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Sex and gender differences in clinical and functional indices in subjects with schizophrenia and healthy controls: Data from the baseline and 4-year follow-up studies of the Italian Network for Research on Psychoses

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ABSTRACT

Gender differences in clinical and psychosocial aspects of schizophrenia have been widely reported. Findings have not always been consistent, and some of them need further research. In a large sample of community dwelling persons with schizophrenia, we investigated gender differences in clinical, cognitive and functional indices, as well as their changes over a 4-year follow-up and their impact on real-life functioning. Gender differences in personal resources, cognitive and functional indices were explored also in a sample of healthy controls. Men with respect to women had an earlier age of illness onset, a worse premorbid adjustment in the academic domain, more severe avolition, expressive deficit and positive symptoms, lower prevalence of comorbidity for affective disorders, less frequent use of two coping strategies ('religion' and 'use of emotional support') and more frequent positive history of substance and alcohol abuse. In addition, men were more

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impaired in verbal learning, while women in reasoning/problem solving. Some patterns of gender differences observed in healthy controls were not confirmed in patients. Men's disadvantages in the clinical picture did not translate into a worse outcome. This finding may be related to the complex interplay of several factors acting as predictors or mediators of outcome.

1. Introduction

Sex and gender differences in persons with schizophrenia involve several aspects of the disorder, such as epidemiological distribution, clinical picture, biological correlates, course of illness and outcome (Ochoa et al., 2012; Riecher-Rössler et al., 2018; Seeman, 2019; Kotov et al., 2020).

Attempts to explain these differences include biological (genetic, neurodevelopmental or hormonal), psychological (different psychological vulnerability and/or trauma exposure among the two genders) and social models (mainly related to cultural aspects, such as different gender role expectations) which are most likely strictly related to each other (Taylor and Langdon, 2006; Falkenburg and Tracy, 2014; Feldman, 2020), thus involving both the concepts of "sex" and "gender". In this paper we adopt the term "gender" in order to refer mainly to the notion of psychosocial differences between men and women, given that the notion of biological differences is already included in the classification of patients according to the demographic variable man/woman adopted in our study as well as in all cited papers.

Men, with respect to women, have an earlier age of illness onset, with a difference ranging from 1 to 5 years across studies, and a peak of onset in the early- to mid-twenties in men and in the late-twenties in women (Taylor and Langdon, 2006; Riecher-Rössler et al., 2018), a worse premorbid adjustment, a greater severity of negative symptoms, a lower severity of affective symptoms, and a lower prevalence of comorbid affective disorders (Taylor and Langdon, 2006; Ochoa et al., 2012; Li et al., 2016; Riecher-Rössler et al., 2018; Giordano et al., 2021). Although these findings have been confirmed in many studies, some aspects deserve further investigation. In particular, the negative dimension has been assessed in most studies as a unitary construct, without considering the heterogeneity of this psychopathological dimension which, according to the most recent literature, includes at least two factors – "avolition" and "expressive deficit" – that may be underpinned by different pathophysiological substrates and show different correlates and impact on outcome (Giordano et al., 2018; Galderisi et al., 2018a; Galderisi et al., 2021). Only two studies explored gender differences in the two factors of negative symptoms: one of them assessed negative symptoms by means of the Positive and Negative Syndrome Scale, and found that the greater severity of negative symptoms in men was limited to the "experiential deficit" (Muralidharan et al., 2018), while the other (Wojciak et al., 2021) used a new-generation rating scale – the Brief Negative Symptom Scale – and found that, besides the item "distress" which measures lack of normal distress and does not specifically represent a domain of negative symptoms (Kirkpatrick et al., 2011; Mucci et al., 2015), only the item "asociality" was more severe in men, in line with the finding of a previous study assessing asociality by means of the SANS (Häfner et al., 1993). Moreover, no study considered the distinction between primary and secondary negative symptoms, which is crucial even in early stages of illness (Bucci et al., 2020; Galderisi et al., 2021). The scarcity and heterogeneity of findings relevant to different aspects of negative symptoms indicate the need to further explore gender differences in this complex psychopathological dimension. Similar considerations apply to premorbid adjustment. In fact, it is still unclear whether the disadvantage in premorbid adjustment reported in men is limited to a specific domain, namely the social or academic one. As a matter of fact, many studies did not consider this distinction when exploring gender differences in premorbid adjustment, while those exploring separately social and academic domains reported discrepant findings (Ochoa et al., 2012; Giordano et al., 2021).

A higher frequency of positive symptoms has been reported in women in some studies (Häfner, 2003; Heitz et al., 2019), but not in others (Riecher-Rössler et al., 2018). A few studies investigated the disorganization dimension, reporting either no gender differences (Quattrone et al., 2019; Reininghaus et al., 2019) or greater severity in men (Galderisi et al., 2012). Lack of gender differences in psychopathological domains have also been reported (Häfner, 2002). Discrepancies in psychopathological findings may also be related to the fact that only very few studies (Häfner et al., 1992) were based on representative samples so far.

Gender differences in other clinical determinants of outcome, such as social and non-social cognition and personal resources, have received less attention and/or relevant studies provided discrepant findings so far.

The literature on gender differences in cognitive functions has also been inconsistent. Some studies found better cognitive functions in women than in men, while others found an opposite pattern or no gender difference (Mendrek and Mancini-Marie, 2016). More recent studies did not clarify this controversial picture (Zhang et al., 2017; Fond et al., 2018; Pu et al., 2019; Mu et al., 2020; Wei et al., 2020; Zhao et al., 2021). Moreover, when gender differences were found, the pattern of impaired cognitive domains in men and women varied across studies (Mendrek and Mancini-Marie, 2016; Zhang et al., 2017; Pu et al., 2019). Heterogeneity in the clinical expression of schizophrenia and in sample size may represent possible sources of discrepancies (Mendrek and Mancini-Marie, 2016), along with heterogeneity of tests adopted to assess cognitive functions. As a matter of fact, only a few studies used the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) (Zhang et al., 2017; Mu et al., 2020; Zhao et al., 2021), which is considered the gold standard to reliably assess cognitive functions in subjects with schizophrenia.

A few studies explored gender differences in social cognition, a domain relatively independent of neurocognition, defined as the ability to perceive, interpret and process social stimuli for adaptive social interactions (Davidson, 2019; Green et al., 2020). Several studies reported that social cognition is associated with functional outcome and mediates the impact of neurocognition on real-life functioning (Green et al., 2019; Galderisi et al., 2020; Mucci et al., 2021). Although non-conclusive data have been reported so far, a disadvantage in men vs. women has been found in some studies (Perez-Garza et al., 2016; Zhang et al., 2017; Caqueo-Urizar et al., 2018). Inconsistencies in findings relevant to social cognition may be related to the complexity of the construct, which includes different abilities, in particular emotion processing, social perception, theory of mind/mental state attribution and attributional style/bias (Pinkham et al., 2018).

Gender differences in personal resources, such as resilience and coping strategies, may also deserve attention for their impact on functional outcome of patients with schizophrenia (Ritsner et al., 2006; Galderisi et al., 2014; Galderisi et al., 2020); however, these differences have been scarcely investigated so far. Women seem to need more exposure to stressful life events than men to develop a psychotic disorder (Ochoa et al., 2012), which may be due to a higher resilience in women in coping with stress situations (Häfner, 2002; Ochoa et al., 2012). However, further studies are needed to confirm these observations.

