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Sex differences in first-episode psychosis and in people at ultra-high risk

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ABSTRACT

Sex-related differences in the clinical expression and outcome of schizophrenia have long been recognized; this study set out to evaluate whether they extend to those subjects who are at high risk of developing psychosis. In a sample enrolled in two early intervention programs in northern Italy, patients with first-episode psychosis (FEP; $n=152$) were compared to patients at ultra-high risk of psychosis (UHR; $n=106$) on a series of sex-related clinical characteristics of schizophrenia. In both the FEP and the UHR samples, males outnumbered females. In FEP patients, women had been referred at an older age than men and had a shorter duration of untreated illness (DUI) and of untreated psychosis. In UHR patients no sex differences were found in age of onset or DUI. There was no diagnosis by sex interaction on symptoms severity or level of functioning at presentation. The limited number of women in both samples, and the exclusion of people who were older than 30 and of those with substance dependence may have reduced the extent of sex-related differences in this study. Sex differences of precipitating factors for psychosis might be worthy of further investigation.

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1. Introduction

Epidemiological studies and meta-analyses have challenged the held belief that schizophrenia affects men and women equally (Aleman et al., 2003; McGrath et al., 2004). The studies that use currently shared criteria for the diagnosis of schizophrenia have found that incident rates (cases per 100,000 per year) are consistently higher for males (median: 15.0) than for females (10.0), with a median rate ratio of 1.4 (McGrath et al., 2008). Sex ratio becomes even higher when the most stringent criteria for diagnosis are used (Beauchamp and Gagnon, 2004). The differences in incidence rates disappear when the analysis is confined to prevalence rates, with median lifetime prevalence (per 1000) largely overlapping by sex: males – 3.7 vs. females – 3.8 (McGrath et al., 2008).

The differences related to sex in the clinical expression and outcome of schizophrenia have long been recognized (Seeman, 1982; Leung and Chue, 2000). Males are reported to have an

earlier onset of the disorder, or earlier detection of the symptoms than females (Angermeyer and Kuhn, 1988; Cascio et al., 2012). Earlier onset of schizophrenia in male patients was consistently found in Western countries (Angermeyer and Kuhn, 1988; Faraone et al., 1994; Häfner, 2003; Hambrecht et al., 1992; Szymanski et al., 1995) and in non-Western countries (Gureje, 1991; Hambrecht et al., 1992; Tang et al., 2007; Zhang et al., 2012). No sex difference in age of onset was found in cases with a high genetic load (DeLisi et al., 1994; Könncke et al., 2000). A family history of psychosis, therefore, should be taken into account in studying sex differences in age of onset of schizophrenia.

Females often have a better course and outcome (Addington and Addington, 2008; Grossman et al., 2006; Häfner and an der Heiden, 1999; Perkins et al., 2005), and they are less likely to suffer from substance abuse, social drift and law infringement (Biancosino et al., 2009; Cantor-Graae et al., 2001; Romm et al., 2010; Thorup et al., 2007; Walker et al., 1985). Better outcome in women was not always reported in non-Western countries (Rangaswamy and Greeshma, 2012). For example, in Colombia men were found to have a better outcome (Hopper et al., 2007). Environmental factors unevenly distributed across geographical areas might be involved in the geographical outcome differences by gender.

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Several environmental factors of small effect, such as cannabis abuse, winter/spring birth, prenatal infection and famine, obstetric and perinatal complications, or social stress, are associated with an increased risk of developing schizophrenia (Arendt et al., 2008; Gracie et al., 2007; Mortensen et al., 1999; Scott et al., 2007; Tandon et al., 2008). These risk factors could affect males more than females, although specific investigations on this topic are lacking. Past studies indicated a greater risk of obstetric complications in males compared to females (Insel et al., 2005; Jones et al., 1998; Preti et al., 2000), and this may parallel the greater risk of schizophrenia in people born after pre-/peri-natal complications (Cannon et al., 2002; Clarke et al., 2006; Preti and Miotto, 2005). Alcohol and drug abuse appeared significantly more often among men, impacting on social functioning (Køster et al., 2008). Conversely, estrogens were supposed to modulate dopaminergic hyperactivity in females, thus leading to a smoother course of the disorder and a later onset of the frank episode of psychosis (Reicher-Rossler et al., 1994; Seeman and Lang, 1990; Kulkarni et al., 2012).

