Aps drugs, n (%)			
Yes	238 (66.3%)	189 (72.7%)	0.124
No	121 (33.7%)	71 (27.3%)	

Table 2 (continued)

	CLUSTER 0 N = 359 (58.0%)	CLUSTER 1 N = 260 (42.0%)	p-value*
BPRS total rating, Mean (SD)	40.84 ± 10.98	55.21 ± 15.39	**< 0.001**
Depression/anxiety	13.97 ± 4.83	16.54 ± 6.23	**< 0.001**
Excitement	9.09 ± 4.02	11.33 ± 5.03	**< 0.001**
Positive symptoms	7.39 ± 3.32	10.24 ± 4.03	**< 0.001**
Negative symptoms	6.39 ± 2.29	11.28 ± 3.86	**< 0.001**
Cognitive symptoms	4.02 ± 1.57	5.92 ± 2.65	**< 0.001**
BNSS total rating, Mean (SD)	13.16 ± 9.24	36.18 ± 12.67	**< 0.001**
Anhedonia	3.26 ± 3.51	8.50 ± 4.10	**< 0.001**
Distress	1.20 ± 1.46	2.59 ± 1.66	**< 0.001**
Asociality	2.19 ± 1.91	6.77 ± 2.27	**< 0.001**
Avolition	2.28 ± 2.28	6.01 ± 2.76	**< 0.001**
Blunted affect	2.70 ± 3.27	7.58 ± 4.61	**< 0.001**
Alogia	1.53 ± 2.21	4.73 ± 3.13	**< 0.001**
SLOF total rating, Mean (SD)	187.46 ± 17.03	166.69 ± 20.39	**< 0.001**
Interpersonal Relationships	27.58 ± 4.55	20.38 ± 4.44	**< 0.001**
Activities	48.49 ± 6.30	42.57 ± 8.32	**< 0.001**
Work skills	22.56 ± 5.77	18.72 ± 6.09	**< 0.001**
Social acceptability	32.70 ± 2.84	31.60 ± 3.49	**< 0.001**
Physical functioning	24.12 ± 2.20	23.93 ± 1.83	0.281
Personal care skills	32.02 ± 3.79	29.46 ± 4.77	**< 0.001**
WHODAS total score, Mean (SD)	11.91 ± 8.62	14.48 ± 9.89	**0.001**
Missings	1	4	
WHOQOL-Bref total rating, Mean (SD)	90.46 ± 12.89	86.53 ± 16.23	**0.001**
Missings	8	5	
Physical domain	25.90 ± 4.39	24.67 ± 5.09	**0.001**
Psychological domain	19.80 ± 3.91	18.84 ± 4.70	**0.006**
Social relationship domain	9.78 ± 2.28	9.27 ± 2.61	**0.011**
Environment domain	28.11 ± 4.49	27.26 ± 5.43	**0.035**
ZTPI total score, Mean (SD)	185.08 ± 18.22	179.31 ± 20.57	**< 0.001**
Missings	9	6	
Past-Negative	34.80 ± 6.75	34.55 ± 7.79	0.665
Past-Positive	30.04 ± 5.55	28.62 ± 6.36	**0.003**
Present-Hedonistic	48.54 ± 7.97	46.13 ± 8.80	**< 0.001**
Present-Fatalistic	25.90 ± 5.94	26.63 ± 6.17	0.141
Future	45.92 ± 6.35	43.72 ± 6.61	**< 0.001**
POS total score, Mean (SD)	28.74 ± 6.05	26.03 ± 7.70	**< 0.001**
Missings	2	2	

Aps = antipsychotics

*Bold values indicate statistical significance at the $p < 0.05$ level

**The missing data include both non-smokers and unanswered responses

BPRS Brief Psychiatric Rating Scale, *BNSS* Brief Negative Symptom Scale, *SLOF* Specific Level of Functioning Scale, *WHODAS* World Health Organization Disability Assessment Schedule, *WHOQOL-Bref* World Health Organization Quality of Life-BREF, *ZTPI* Zimbardo Time Perspective Inventory, *POS* Positivity Scale

in BPRS in Cluster 0 and ZTPI in Cluster 1, suggesting that same-cluster populations are homogeneous in terms of clinical manifestation. Instead, significant intra-sex (M vs M and F vs F) differences between Cluster 0 and Cluster 1 (third and fourth rows) were observed, showing consistent differences in disease severity between the clusters. Similar statistical differences are also observed in the inter-sex (M vs F and F vs M) comparisons between the two clusters (fifth and sixth rows).