Based on the data reviewed above, a less favourable illness outcome would be expected in men than in women with schizophrenia, given the fact that most factors reported as more severe in men have a known

impact on the outcome of schizophrenia (Galderisi et al., 2014; Gaebel et al., 2020; Galderisi et al., 2020; Moritz et al., 2020; Chekroud et al., 2021). Instead, findings on gender differences in outcome did not provide clear-cut findings so far; heterogeneity in indices of outcome considered in the relevant literature, and the uncertain validity of some of them, may partly account for discrepancies.

Most studies reported lower frequency of being partnered/married and higher rates of comorbid alcohol/substance abuse in men vs. women (Taylor and Langdon, 2006; Ochoa et al., 2012; Petkari et al., 2017; Drake et al., 2020). However, both are non-specific indices of outcome as marriage may be or not an index of good outcome depending on the quality of the partner relationship (Seeman, 2019); in addition, the higher rate of marriage reported in women may be related to their later age of illness onset and their usual earlier age of marriage, giving them a better chance to get married before the illness starts. As to alcohol/substance abuse, it may be considered a risk factor rather than an index of poor outcome. No conclusive data have been reported on other indices of outcome, such as rate of employment (Cotton et al., 2009; Thorup et al., 2014; Bouwmans et al., 2015; Caqueo-Urizar et al., 2018) and duration of hospitalization or frequency of readmission (Häfner et al., 1989; Cotton et al., 2009; Ochoa et al., 2012; Tseliou et al., 2017; Seeman, 2019).

Discrepant findings have been reported also on gender differences in functional outcome and recovery rates both in chronic and first-episode patients (Galderisi et al., 2012; Ochoa et al., 2012; Jaaskelainen et al., 2013; Thorup et al., 2014; Caqueo-Urizar et al., 2018; Cechnicki et al., 2018; Mayston et al., 2020; Peng et al., 2021; Shafie et al., 2021). It is worth noticing that, according to the results of some studies (Riecher-Rössler, 2010; Dama et al., 2019; Seeman, 2019), gender differences in outcome indices and rates of recovery depend on the time of evaluation, with better outcome for women in the short- and mid-term (until 10 years of illness duration) and an attenuation of gender differences in the long-term (up to 10 years), as well as on the age of onset, with women showing a better course when the onset is up to age 40 (Riecher-Rössler, 2010) and a worse outcome when the onset occurs later (Riecher-Rössler et al., 1997). Therefore, age of onset and duration of illness should be controlled for in the investigation of gender differences in outcome. In addition, research in this area should take into account the complexity of the concept of functional outcome and recovery which includes different areas of real-life functioning that may be differentially impacted by various determinants of outcome in the two genders.

The present study was carried out in a large sample of community dwelling persons with schizophrenia and one of healthy controls within the activities of the Italian Network for Research on Psychoses (NIRP). We used the databases relevant to the baseline study (Galderisi et al., 2014; Galderisi et al., 2018b) and to the 4-year follow-up (Galderisi et al., 2020; Mucci et al., 2021). In the light of the above-reported findings and possible sources of discrepancies, we aimed to investigate: baseline differences between men and women with schizophrenia in several determinants of outcome, such as socio-demographic and clinical indices, premorbid adjustment, psychopathological dimensions, social and non-social cognition, personal resources, functional capacity, as well as differences in real-life functioning, rates of clinical remission and recovery at follow-up, and in change scores of determinants of outcome from baseline to follow-up. We also investigated gender-related differences in the association with real-life functioning at follow-up of variables showing statistically significant gender differences at baseline or in change scores.

In addition, the study aimed at exploring differences between men and women in a group of healthy controls in social and academic adjustment in early life epochs, social and non-social cognition, functional capacity and personal resources, in order to verify whether eventual gender differences relevant to these domains found in the group of patients are specific to the disorder.

Possible confounding factors, such as age of onset and duration of illness, were taken into account. New-generation tools were used to assess complex domains such as negative symptoms, neurocognition, social cognition and real-life functioning. Clinical remission and recovery were assessed by using operational criteria.

2. Methods

2.1. Participants

Study participants were recruited from patients living in the community in rural, urban and metropolitan areas, and consecutively seen at the outpatient units of 24 Italian university psychiatric clinics and/or mental health departments. The 24 study sites were distributed across geographic areas: Northern Italy (8 centers), Southern Italy (7 centers, including the isles Sicily and Sardinia) and Central Italy (9 centers). Inclusion criteria were a diagnosis of schizophrenia confirmed with the Structured Clinical Interview for DSM-IV - Patient version (SCID-I-P) - and an age between 18 and 66 years. Healthy subjects were recruited through flyers from the community at the same sites as the patient sample. Exclusion criteria for patients and healthy controls are reported in Table 1S (Supplementary materials).

All subjects were asked to sign a written informed consent form to participate in the study, after receiving a comprehensive explanation of the study procedures and goals. The study protocol was approved by the local Ethics Committees of the participating centers.

2.2. Study design

Group comparisons between men and women with schizophrenia patients were performed on socio-demographic and clinical indices, premorbid adjustment, psychopathology, social and non-social cognition, personal resources, functional capacity and real-life functioning assessed at baseline, as well as on rates of clinical remission and recovery at follow-up, and on change scores of indices assessed at follow-up with respect to baseline. The association with real-life functioning at follow-up was separately investigated in men and women for all the variables showing a statistically significant gender-related difference at baseline or in change score from baseline to follow-up.

Gender comparisons were carried out in healthy controls for demographic variables, substance/alcohol abuse, early functioning, social and non-social cognition, personal resources, functional capacity and real-life functioning.

2.3. Assessments

A detailed description of the study assessment procedures is reported in Table 2S (Supplementary materials). In brief, the following instruments were used: Premorbid Adjustment Scale (PAS) to assess premorbid adjustment in patients and early functioning in healthy controls; Positive and Negative Syndrome Scale (PANSS) to rate symptom severity (positive and disorganizazion dimensions); Brief Negative Symptom Scale (BNSS) to assess two dimensions of negative symptoms (expressive deficit and avolition); Calgary Depression Scale for Schizophrenia (CDSS) to assess depression; MCCB for neurocognitive assessment; Facial Emotion Identification Test (FEIT) and Awareness of Social Inference Test (TASIT) to assess social cognition; Coping Orientation to Problems Experienced inventory – Brief (Brief-COPE) to explore coping styles; Self-Esteem Rating Scale (SERS) to assess self-esteem; Resilience Scale for Adults (RSA) to assess different areas of resilience; Recovery Style Questionnaire (RSQ) to assess recovery style; Service Engagement Scale (SES) to explore the relationship with mental health services; St. Hans Rating Scale (SHRS) to investigate the presence of extrapyramidal symptoms; short version of the University of California San Diego (UCSD) Performance-based Skills Assessment Brief (UPSA-B) to assess functional capacity; Specific Levels of Functioning Scale (SLOF) to assess areas of real-life functioning.

2.4. Indices of clinical remission and functional recovery

Patients were classified according to the presence or absence of symptomatic remission and functional recovery at the 4-year follow-up. Andreasen et al.'s (Andreasen et al., 2005) symptomatic criteria for remission were used. In the absence of standardized criteria for functional recovery based on the scales of the Specific Level of Functioning Scale, SLOF (Mucci et al., 2014), a preliminary ROC analysis was carried out on the sample ($N = 921$) of the baseline study (Galderisi et al., 2014) using a Personal and Social Performance (PSP) score ≥71 as the gold standard for functional recovery (Nasrallah et al., 2008). We found that a weighted mean of SLOF Interpersonal, Work and Everyday Life Skills scales provided a more accurate prediction of functional recovery as assessed by PSP than each individual scale. A weighted mean score of 76.2/100 was the optimal cut-off, with a sensitivity of 86.9 %, a specificity of 68.5 % and an area under the curve of 0.84.