The higher risk of mortality in males compared to females, especially in the first years after the onset of the disorder, might also contribute to explaining the finding of different incidences, although with comparable prevalence in the two sexes (Joukamaa et al., 2001; Heilä et al., 2005). Overall, sex differences among patients with schizophrenia include age of onset, symptoms severity at presentation, treatment response, course of illness and outcome (Grossman et al., 2006; Häfner, 2003; Tamminga, 1997).

1.1. Sex differences in subjects at ultra-high risk of developing psychosis

It is unknown whether sex differences in the epidemiology, course and outcome of schizophrenia extend to those subjects who are at ultra-high risk of developing psychosis. This recently defined category includes people with signs of incipient psychosis, and principally involves three clusters of subjects: young people with attenuated positive symptoms, as revealed by dedicated interviews (Olsen and Rosenbaum, 2006); people with diagnosable transient psychotic symptoms, not stabilized in a syndrome yet (Simon et al., 2006; Phillips et al., 2007); and a third category of people with genetic risk (first degree relatives of subjects with psychosis), or meeting the criteria for Schizotypal Personality Disorder, who are showing symptoms of deterioration (Cornblatt et al., 2003). There is evidence that focused treatments with UHR people are effective in reducing the risk of transition to full-blown psychosis over a 12 month period (Preti and Cella, 2010; van der Gaag et al., 2013).

An overlap of sex differences between first-episode patients and the subjects at ultra-high risk of developing psychosis would further corroborate the classification of people at ultra-high risk of psychosis in the spectrum of schizophrenia. The finding may have implications also for research on the etiology of schizophrenia and in clinical practice, since disease characteristics that differ by sex point to gender specificity in altered neurobiology and may suggest new treatment approaches – for example, estrogen augmentation (Begemann et al., 2012).

However, only a minority of UHR people develops full-blown psychosis (de Koning et al., 2009). For this reason, sex differences might be less evident in UHR samples than in samples of people diagnosed with schizophrenia. Indeed, when investigated, no relevant sex differences were found in samples of patients diagnosed as ultra high risk (UHR) or with sub-threshold symptoms of psychosis (Johnstone et al., 2005; Willhite et al., 2008; Lemos-Giráldez et al., 2009; Ziermans et al., 2011; Rössler et al., 2012). Nevertheless, some studies reported sex differences in baseline social and role

functioning among UHR people prior to psychosis onset (Statucka and Walder, 2013).

1.2. Changes in services organization and sex differences in clinical and prognostic factors

Changes in the provision of healthcare, and the settlement of community-based mental health services in Italy in the past decades (de Girolamo et al., 2007a, 2007b), might have changed the impact of sex differences on the course and outcome of schizophrenia in Italy. Greater access to psychiatric services might have favored the early diagnosis and treatment of people who are developing a psychosis, thus reducing the severity of the disorder at its onset and decreasing its impact on patient's functioning. In recent years, early intervention programs of care were developed in Italy (Cocchi et al., 2008), as elsewhere (Kovasznyay et al., 1997; Lambert et al., 2005; Yung et al., 2007), to reduce the most negative consequences of schizophrenia. Since women are more likely to disclose symptoms of distress (Galdas et al., 2005), they might have benefited more from these programs, with a lower duration of untreated psychosis (DUP) and less severe symptoms at presentation.

Sex differences in schizophrenia were not always reported (Addington et al., 1996; Huber et al., 1980; Klinkenberg and Calsyn, 1998). The research has suffered in part from relatively small sample sizes, and has focused on chronic patients mostly. Only one study has been carried out on this topic in Italy in recent years. Bertani et al. (2012) analyzed a large epidemiologically representative cohort of first episode of psychosis (FEP) patients ($n=517$) who were assessed within a multi-site research project examining incident cases of psychosis in the Veneto region of Italy, and found that males were nearly 3 years younger and had longer DUP than female patients. No statistically significant differences by gender were seen in symptoms at presentation as assessed on the Positive and Negative Syndrome Scale (Kay et al., 1987). However, males reported greater pre-morbid functioning and higher social disability at illness onset, but fewer unmet needs in the functioning domain than females did (Bertani et al., 2012). No study has investigated sex differences in Italian samples of UHR patients so far.