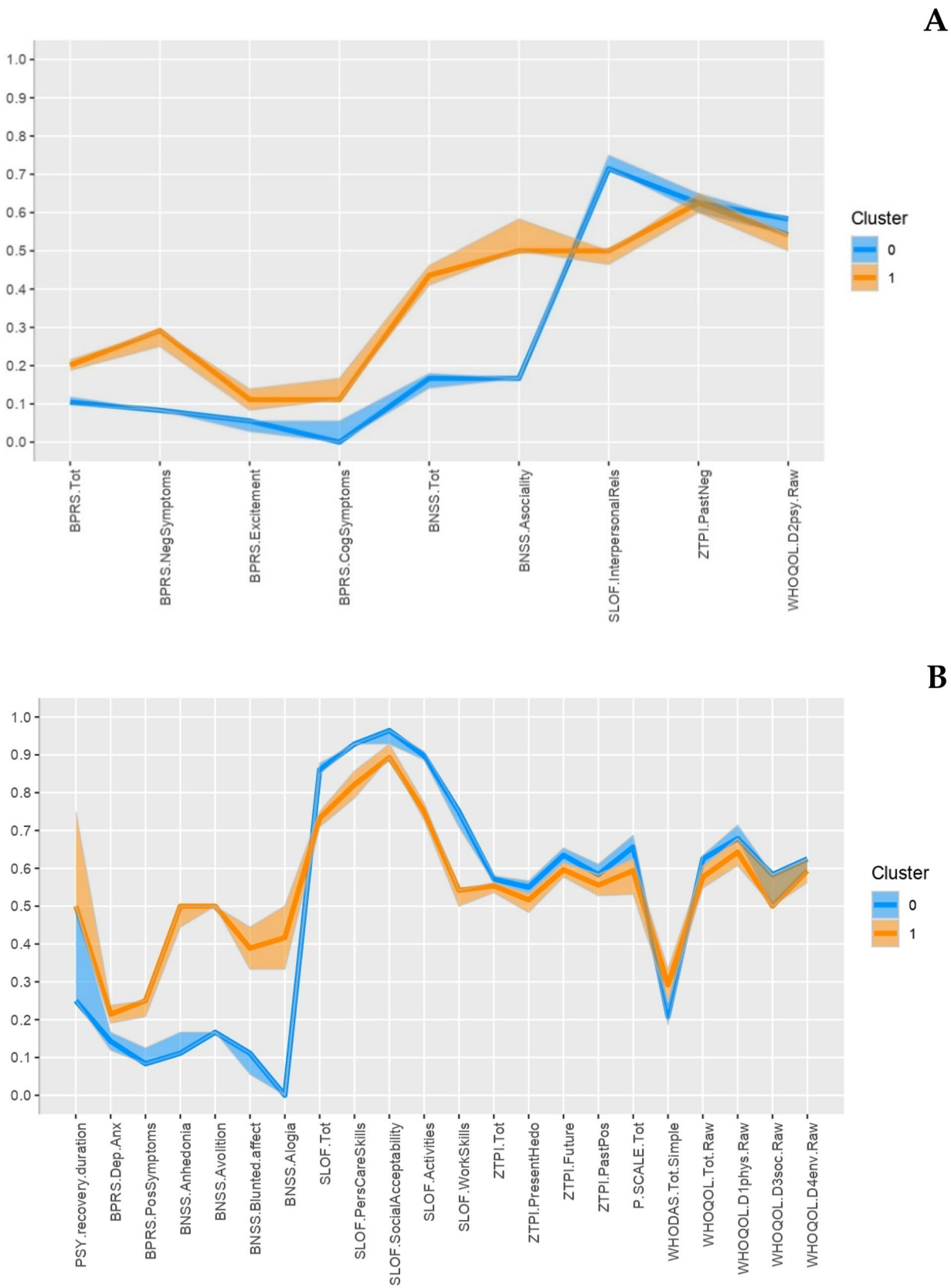

Fig. 1 Parallel coordinate plots with confidence intervals. median values and 95% confidence intervals for normalized clinical scores in the two clusters are shown. the cluster assignment was performed in the logo-cv scenario. panel a shows the training features of the pca-gmm, panel b shows the features not used in the training that differed significantly ($p < 0.05$) between the clusters