2.5. Data analysis

Raw scores on the MCCB were standardized to T-scores based on the Italian normative sample of community participants as described in Mucci et al. (Mucci et al., 2018). All the other variables were transformed into z-scores.

Differences among groups on categorical variables were investigated by using Pearson's chi square test.

Independent one-way analyses of variance (ANOVAs) were used to test group differences (for baseline and for change scores from baseline to follow-up) on demographic variables, and on SERS, RSQ, SES, SHRS, UPSA-B.

Multivariate analyses of variance (MANOVAs) were run to investigate group differences on premorbid adjustment domains, psychopathological dimensions, non-social and social cognitive domains, coping styles, areas of resilience and domains of real-life functioning. When a group difference or an interaction between group and domains was statistically significant, univariate effects were examined using Fisher's post-hoc test.

Separate stepwise multiple regressions were run, in men and women, in which the three areas of real-life functioning at follow-up were entered as dependent variables, while independent variables included indices which differed at baseline or change scores from baseline to follow-up which differed between the two groups.

To control for the possible confounding effect of age of onset and duration of illness, all ANOVAs and MANOVAs in patients were carried out by covarying for these two variables. In the MANOVA of domains of premorbid adjustment, only age of onset was used as covariate, as duration of illness cannot impact premorbid functioning. In addition, Chi square tests on rates of symptomatic remission and functional recovery were run in the whole experimental sample, as well as in a subgroup of patients with age of onset <40 years and duration of illness <10 years. To control for the effect of possible confounding factors which may affect response to antipsychotics (i.e., smoking, substance abuse, antipsychotic type and body mass index) we included those resulting different between the two groups as dependent variables in the stepwise multiple regression analyses.

3. Results

3.1. Subjects

Six-hundred-eighteen subjects with schizophrenia (427 men, 191 women) out of the 921 recruited at baseline participated in the follow-up study and were therefore included in the present investigation, along with 780 healthy controls (402 men, 378 women). In both groups, men and women were comparable for age and education (Table 1).

Table 1
Gender comparisons on socio-demographic variables, clinical variables and early functioning.

	Patients		Healthy controls	
	Males (N = 427)	Females (N = 191)	Males (N = 378)	Females (N = 402)
Age (years, mean ± SD)	40.1 ± 10.2	41.0 ± 11.0	40.3 ± 12.3	40.8 ± 12.8
Education (years, mean ± SD)	11.6 ± 3.2	12.1 ± 3.5	12.9 ± 4.1	13.1 ± 3.9
Partnered/Married [n (%)]	47 (11.1 %)***	45 (23.6 %)	294 (78.2 %)	326 (81.3 %)
Working [n (%)]	127 (30.5 %)	47 (26.1 %)	289 (77.3 %)	244 (61.3 %)##
Substance abuse [n (%)]	130 (30.8 %)***	29 (15.3 %)	8 (2.1 %)	4 (1 %)
Alcohol abuse [n (%)]	80 (18.9 %)***	17 (8.9 %)	2 (0.53 %)	2 (0.5 %)
Cigarette smoking [n (%)]	186 (44.5 %)	70 (36.8 %)		
Body Mass Index ≥25[a] [n (%)]	51 (60 %)	19 (51.3 %)		
Age of onset (years, mean ± SD)	23.3 ± 6.5**	24.5 ± 7.7		
Duration of illness (years, mean ± SD)	16.8 ± 10.5	16.1 ± 10.4		
Current drug treatment				
FGA [n (%)]	59 (14.5 %)	33 (17.5 %)		
SGA [n (%)]	296 (70.5 %)	136 (72.3 %)		
Both FGA and SGA [n (%)]	65 (15.5 %)	19 (10.1 %)		
Chlorpromazine EDD (mg)	549.9 ± 361.6***	416.2 ± 298.7		
Number of hospitalizations (mean ± SD)	3.8 ± 4.4	3.5 ± 3.6		
Suicide attempts [n (%)]	73 (17.4 %)	36 (18.9 %)		
Affective disorders comorbidity [n (%)]	24 (5.6 %)*	19 (10 %)		
St. Hans Rating Scale total (mean ± SD)	0.04 ± 1.0	−0.09 ± 0.9		
PAS Academic domain	0.09 ± 1.0**	−0.21 ± 1.0	0.21 ± 1.1##	−0.20 ± 0.9
PAS Social domain	−0.01 ± 1.0	0.02 ± 0.9	−0.08 ± 0.9	0.07 ± 1.04#

FGA = First generation antipsychotics, SGA = Second generation antipsychotics, Chlorpromazine EDD = Chlorpromazine equivalent daily dose, PAS = Premorbid Adjustment Scale.
For statistically significant differences in patients and healthy controls, the symbols "*" and "#", respectively, were reported throughout the table near the numbers.
[a] Body mass index was available in a subsample of 122 patients (85 males, 37 females).
* $p \leq .05$.
** $p \leq .01$.
*** $p \leq .002$.
# $p \leq .05$
$p \leq .0001$.

3.2. Gender differences in patients and healthy controls: baseline data

3.2.1. Demographic and clinical indices

In the group of patients, gender comparisons on socio-demographic and clinical variables showed that men, with respect to women, had an earlier age of illness onset, were less frequently partnered/married, more frequently had a history of substance and alcohol abuse and less frequently a comorbidity with affective disorders (Table 1). In healthy controls, gender comparisons showed that women were less frequently employed with respect to men (Table 1).

3.2.2. Premorbid adjustment/early functioning

In the group of patients, gender comparisons on academic and social domains of premorbid adjustment showed a significant interaction gender-by-domain ($F_{1,611} = 14.25$, $p = .0002$), due to a more severe impairment of premorbid adjustment in men than in women for the academic domain ($p = .0005$) (Table 1). In healthy controls, a significant gender effect ($F_{1,776} = 4.91$, $p = .03$) and a significant interaction gender-by-domain ($F_{1,776} = 42.85$, $p < .000001$) were observed, due to a worse early functioning for the academic domain in men ($p < .000001$), and a worse early functioning for the social one in women (p = .03) (Table 1).

3.2.3. Psychopathology

Group comparisons on psychopathological dimensions showed a significant effect of gender ($F_{1,612} = 5.30$, $p = .02$) and a significant interaction gender-by-dimension ($F_{4,2448} = 3.48$, $p = .008$). Post-hoc analyses revealed a greater severity of positive symptoms ($p = .001$), avolition ($p = .01$) and expressive deficit (0.006) in men than in women (Fig. 1).

3.2.4. Neurocognition, social cognition and functional capacity

A significant interaction gender-by-cognitive domain emerged from the comparison on MCCB ($F_{6,3510} = 5.89$, $p < .000004$) in the patient group, due to a greater impairment of verbal learning in men ($p = .01$) and of reasoning and problem solving in women ($p = .0003$) (Fig. 2). In healthy controls a significant gender-by-domain interaction was observed too ($F_{6,4638} = 10.83$, p < .000001); however, in this group it was due to a worse performance on attention/vigilance ($p = .004$), working memory ($p = .0002$) and reasoning and problem solving tests ($p = .00002$) in women, while men showed a worse performance on the MCCB social cognition test ($p = .003$) (Fig. 2).