The investigation of sex differences in schizophrenia and its prodroms may be more helpfully pursued in patients at their first episode, given the lower impact of confounding factors such as illness duration, effects of medication, medical comorbidity and other consequences of illness chronicity (Buckley and Evans, 1996). Data from two Italian comprehensive programs targeted at the early detection of and early intervention for subjects at the onset, or showing prodromal signs of psychosis, and operating in Milan and its surroundings (Desio), were used to evaluate: (a) whether women with first-episode schizophrenia who had accessed the service since its opening had a lower DUP and less severe symptoms and better level of functioning at presentation than males; (b) whether men with first-episode schizophrenia had younger age at enrollment (a proxy of age of onset) than women; (c) whether sex differences in symptoms presentation or age at onset extend to people at high risk of psychosis enrolled in the same period of time. The factors that may influence uneven symptoms presentation by sex, such as obstetric complications, substance use, duration of untreated illness (DUI) and DUP, suicidal behavior and traumatic events were taken into account when analyzing sex differences in age of onset, symptoms and level of functioning at presentation. Obstetric complications and substance use are expected to be more frequent in male patients than in female ones and might impact on the severity of symptoms or level of functioning at presentation. Longer DUP was related to male sex and younger age of onset (Bertani et al., 2012;

Chang et al., 2012). Conversely, suicidal behavior or traumatic events could accelerate referral to treatment for cases with an ongoing psychosis (Preti et al., 2009).

2. Methods

The data were collected during the routine assessment of the patients referred to the two centers where the study was carried out. Both centers follow the same protocol, previously described elsewhere (Cocchi et al., 2008; Meneghelli et al., 2010). The competent institutional review boards approved the study, and all patients gave their informed consent. The *Programma2000* was started in Milan in 1999 as an autonomous center specifically devoted to the early diagnosis and intervention for people with, or at high risk of psychosis, under the authority of the Niguarda Ca' Granda General Hospital. The *Programma2000* sample included 206 patients out of a catchment area catering for approximately 200,000 inhabitants. The *Desio Early Intervention Service* was implemented in 2006 under the Department of Mental Health of Desio, which covers a catchment area of about 230,000 residents, north of Milan. The *Desio Early Intervention Service* sample included 52 patients out of a catchment area specifically catering for approximately 80,000 inhabitants.

2.1. Diagnosis and assessment

In both centers patients are enrolled in treatment provided that they are at their first contact with any public mental health service of the catchment area for a first episode of psychosis or have been referred to the program on the basis of a suspicion of psychosis. All the patients referred for evaluation undergo a comprehensive, multidimensional evaluation. For the purpose of this study, the following standardized assessment instruments were considered: (i) a socio-demographic form; (ii) the Early Recognition Inventory Retrospective Assessment of Symptoms (ERIRAOS) (Häfner et al., 1992; Raballo et al., 2013), a 17-item screening checklist intended to select the subjects requiring a more in-depth assessment; (iii) the Health of the Nation Outcome Scale (HoNOS) (Wing et al., 1998; Preti et al., 2012b), which was used to assess psychopathology and disability; it includes 12 five-point items to evaluate clinical and social functioning in the past 2 weeks; (iv) the 24-item Brief Psychiatric Rating Scale (Overall and Gorham, 1962; Roncone et al., 1999), to assess general psychopathology; (v) the Global Assessment of Functioning (GAF) (Moos et al., 2000).

All assessors were psychologists and had a minimum of 2 years experience in rating patients diagnosed with psychosis or in the prodromal phase. Inter-rater agreement among the clinical staff was regularly checked to assure good-to-acceptable concordance on the scales; intra-class correlation coefficients were 0.70 or above in all scales when performed on a small sample of patients ($n=25$) during training; k-agreement for GAF was 0.80 during training.

After the initial screening on the ERIRAOS, patients meeting criteria for inclusion (see below) were further evaluated on the severity of their symptoms on the BPRS and of their current problems and levels of disability on the HoNOS, and also received an estimate of their current level of functioning on the GAF. For both FEP and UHR cases the treating therapist made a diagnosis after detailed evaluation by at least two assessors and a staff meeting for a thorough discussion of the assessment results (details in Meneghelli et al. (2010)).