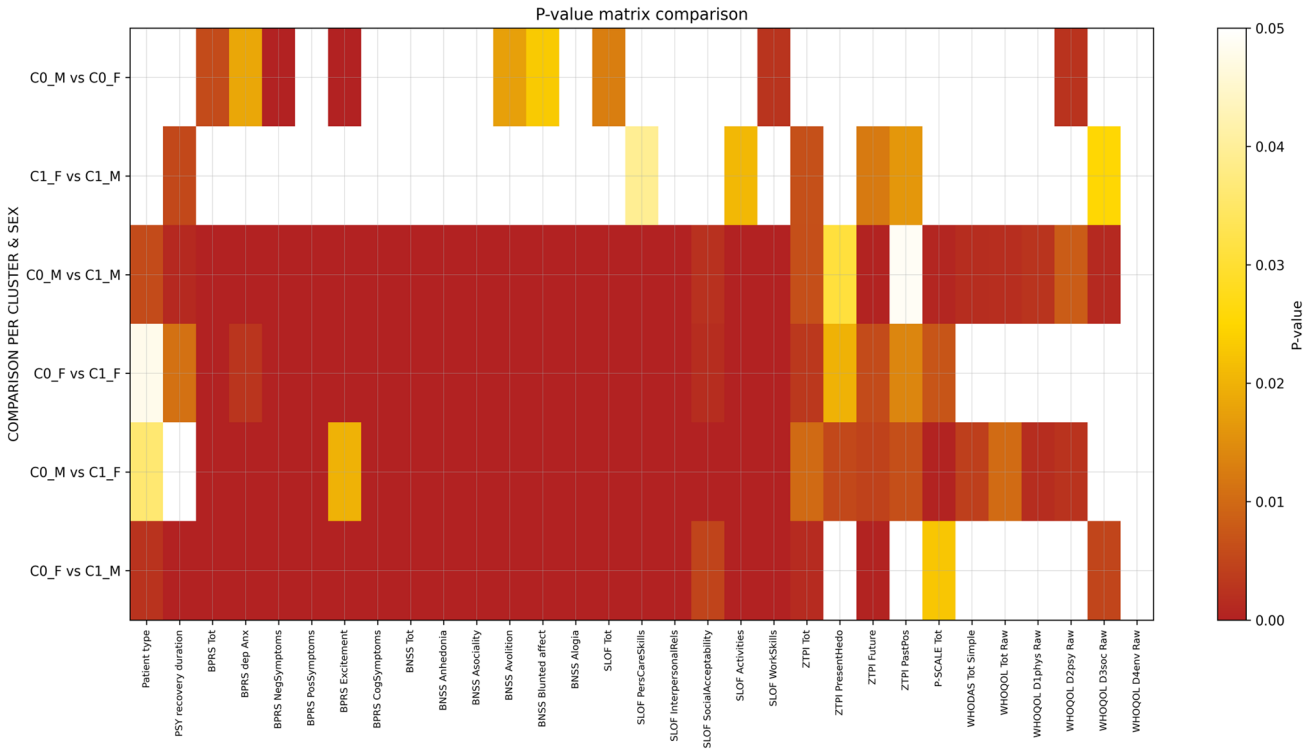

Fig. 2 Intra- and inter-sex differences between two clusters. the figure shows the statistical differences between each permutation of the two clusters and sexes. the p-values were calculated with ancova using age as a covariate and bonferroni correction. acronyms: c0: cluster 0, c1: cluster 1, m: men, w: women

Discussion

This study aimed to describe sex differences in an Italian sample of people with SSD, focusing also on under-investigated areas, and offer new insights about sex differences among individuals with SSD using for the first time a data-driven approach.