In the patient sample, the MANOVA on the indices of social cognition FEIT and TASIT showed a gender effect approaching statistical significance ($F_{1,552} = 3.42$, $p = .06$), due to a worse performance in men independently of the test (Table 2). In the group of healthy controls, a significant gender-by-domain interaction was observed ($F_{1,724} = 6.80$, $p = .01$), as on FEIT women performed better than men (p = .01) (Table 2).

No statistically significant gender difference was observed on UPSA-B in either patients or healthy controls.

3.2.5. Personal resources

For coping strategies, group comparison on Brief-COPE in patients showed a significant interaction gender-by-scale ($F_{13,7956} = 2.09$, p = .01): men had lower scores than women on the scales 'religion' ($p = .006$) and 'use of emotional support' ($p = .02$) indicating that they use these coping strategies less frequently (Table 3). Group comparison in healthy controls showed a significant effect of gender ($F_{1,778} = 4.74$, $p = .03$) and a significant interaction gender-by-scale ($F_{13,10,114} = 7.46$, $p < .000001$). Post-hoc analyses showed that men had lower scores than women on the scales 'expression' ($p = .00002$), 'religion' ($p < .000001$), 'use of emotional support' ($p = .00001$) and 'self-blame' ($p = .03$), meaning that they adopt these coping strategies less frequently, while women had lower scores than men on the scale 'humor' ($p = .0001$) (Table 3).

As to resilience, in the group of patients no gender differences were observed in the areas of RSA (Table 3). In the group of controls, a significant effect of gender ($F_{1,775} = 10.38$, $p = .001$) and a significant interaction gender-by-dimension ($F_{3,2325} = 12.99$, $p < .000001$) were observed, due to lower scores in women for the areas 'Perception of self' ($p = .000001$) and 'Perception of future' ($p = .004$), indicating worse resilience in these areas with respect to men (Table 3).

Group comparison on self-esteem did not show gender differences in patients (Table 3). In healthy controls, a gender effect was observed ($F_{1,778} = 18.87$, p = .00002) due to higher scores on SERS in men indicating higher self-esteem with respect to women (Table 3).

Group comparison on the Service Engagement Scale showed a gender effect approaching statistical significance ($F_{1,612} = 3.64$, $p = .06$) due to higher scores in men than in women indicating a worse engagement with mental health services in men. (Table 3).

Group comparison on the recovery style questionnaire didn't reveal any gender effect.

3.3. Gender differences in real-life functioning, rates of clinical remission and recovery at follow-up

In the group of patients, gender comparison on the areas of SLOF showed no statistically significant gender effect or gender-by-domain

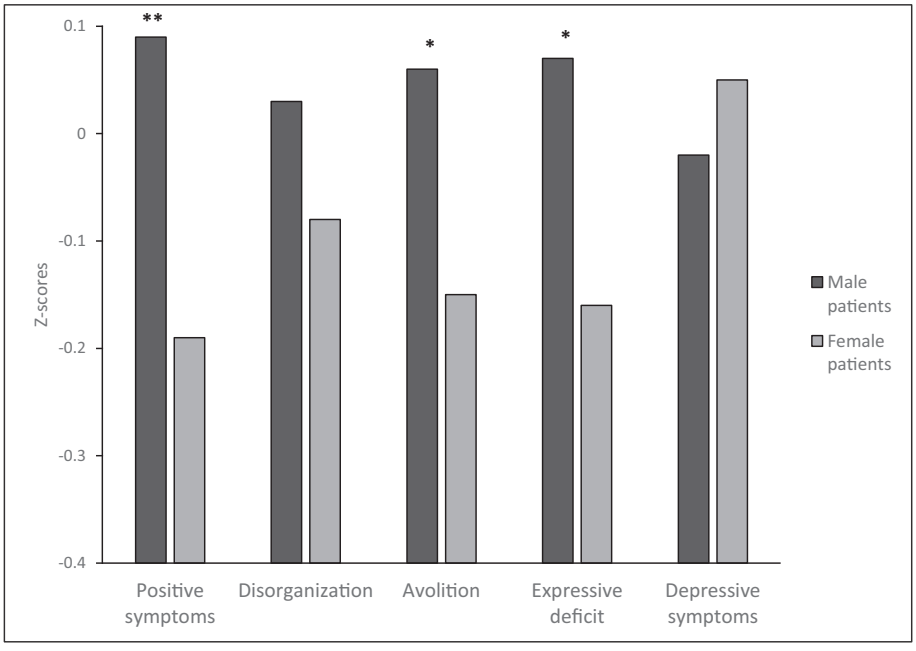

Fig. 1. Gender comparisons on psychopathological dimensions.
*Gender differences: *p ≤ .01; ** ≤ 0.001.

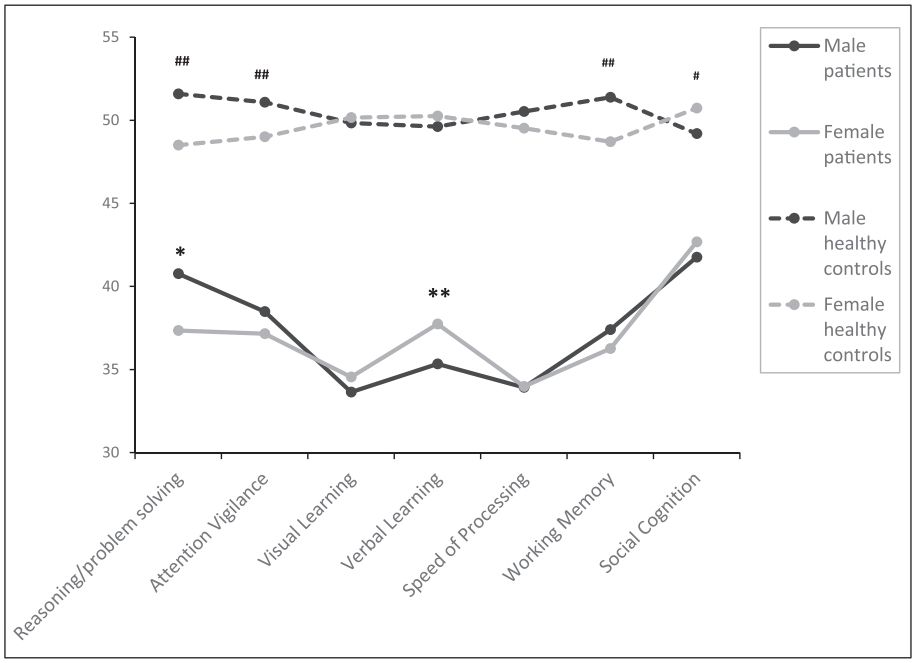

Fig. 2. Gender comparisons on MATRICS Consensus Cognitive Battery (MCCB) T-scores in patients and healthy controls.
*Gender differences in patients: $^{*}p \leq .01$; $^{**}p \leq .0003$.
$^{\#}$Gender differences in healthy controls: $^{\#}p \leq .004$; $^{\#\#}p \leq .00002$.

Table 2
Gender comparisons on social cognition.