2.2. Inclusion and exclusion criteria

All consecutive admissions were enrolled in the study. A total of 527 subjects had been referred to the services since their establishment (available data up to December 2012). Among these, 25 did not complete the assessment. Among those who completed the assessment ($n=502$), 211 were sent to the service that had originally asked for the evaluation, either because they were living in other regions of Italy ($n=52$), or they had a DUP longer than 24 months ($n=55$), or they did not meet the a priori criteria to identify a UHR case ($n=104$). Among the patients meeting inclusion criteria, no individual was excluded due to inability to comprehend consent procedures or due to acute clinical status that made interviewing assessment difficult or unreliable; 291 subjects were offered a dedicated protocol of care: 258 accepted and were enrolled in the Program, 18 refused and 15 did not show up after accepting the proposal (see Fig. 1 for details). The rejected cases and those who refused treatment received appropriate advice for future treatment.

2.2.1. Inclusion criteria

Patients were included as an FEP case when at admission they had received a diagnosis of schizophrenia or related syndromes (F20–29 in ICD-10) according to ICD-10 (WHO, 1992). Additional inclusion criteria for an FEP case were as follows:

- they had never received antipsychotic treatment before the current episode;
- they were aged 17 to 30;
- they had a DUP \leq 24 months.

Under the early intervention paradigm, DUP lower than 24 months is the threshold to start an early intervention protocol of care (Birchwood, 2000). Of course, patients with longer DUP are still worthy of treatment, but they need different protocols of care to take into account the impact of the consequences of a long period of untreated psychosis (Häfner et al., 2003; O'Donoghue et al., 2013). The age limit was introduced to maximize the chance of enrolling patients at their real first episode of psychosis. This age cut-off might have reduced the chance of including in the study the fraction of women who have a late onset of psychosis (Angermeyer and Kuhn, 1988; Häfner et al., 1998).

Patients were included in the UHR group when they met the criteria of the Personal Assessment and Crisis Evaluation (PACE) Clinic in Melbourne, the so-called Melbourne criteria for the identification of young people at incipient or 'ultra high risk' of developing a psychotic disorder (Yung et al., 1996, 2004; Phillips et al., 2007). To screen UHR patients, the ERIRAOS was used rather than the Comprehensive Assessment of At-Risk Mental States (Yung et al., 2005). A score \geq 12 on the 17-item ERIRAOS was deemed necessary for UHR to be included in the study. This threshold proved able to discriminate between patients in need of treatment, and those whose symptoms were likely to fluctuate without any serious risk of transition to psychosis (Maurer et al., 2006). Patients screened positive on the ERIRAOS-CL were further evaluated and enrolled when they met one of these PACE operational criteria for UHR: (1) attenuated Positive Prodromal Syndrome; or (2) brief, limited, and intermittent psychotic syndrome; or (3) familial genetic risk or Schizotypal Personality Disorder and evidence of deterioration in functioning in the past year, i.e. they showed a 30% decrease on the GAF with respect to the estimated premorbid functioning (Yung et al., 1996, Phillips et al., 2007).

Additional inclusion criteria for a UHR case were as follows:

- they had never received antipsychotic treatment before admission;
- they were aged 17 to 30;
- no limits on DUI were imposed.

2.2.2. Exclusion criteria

A past or present diagnosis of psychosis in the spectrum of schizophrenia was a mandatory exclusion criterion for UHR diagnosis.

In both FEP and UHR patients, affective psychosis (bipolar disorder, or unipolar disorder with psychotic features) was an exclusion criterion, as was a co-morbid persistent substance-use dependent disorder, while substance use/abuse without dependence was not.

2.3. Variables of interest

Diagnosis (FEP versus UHR status) and sex were the main predictors of this study. Severity of symptoms and level of functioning at presentation were the main target measures of this study. Additional variables were investigated, whether as confounding (e.g., age at enrollment) or as a mediators of possible differences (e.g., family psychiatric history, DUI or DUP).

Socio-demographic data concerning the patients, such as age at enrollment, school education and marital status, were collected at enrollment.

Data on family psychiatric history and obstetric complications were based on a detailed interview with each patient's parents. All parents were offered a psychoeducation session on the disorder, and while they received information and support on the disorder and its risk factors, they were also enquired about them on an item-by-item basis.