Over thirty years ago, one of the authors of this paper (RM) summarised the state of knowledge on sex differences in schizophrenia [65]. This seminal work clarified that in schizophrenia, males typically experience a more severe form characterised by early onset, poor premorbid adjustment, increased negative symptoms, and poorer outcomes. These characteristics are associated with higher rates of pre- or peri-natal complications, the lack of protective effects of oestrogens, structural brain abnormalities, likely due to greater neurodevelopmental anomalies. Over the past three decades, research has further elucidated additional critical areas of divergence between males and females suffering from SSD [10, 15–22, 66]. In line with the first objective of our study, the socio-demographic and clinical characteristics of our sample are generally consistent with previous research on sex differences in people with SSD, with some exceptions. For instance, in this sample females exhibited higher tobacco use, which may reflect a stronger perceived dependence or the attempt to alleviate symptoms, such as anxiety and depression, using nicotine as a means to temporarily improve their mental state [67]. Furthermore, according to the self-medication hypothesis, the increased rates of cigarette use among women appears to be associated with neurocognitive benefits, including an enhanced cognitive performance and attention—potentially incentivising tobacco use—[68, 69]. Furthermore, epidemiological data of this study suggest distinct patterns of functioning and perception between males and females with SSD. Females demonstrated better interpersonal functioning, indicating stronger social relationships compared to males. However, no significant differences were found in self-reported functioning. Females also reported a more negative or painful perception of past experiences, which may indicate a tendency to dwell on past struggles or challenges. On the other hand, males reported a more positive perception of their psychological health, suggesting a more favourable self-assessment of mental well-being compared to females. No significant differences in positivity ratings were found between sexes, consistent with another study part of the DiAPAson project, where individuals with SSD showed similar positivity levels to an Italian normative sample. This may suggest that a positive outlook could be a resilient trait, even in

those with severe mental disorders and varying degrees of psychosocial disability [47, 70].

Overall, our findings show sex differences in specific domains, which could inform tailored approaches to treatment for people with SSD. For females, interventions may focus on leveraging their strengths in interpersonal relationships while addressing negative perceptions of past experiences. Males, with a more positive psychological self-assessment, may benefit from maintaining this outlook while improving interpersonal skills.

The data-driven analysis divided patients with SSD into two distinct phenotypic subgroups, with individuals in Cluster 1 showing a more severe clinical profile, marked by a higher proportion of males. In contrast, individuals with a milder clinical disorder were identified in Cluster 0, which included a significantly higher number of female participants.These participants exhibited fewer psychological and behavioural symptoms, better social and occupational functioning, higher QoL, positivity, and higher perceived functioning and a better time perception. This suggests that while sex differences are typically observed in milder cases, the severity of the disorder may diminish these differences. Both clusters would benefit from ongoing monitoring and tailored support, with particular attention to sex-specific needs. For example, while males in Cluster 1 may benefit from more intensive management, females in Cluster 0 may benefit from interventions that emphasise emotional regulation and maintaining positive self-perception.

The lack of distinct sex differences between the two clusters, as opposed to clear male and female groupings, can be attributed to several factors. While SSD are traditionally considered more prevalent in males, this has been challenged by research highlighting the influence of demographic, social, and environmental variables on incidence rates [9, 10]. Drawing on van Os and Guloksuz's (2021) [71] concept of schizophrenia as an umbrella disorder, a trans-syndromal framework aligning with clinical practice may offer a more nuanced perspective. This framework views schizophrenia as a spectrum of disorders with varied manifestations, potentially explaining the modest differences observed between clusters in our study. These findings highlight the diagnostic heterogeneity of SSD and underscore the importance of flexible criteria to accommodate this complexity, paving the way for tailored treatments to enhance outcomes and QoL.

Strengths and limitations

This study has some limitations. First, the investigation was conducted during the Sars-Cov-2 pandemic, which influenced daily clinical practice and routine activities in patients' living settings. Additionally, the diagnosis of SSD relied solely on medical records. Finally, the lack of qualitative data hinders a deeper understanding of the sex differences in the ways male and female patients live their psychopathology.

Given the limitations of utilising the MMSE with a cut-off of 24, it is important to acknowledge that the identified sex differences in cognitive impairments among males with SSD could be influenced by the constraints inherent in the MMSE.