	Patients		Healthy controls	
	Males ($N = 386$)	Females ($N = 170$)	Males ($N = 353$)	Females ($N = 373$)
FEIT - total	−0.04 ± 0.99	0.12 ± 0.98	−0.09 ± 1.03$^{\#}$	0.08 ± 0.97
TASIT - mean of sections 1, 2, 3	−0.05 ± 0.87	0.08 ± 0.85	0.008 ± 0.80	−0.02 ± 0.88

FEIT = Facial Emotion Identification Test; TASIT = The Awareness of Social Inference Test.
The symbol "#" was used to indicate the statistically significant difference in healthy controls.
$^{\#}$ $p \leq .01$.

interaction (Fig. 3). In healthy controls, the MANOVA on the investigated SLOF areas showed a significant interaction gender-by-area ($F_{2,61,540} = 3.67$, $p = .03$), due to higher scores in women on everyday life skills, meaning that they have a better functioning in this area with respect to men. This difference was no more statistically significant after excluding 3 outliers (two men scoring as "Totally dependent" and one as "Needs substantial help" at the item "household responsibilities") (Fig. 3).

In the whole group of patients, no difference was found between men and women in the number of remitted/non remitted or recovered/non-recovered subjects (Table 4).

Lack of gender-related differences in remission and recovery rates was confirmed in the subsample of patients with early onset and short duration of illness (Table 4).

3.4. Gender differences in change scores from baseline to follow-up

No statistically significant gender effect or gender-by-domain interaction was observed for any of the considered change scores, with the exception of the Service Engagement Scale for which a significant effect of gender was observed ($F_{1,607} = 4.69$, $p = .03$), due to a greater improvement of engagement with mental health services in men than in women.

3.5. Stepwise multiple regression analyses in men and women

Results of multiple regression analyses are reported in Table 5. The three areas of real-life functioning (Interpersonal relationships, Everyday life skills and Work skills) at follow-up were entered as dependent variables, while independent variables were all variables showing a gender difference.

In both men and women, greater impairment of verbal learning and of reasoning/problem solving, and more severe positive symptoms at baseline, as well as smaller change in service engagement at follow-up vs. baseline, were associated with worse functioning in the area 'Everyday life skills' at follow-up. Only in men, greater severity of expressive deficit was associated with worse functioning in everyday life skills, while only in women higher frequency of substance abuse was associated with it.

In both men and women, more severe avolition and positive symptoms at baseline, and smaller change in service engagement at follow-up vs. baseline, were associated with a worse functioning in the area 'Interpersonal relationships' at follow-up. Only in men, greater impairment in verbal learning at baseline was associated with worse interpersonal relationships, while only in women a more frequent adoption of the coping strategy 'use of emotional support' was associated with a better functioning in this area.

In both genders, worse premorbid functioning in the academic domain, more severe positive symptoms at baseline, and smaller change in service engagement at follow-up vs. baseline were associated with worse functioning in 'Work skills' at follow-up. Only in men, more severe avolition at baseline and greater impairment of verbal learning and reasoning/problem solving, together with lower frequency of being partnered/married, were associated with worse functioning in 'Work skills'.

Table 3
Gender comparisons on personal resources.

	Patients		Healthy controls	
	Males ($N = 425$)	Females (N = 191)	Males (N = 378)	Females (N = 402)
Brief-COPE				
Positive reframing	0.007 ± 0.99	−0.02 ± 1.03	0.003 ± 0.99	−0.002 ± 1.01
Self-distraction	−0.05 ± 1.00	0.11 ± 0.99	−0.06 ± 0.99	0.05 ± 0.99
Expression	−0.01 ± 1.01	0.03 ± 0.99	−0.16 ± 0.98##	0.15 ± 0.99
Use of instrumental support	−0.02 ± 0.99	0.05 ± 1.03	−0.06 ± 0.98	0.06 ± 1.01
Active coping	0.01 ± 1.01	−0.01 ± 0.99	0.008 ± 1.00	−0.008 ± 0.99
Denial	−0.03 ± 1.0	0.07 ± 1.00	−0.04 ± 0.98	0.04 ± 1.01
Religion	−0.07 ± 0.99*	0.16 ± 1.01	−0.19 ± 0.93##	0.18 ± 1.03
Humor	0.02 ± 1.03	−0.05 ± 0.94	0.14 ± 1.01	−0.13 ± 0.97#
Behavioral disengagement	0.004 ± 0.99	0.01 ± 1.02	0.04 ± 1.03	0.04 ± 0.96
Use of emotional support	−0.06 ± 0.98*	0.14 ± 1.02	−0.16 ± 0.98##	0.15 ± 0.99
Substance use	0.02 ± 1.00	−0.05 ± 1.00	0.01 ± 1.01	−0.01 ± 0.99
Acceptance	0.005 ± 0.98	−0.01 ± 1.05	−0.03 ± 1.00	0.03 ± 0.99
Planning	0.03 ± 0.99	−0.07 ± 1.02	0.06 ± 1.01	−0.06 ± 0.99
Self-blame	−0.04 ± 0.99	0.09 ± 1.01	−0.08 ± 1.02#	0.08 ± 0.97
RSA				
Perception of self	0.03 ± 1.00	−0.07 ± 1.00	0.22 ± 0.89	−0.20 ± 1.06##
Perception of the future	−0.02 ± 1.00	0.04 ± 1.01	0.10 ± 0.95	−0.10 ± 1.03#
Social competence	−0.01 ± 0.99	0.03 ± 1.01	0.06 ± 0.95	−0.05 ± 1.04
Family cohesion	−0.01 ± 0.99	0.01 ± 1.03	−0.02 ± 0.99	0.02 ± 1.01
Self-esteem Rating Scale	0.02 ± 0.99	−0.05 ± 1.02	0.16 ± 0.97	−0.15 ± 1.00##
Recovery style questionnaire	−0.01 ± 1.01	0.04 ± 0.97		
Service Engagement Scale	0.05 ± 0.99	−0.12 ± 1.01		

Brief-COPE = Coping Orientation to Problems Experienced inventory – Brief, RSA = Resilience Scale for Adults.
For statistically significant differences in patients and healthy controls, the symbols "*" and "#", respectively, were reported throughout the table near the numbers.
* $p \leq .03$.
# $p \leq .05$.
$p \leq .0001$.

4. Discussion

In the present study, in a large sample of patients with schizophrenia living in the community, we confirmed gender differences in clinical indices most consistently reported in the literature. Men with respect to women had an earlier age of illness onset, a worse premorbid adjustment (limited to the academic domain), more severe avolition and expressive deficit, a lower prevalence of comorbidity for affective disorders, and a more frequent positive history of substance and alcohol abuse, while no gender difference was observed on the outcome indices.

We controlled for possible confounding factors, in particular age of onset and duration of illness which have been found to impact gender differences in clinical picture and illness outcome, as well as for gender differences on other variables which may affect response to antipsychotics, such as smoking and substance abuse rates, antipsychotic type (first/second generation) and body mass index (although the latter was available only in a subsample of patients).

The finding of a worse premorbid adjustment in men has been consistently reported. It has been questioned whether it is relevant to the functioning preceding the onset of the disorder or is related to the presence of prodromic symptoms, given the earlier age of onset reported in men (Riecher-Rössler et al., 2018). In the present study, to minimize possible contamination with early prodromal and psychotic symptoms of the illness we excluded from the data analyses scores relevant to the adult age period, which is likely to be closer to or in overlap with the illness onset than earlier age periods. A worse premorbid adjustment in men may be explained by their greater susceptibility to neurodevelopmental disorders (Fombonne, 2003), given the hypotheses that schizophrenia may be viewed within a "developmental risk factor model" (Murray et al., 2017) or within a "neurodevelopmental continuum" (Fusar-Poli et al., 2021), the latter more frequent in men (Fombonne, 2003). Since in our sample the greater impairment observed in men is limited to the academic domain, it cannot be excluded that neurodevelopmental abnormalities have a greater impact on the academic than on the social domain, at least in early life periods. However, we found the same pattern of differences in healthy controls, with a marked disadvantage in men for the academic domain, suggesting that such a disadvantage represents a non-specific characteristic of men in the general population, which may impact age of onset and other characteristics of the clinical picture in men developing the disorder.