A family psychiatric history was defined as any first/second degree relative having received a formal diagnosis of a mental disorder and/or having been hospitalized in a psychiatric unit twice or more, and/or having received two or more prescriptions of antipsychotic or antidepressant drugs (drugs were listed). Any positive reply was counted as evidence of a family psychiatric history.

Obstetric complications were defined as any somatic complication occurring during pregnancy, with some potential direct relevance to the physical wellbeing of the offspring. Patients' mothers were asked whether they suffered from any obstetric complication; conditions were listed (details in Preti et al., 2012a).

All the other data on patient's clinical status before referral (e.g., past treatments, past admissions, and exposure to traumatic events) were drawn from a detailed interview with the patient and a key informant.

Each patient and a key relative were inquired to know whether the patient was already in treatment for psychological symptoms before being addressed to the service, and whether s/he had been hospitalized in a psychiatric unit in the past.

Traumatic events were considered as any event within the last 12 months that could potentially cause physical or psychological harm to the patient, e.g. being a victim of a violent act, a road accident, an episode of public humiliation, etc. The history of suicide attempts was investigated by considering any act of purposefully inflicted self-harm with expressed suicidal intent, i.e. the wish to die, as reported by the patient at the assessment and/or by a family member consulted as a key informant (no discrepancy), as in Preti et al., 2009.

Data on substance use, abuse and dependence were based on a detailed interview with the patient and a key informant (a close relative, usually a parent). Substance abuse was investigated by asking whether the patient had received any