A key limitation of the DiAPAson project is that it was not specifically designed to investigate sex differences, leading to an imbalance between males and females in the sample. While no statistical sex differences were observed, this imbalance may have implications for the reliability and validity of the analyses. Additionally, the homogeneity of the sample, which included only Italian citizens, may limit the generalisability of the findings to broader populations. Future research should focus on a larger, more diverse sample.

The higher representation of males in RFs may be attributable to factors such as females' later illness onset, fewer negative symptoms, and better premorbid functioning, all of which reduce their need for intensive care [75–77]. Conversely, males' elevated rates of substance abuse may worsen their clinical trajectories and heighten their care needs [76, 78]. Females' stronger social cognition and faster processing speed likely contribute to better outcomes and a lower reliance on RFs [79, 80].

This study also focuses solely on biological sex differences, without addressing gender identity, as the DiAPAson project was based on biological data and did not include questions on gender. Although this limits the scope of the analysis, the emphasis on biological sex aligns with the study's objective to provide insights for targeted interventions in SSD [59].

Finally, the cross-sectional nature of the study precludes exploration of the underlying mechanisms driving the observed differences. Future research should employ longitudinal or experimental methods to elucidate these factors, enabling more effective and personalised clinical approaches.

Even with the above limitations, strengths of the study include the relatively large sample size with data collected in multiple sites across Italy, leading to good generalisability. Additionally, the reliability of psychopathological profiles and psychosocial functioning data is ensured through the use of multiple, widely established assessment tools.

Conclusions

This study highlights sex differences in specific SSD domains, offering insights for tailored treatments. For females, this includes strengthening interpersonal relationships and addressing negative past perceptions, while for

males, maintaining positive self-assessment and enhancing interpersonal skills is key.

Our findings support the use of ML to delineate sex-specific phenotypes in SSD and demonstrate the utility of standardised tools in identifying nuanced patient differences. By identifying distinct SSD clusters through ML, this study underscores the potential to refine diagnostic criteria, enabling more precise, sex-sensitive interventions that improve outcomes and QoL for both male and female patients.

As emphasised by Riecher-Rössler et al. [81], the current research underscores the necessity for a multifaceted approach to elucidate the observed disparities in SSD between sexes. Such an interdisciplinary approach constitutes a fundamental pillar for advancing our understanding of the disorder.

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Author contributions All authors contributed to the design of the study and reviewed drafts of the report. AM and SL equally contributed to this paper and are co-first authors. GdG was responsible for the conception and the overall supervision of the study. AR, CMB, DA, DM and DM managed data. All the authors gave technical support throughout the study. DM and DM did the data analyses. AM, SL, MM, EC, and ET performed the literature research. CMB, DA, and AR were responsible for the development of the PCA-GMM model. AM and SL wrote the first draft of the study and were responsible for the subsequent collocation of inputs and redrafting. GdG, AM, SL, CMB, DA, AR, EC, MM, MDA, LI, MDF, RMM, AA, GBT, and LL contributed to revising the manuscript. All authors read and approved the final version.

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Data availability Dataset referring to this manuscript is published with restricted access on Zenodo platform and accessible at this link: https://doi.org/10.5281/zenodo.10119250.

Code availability Authors will provide access to the analytic code on reasonable request for purposes of reproducing results or replicating procedures. The PCA-GMM model is freely available on the NewPsy4U platform: https://newpsy4u.eu/. Further requests for the code can be sent via e-mail to: aredolfi@fatebenefratelli.eu.

Declarations The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Competing interest The authors declare to have no conflict of interest.

Ethics approval and consent to participate The study has been approved by the ethical committees (ECs) of the three main participating centres: EC of IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli (31/07/2019; no. 211/2019), EC of Area Vasta Emilia Nord (25/09/2019; no. 0025975/19), and EC of Pavia (02/09/2019, no. 20190075685). All participants provided informed consent before the study began. The authors affirm that all procedures involved in this research adhere to the ethical guidelines set by the pertinent national and institutional committees on human experimentation, as well as the Helsinki Declaration of 1975, updated in 2008.

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