The greater severity of the negative psychopathological dimension in men than in women was confirmed in our sample for both the avolition/experiential and expressive dimension, while the only other study exploring gender differences in the two dimensions (Muralidharan et al., 2018) found that the greater severity in men was limited to the experiential dimension. Actually, in Muralidharan et al.'s study, the experimental sample included also patients with schizoaffective disorders in a not specified percentage, which increases heterogeneity of the sample; moreover, negative symptoms were assessed by means of the Positive and Negative Syndrome Scale, and the domain 'reduced emotional experience' included the item 'active social avoidance', which reflects the severity of anxiety, depression and positive symptoms, more than of negative symptoms; in addition, in that study authors didn't control for any possible cause of secondary negative symptoms. In our experimental sample of much larger size, we included only patients with a diagnosis of schizophrenia, and assessed negative symptoms by using a new-generation rating scale – the BNSS – which allows to calculate the two main domains of negative symptoms not including those items previously considered as part of the negative dimension but now clearly identified as aspects of other dimensions, as it is the case of the above-mentioned item 'active social avoidance' (Marder and Galderisi, 2017). Moreover, in our sample we could reasonably exclude the influence of possible causes of secondary negative symptoms such as extrapyramidal side effects (no gender differences were observed on the SHRS score nor on the type of antipsychotic assumed) or depressive symptoms (no gender difference on the severity of depression was observed and, in any case, it was even more severe in women, although not significantly, strongly indicating that the higher severity of negative symptoms in men could not be confounded by depression). It is worth noticing that, in our sample, both dimensions of negative symptoms not only were more severe in men but also showed a gender-specific impact on real-life functioning domains. In fact, the severity of expressive deficit was associated with functioning in everyday life skills and that of avolition with work skills only in men.

A greater severity of positive symptoms in men with respect to women was also found in our study. Great variability of findings on gender differences in this psychopathological domain may at least in part be related to the fact that it shows a good response to antipsychotic drugs, therefore its severity depends on the medications taken by the patients more than for other domains of the syndrome. In addition, it should be considered that several authors reported a better response to

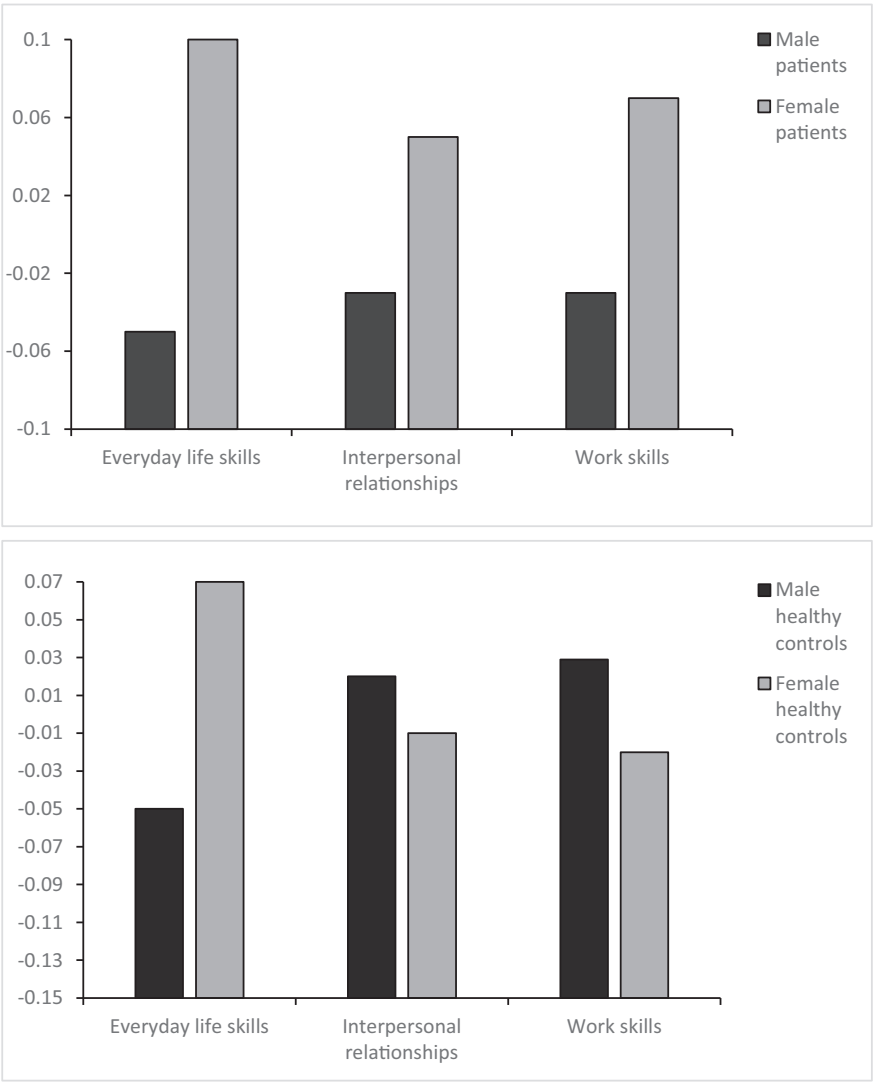

Fig. 3. Gender comparisons on real-life functioning in patients and healthy controls.

Table 4
Group comparisons on clinical remission and functional recovery at follow-up.

Whole experimental sample	Males (N = 427)	Females (*N* = 191)	p
Clinically remitted [n (%)]	123, 28.8 %	62, 32.5 %	0.359
Functionally recovered [n (%)]	81, 19 %	43, 22.5 %	0.309

Subsample with age at onset < 40 yrs and duration of illness < 10 yrs	Males (*N* = 124)	Females (*N* = 61)	p
Clinically remitted [n (%)]	55 (44.3 %)	29 (47.5 %)	0.333
Functionally recovered [n (%)]	41 (33.1 %)	22 (36.12 %)	0.682

antipsychotic treatments in women due to several reasons, including a greater adherence to treatment, gender differences in pharmacokinetics resulting in higher blood levels in women who require lower doses of antipsychotics, as well as the role of estrogens which enhance dopamine blockade (Seeman, 2019). Our finding of a lower severity of positive symptoms in women, despite their lower mean daily dosage of antipsychotics (Table 1), is in line with the above-reported observations.

Lack of gender differences in depressive symptoms in our sample is not in line with the majority of studies investigating this aspect (Taylor and Langdon, 2006; Riecher-Rössler et al., 2018). Actually, we found higher scores for depressive symptoms in women with respect to men, but this difference was not statistically significant. However, in line with most findings of the literature, we found a higher prevalence of comorbidity for affective disorders in women.

Our neurocognition findings showed that, in the group of patients, men were more impaired in verbal learning, while women were more impaired in reasoning/problem solving. In healthy controls, the same pattern observed in patients for reasoning/problem solving was observed, as women showed a disadvantage in this domain; in addition, women showed a worse performance on attention/vigilance and working memory, not observed in the group of patients. Discrepant data have previously been reported on gender differences in neurocognitive performance; when such differences were found, the patterns of involved cognitive domains in men and women varied among studies (Mendrek and Mancini-Marie, 2016). This might be due to differences in size and characteristics of the experimental samples as well as to the heterogeneity of tests used to assess cognitive functions. In the four studies in which the MCCB was used (our present study and Zhang et al., 2017; Mu et al., 2020; Zhao et al., 2021) a consistent pattern was observed in healthy controls, with women showing a worse performance on reasoning and problem solving in all studies, and on working memory in all but one study (Zhao et al., 2021). In our patients, a lack of the advantage of men in working memory was observed, in line with two other studies (Zhang et al., 2017; Zhao et al., 2021), while in a third one

Table 5
Stepwise multiple regression analyses in males and females.

		Males			Females		
		F(5,409)	R^2	p	F (5,179)	R^2	p
SLOF Everyday life skills at follow-up	Baseline:						
	Age of onset						
	Marital status						
	Substance abuse				6.29	0.03	0.01
	Alcohol abuse						
	Comorbidity Affective dis.						
	PAS Academic domain						
	PANSS positive symptoms	12.84	0.02	0.0004	5.19	0.02	0.02
	PANSS disorganization						
	BNSS_avolition						
	BNSS expressive deficit	28.1	0.05	0.000001			
	B-C religion						
	B-C emotional support						
	MCCB – Verbal learning	61.81	0.13	0.000001	14.14	0.07	0.0002
	MCCB – reasoning/probl. solving	9.97	0.02	0.002	5.04	0.02	0.03
	Service engagement change score	7.54	0.01	0.01	4.01	0.02	0.05

		Males			Females		
		F(4,410)	R^2	p	F (4,182)	R^2	p
SLOF Interpersonal relationships at follow-up	Baseline:						
	Age of onset						
	Marital status						
	Substance abuse						
	Alcohol abuse						
	Comorbidity Affective dis.						
	PAS Academic domain						
	PANSS positive symptoms	5.77	0.01	0.02	5.83	0.02	0.02
	PANSS disorganization						
	BNSS_avolition	46.82	0.10	0.000001	18.77	0.09	0.00002
	BNSS expressive deficit						
	B-C religion						
	B-C emotional support				7.57	0.03	0.006
	MCCB – Verbal learning	10.73	0.02	0.001			
	MCCB – reasoning/probl. solving						
	Service engagement change score	13.40	0.03	0.0003	13.79	0.06	0.0003

		Males			Females		
		F(7,407)	R^2	p	F (3,184)	R^2	p
SLOF Work skills at follow-up	Baseline:						
	Age of onset						
	Marital status	4.91	0.009	0.03			
	Substance abuse						
	Alcohol abuse						
	Comorbidity Affective dis.						
	PAS Academic domain	7.94	0.01	0.005	6.84	0.03	0.01
	PANSS positive symptoms	25.04	0.05	0.000001	20.27	0.10	0.00001
	PANSS disorganization						
	BNSS_avolition	14.26	0.03	0.0001			
	BNSS expressive deficit						
	B-C religion						
	B-C emotional support						
	MCCB – Verbal learning	64.42	0.13	0.000001			
	MCCB – reasoning/probl. solving	5.56	0.01	0.02			
	Service engagement change score	7.56	0.01	0.006	15.62	0.07	0.0001

SLOF = Specific Levels of Functioning, PAS = Premorbid Adjustment Scale, PANSS = Positive and Negative Syndrome Scale, BNSS = Brief Negative Symptom Scale, BC = Coping Orientation to Problems Experienced inventory – Brief, MCCB = Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery.

even an inverted pattern was reported, with women showing and advantage on digital sequence (one of the tests exploring working memory) (Zhao et al., 2021); these data suggest that the impairment in this domain in men is specifically related to the illness. The greater impairment of verbal learning observed in men in our sample of patients was confirmed in two studies using the MCCB (Zhang et al., 2017; Zhao et al., 2021), and the greater impairment of reasoning/problem solving observed in women patients was confirmed in the third one (Mu et al., 2020). On the whole, these data suggest that, in men, an impairment of verbal learning and a lack of the advantage observed in healthy controls for working memory may represent a gender-specific pattern of cognitive impairment related to the illness and one of the possible risk factors for developing psychosis. In addition, we found that verbal learning has a gender-specific impact on real-life functioning, as it was associated to the areas interpersonal relationships and work skills only in men. Discrepant data on gender-related differences in cognition were

reported in studies using the MCCB, confirming that the heterogeneity of clinical expression of the illness and of treatments may affect results in patient populations thus producing more discrepancies than in healthy controls. In the light of these observations, an accurate assessment of cognitive functions in subjects at risk for psychoses and/or in subjects in the early stage of illness may identify the specific cognitive domains impaired in men and women and contribute to the implementation of gender-tailored rehabilitation interventions.

As to social cognition, in our study women showed an advantage in FEIT and TASIT with respect to men in the group of patients; the difference only approached statistical significance. In our sample of healthy controls, this advantage was limited to the FEIT, was statistically significant and in line with previous studies reporting an advantage in women in the general population on emotion recognition (Hall et al., 2004; Vaskinn et al., 2007; Alaerts et al., 2011; Navarra-Ventura et al., 2021). Non conclusive data have been reported so far on this topic, as a disadvantage in men vs. women on social cognition has been found in some studies, mainly for emotion perception (Vaskinn et al., 2007; Erol et al., 2013), but not confirmed in others (Pinkham et al., 2017; Navarra-Ventura et al., 2018). Our findings are in line with those reported in a meta-analysis (Kohler et al., 2010), as well as in a recent paper (Navarra-Ventura et al., 2021) in which an advantage in social cognition only in healthy women was found. It cannot be excluded that the advantage in social cognition observed in women is a characteristic of the general population that undergoes a gradual reduction in chronic patients, probably due to the disease itself and/or its consequences on social life, thus suggesting the need to carefully assess emotion perception in early stages of illness, and eventually implement early psychosocial interventions to counteract its progression.

In the present paper we also explored gender differences in personal resources, a factor impacting outcome (Galderisi et al., 2014; Galderisi et al., 2020), whose differences between the two genders have been scarcely explored. Higher resilience and better coping strategies in women than in men have been hypothesized in some studies (Häfner, 2002; Ochoa et al., 2012) but no consistent data have been provided so far. Our findings in patients and healthy controls showed a quite complex picture. Two coping styles (religion and use of emotional support) were more frequently used by women than by men in the group of patients. In healthy controls, the advantage of women as compared to men for these two coping styles was highly significant, along with an advantage in two more coping styles (expression and self-blame). Self-blame cannot be considered an efficient coping strategy, however the observed difference was less marked than for the other coping strategies. Overall, in the control group we found a more frequent use of effective coping strategies in women; a similar trend was observed in the patient group, but differences involved a lower number of items and were less marked than in control subjects. On the contrary, some items of resilience and self-esteem showed an advantage in men in the sample of healthy controls, and no gender differences in the group of patients. This opposite pattern of gender differences observed in healthy controls for coping strategies and resilience may be explained by the specific aspects of personality explored by the items in question. In fact, men show higher self-esteem, in line with several other studies (Van Damme et al., 2014; Bleidorn et al., 2016; Pazzaglia et al., 2020), as well as better resilience in the areas of perception of self and perception of the future, which both include items in overlap with the concept of self-esteem (e.g., "I strongly believe in/I am uncertain about my abilities"; and "I trust completely/I often doubt my judgements and decisions"). On the other hand, women show a more frequent use of emotionally oriented coping strategies, such as the attitude to express emotions and the use of emotional support, as compared to men. These differences in the general population are probably mainly related to socio-cultural factors and to gender role expectations and are attenuated in our sample of subjects with chronic schizophrenia, with the exception of emotional support which was more frequent in women vs. men also in patients and showed a positive influence on the interpersonal relationships domain of real-life functioning only in women. The presence of such characteristics before the development of psychosis or in the early stage of the illness may impact the symptom trajectories. As an example, the lower emotionally-oriented coping strategy in men may predispose them to develop negative symptoms such as the expressive deficit although it may even be related to the presence of this symptom before the onset of psychosis. On the whole, gender differences in personal resources deserve further investigations, especially in subjects at risk of psychosis and in the early stages of illness.

Thanks to the longitudinal design of our study, we could explore gender differences in change scores from baseline to follow-up in all clinical, cognitive and outcome assessed indices. As a matter of fact, we found no gender difference for any of the variables explored over time, with the exception of the engagement with mental health services that improved significantly more in men than in women. Men, who showed a lower level of engagement at baseline, improved on this aspect during the follow-up and reached the level of engagement of women. This was not related to gender differences in the frequency of psychosocial intervention during the follow-up period, as this frequency was comparable in the two genders (data not shown). Lack of gender differences on all other changes may be due to the characteristics of the experimental sample including chronic patients stabilized on treatment. Further studies investigating gender differences in change score at follow-up in first episode patients by using new-generation tools may clarify this issue.

Despite the more severe clinical picture in men than women observed in our study, we did not find a worse outcome: the three domains of real-life functioning, as well as functional capacity, were comparable between the two groups. In addition, we found no gender difference in the rates of clinical remission or in the rates of functional recovery at follow-up.

A lack of gender differences in these outcome indices has been found in several studies (Galderisi et al., 2012; Jaaskelainen et al., 2013). It has been hypothesized that a better outcome may be achieved in women only in the early- and medium-term of illness and/or only in patients with early-onset schizophrenia (Riecher-Rössler et al., 2018; Seeman, 2019). For this reason, we compared the rate of remission and recovery also in a subsample of patients with an onset before age 40 and a duration of illness lower than 10 years – and found no gender difference even in this case.

In conclusion, in a large sample of community dwelling persons with schizophrenia, we observed a greater severity of several clinical, cognitive and premorbid adjustment characteristics in men as compared to women. In spite of the repeatedly demonstrated relationship of these variables with functional outcome, we did not find gender related differences in rates of clinical remission and recovery. A possible explanation of this finding may be the fact that recovery is a complex construct (Heckers and Kendler, 2020) which is influenced by several factors, among which negative symptoms, social and non-social cognition, functional capacity and personal resources, acting in a complex relationship as predictors or mediators of outcome (Green et al., 2000; Leifker et al., 2009; Harvey and Strassnig, 2012; Galderisi et al., 2014; Rossi et al., 2017; Galderisi et al., 2018b; Galderisi et al., 2020; Mucci et al., 2021; Lahey et al., 2021; Ventura, 2022). Among the above-listed factors, some were more severe in men in our sample, while others were not. Cognitive deficits, which are considered among the most important factors impacting outcome, were not univocally more impaired in men, as opposite patterns of gender differences were observed for verbal learning and reasoning and problem solving; resilience and functional capacity didn't show any gender difference in the patient sample. In addition, it cannot be excluded that the higher frequency of comorbidity for affective disorders observed in women has a negative impact on recovery, thus counterbalancing at least in part the influence of other risk factors resulting more severe in men. Moreover, regression analyses showed some gender-specific associations with domains of real-life functioning, indicating that a given risk factor may have a different

impact on social functioning in the two genders.

As to the lack of gender differences in clinical remission observed in our sample despite the lower severity of positive and negative symptoms in women, it may be explained by the fact that symptoms for which a threshold is required in Andreasen et al.'s criteria are not fully in overlap with symptoms included in the positive and negative dimensions. Moreover, remission according to those criteria requires a threshold of low-mild severity, therefore positive and negative symptoms in women, although less severe, do not reach this threshold with a significantly higher frequency than men.

Our finding of lack of gender differences in recovery/remission rates despite the greater severity of several risk factors observed in men at baseline could also be due to an attenuation of the clinical and functional advantage in women who started menopause during the 4-year follow-up period, related to the reduction of estrogen levels which are known to play a protective role in women. This possibility cannot definitely be ruled out since data on menopausal status were not available in our sample. However, we can reasonably assume that this aspect has small or no impact on our findings if considering that no gender difference was observed for any of the considered change scores (except for the engagement with mental health services, which resulted more improved in men than in women) thus indicating that differences between men and women for explored risk factors as well as for real life functioning were stable over the follow-up period.

The duration of follow-up in our study may be a further factor influencing lack of gender differences in outcome, as it cannot be excluded that such differences may reveal after a period longer than 4 years, although it is worth noting that no gender difference was observed on social functioning even in a 34-year follow-up study (Newman et al., 2012).

On the whole, our finding of lack of gender differences in outcome indices, although somewhat unexpected on the basis of the observed differences in several risk factors, is in line with those of other studies and has been controlled for several potential methodological biases. However, it should be acknowledged among study limitations that our sample is not representative for all patients with schizophrenia, which might affect generalizability of our findings. This is particularly true for gender differences relevant to functional outcome, which can be more influenced by social and cultural aspects such as gender-determined social roles, pressures and expectations differing across diverse regions of the world and social contexts, which cause differences between men and women on several factors impacting functioning, including level of family tolerance for symptomatic behaviors, degree of social support, rate of employment, access to healthcare and severity of discrimination (Xiang et al., 2010; Novick et al., 2016; Mayston et al., 2020).

Findings observed in our sample of healthy controls showed that, for some of the explored variables, gender differences in the general population may be attenuated or absent in patients with chronic schizophrenia, probably due to the illness process, or may even represent a gender-specific vulnerability factor to develop the illness. However, it is possible that some of the disadvantages observed in men or women in the general population impact the age and modality of onset and/or symptoms trajectories in subjects developing psychosis. This may be the case of the coping strategy "emotion expression" which in healthy controls is more impaired in men, or of self-esteem, which is lower in women. A word of caution should be added on generalizability of findings observed in healthy controls, given the lack of representativeness affecting also this group.

In the light of the need for early and personalized treatments to improve outcome of schizophrenia, highlighted in the recent literature (Bond et al., 2020; Singh and Javed, 2020; Carpenter, 2021; Maj et al., 2021; Killaspy et al., 2022) our findings underscore the importance of an accurate assessment of factors which may show gender differences, in order to implement comprehensive and personalized intervention programs. In addition, patterns of gender differences observed in healthy controls vs. those observed in patients suggest that early detection of gender differences before the onset or at the early stages of psychosis represents a further strategy to implement gender-tailored interventions to prevent and/or to successfully treat schizophrenia.

CRediT authorship contribution statement

Silvana Galderisi, Paola Bucci and Mario Maj contributed to the conception and design of the study. Silvana Galderisi and Paola Bucci drafted the manuscript. Paola Bucci analyzed the data. All Authors participated in the coordination of recruitment, assessment and data collection as well as in the critical revision of the manuscript, providing the final approval of the version to be published.

Role of the funding source

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Declaration of competing interest

None.

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Appendix A. Supplementary data

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