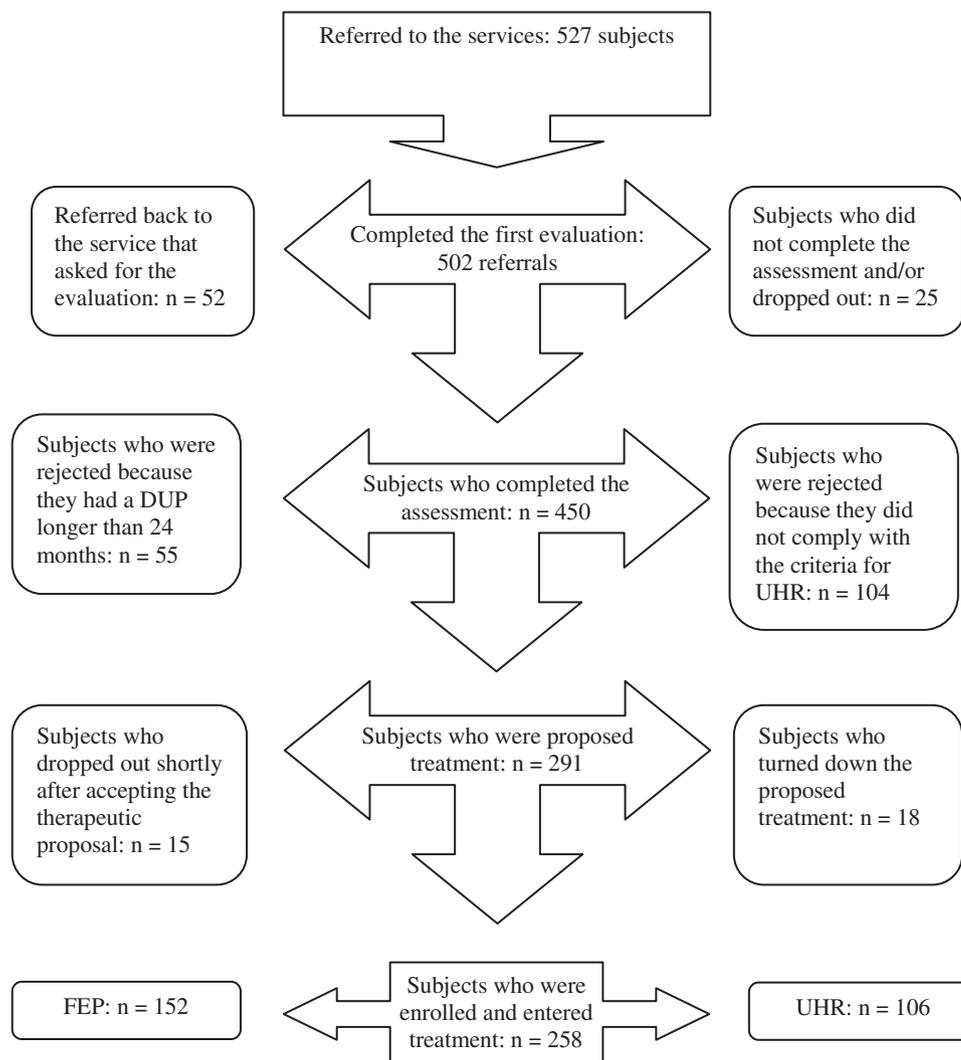


Fig. 1. Flowchart of referrals to Programma2000 and the *Desio Early Intervention Service*. Note: DUP=Duration of untreated psychosis, UHR=Ultra high risk of psychosis, FEP=First episode of psychosis.

diagnosis of substance abuse in the last 24 months, or habitually consumed a drug from a list including alcohol, tobacco, cannabis, cocaine, heroin/opiates, amphetamine and its derivatives, hallucinogens and a residual class of "others". The threshold for abuse was defined according to the ICD-10 (WHO, 1992), i.e. the inability to stop using the drug despite awareness of a health risk.

DUI and DUP were both measured as the time elapsed from the onset of key symptoms (anxiety, depression or social withdrawal for DUI; hallucinations, delusions or bizarre behavior for DUP) to the beginning of treatment (pharmacotherapy or psychotherapy) prescribed by a psychiatrist; DUP was measured in days, DUI in months. To measure DUP/DUI, we considered the symptoms as they were elicited by the ERiraos-CL, and considered patient's estimated time of onset of key symptoms as listed in the tool. Further information on key symptoms onset was collected during the direct interview of a key informant. A therapist (usually a psychiatrist) and a researcher (usually a psychologist or an educator) of the team made the DUI/DUP assessment jointly. In problematic cases consensus with a senior clinician was sought.

2.4. Statistical analyses

Data were analyzed with the Statistical Package for Social Science (SPSS) for Windows (Chicago, Illinois 60606, USA), version 17. All tests were two-tailed, with $\alpha=0.05$. As a correction for multiple testing we used the approximate false discovery rate, also known as the Benjamini and Hochberg correction (Benjamini and Hochberg, 1995), as implemented in the R package (p.adjust function) (R Core Team, 2012). This procedure is valid when the tests are independent and in various scenarios of dependence (Benjamini and Yekutieli, 2001). The class of false discovery rate procedures has greater power than family-wise error rate

procedures (such as the Bonferroni correction), but at the cost of increasing the rate of type I errors, i.e., rejecting the null hypothesis of no effect when it should be accepted (Shaffer, 1995).

Categorical data were analyzed in inter-group comparisons with χ^2 , or Fisher's exact test, when appropriate ($n < 5$ in any cell). Student *t*-test, or the Mann-Whitney test when appropriate, was used to compare the ordinal variables. We used two-way ANOVA to analyze sex differences by diagnostic group.

For categorical variables, relative risk (RR) with confidence of interval (C.I.) was used as a measure of effect size. For ordinal variables, effect sizes of statistically significant difference were expressed through Hedges's *g* (a bias corrected version of Cohen's *d*) with 95% CI (Kraemer and Kupfer, 2006).

3. Results

The sample included 152 patients diagnosed with FEP and 106 patients diagnosed as UHR.

Males formed the majority in both groups: 117 (77%) in the FEP group, 73 (69%) in the UHR group. A two-way ANOVA model revealed that FEP patients were older than UHR patients at presentation ($F[3;1]=6.66$, $p=0.010$), and males were marginally younger than females ($F[3;1]=3.73$, $p=0.054$). However, there was no interaction of diagnosis with sex ($F[3;1]=2.96$, $p=0.086$). In FEP patients, males were younger at enrollment than female patients (Hedges's $g=-0.48$; 95% CI: -0.86 to -0.10). In UHR

Table 1

Baseline characteristics of the patients enrolled in the two centers since the beginning. All data mean (S.D.), or No. (%).

Variables of interest	First-episode patients		High-risk patients	
	Males No.= 117	Females No.= 35	Males No.= 73	Females No.= 33
Age at entry	22.5 (4.4)	24.7 (5.0)	22.0 (3.7)	22.2 (3.7)
	t -test = -2.50, d.f.=150, p =0.01		t -test = -0.16, d.f.=104, p =0.87	
School education				
College graduate or higher	7 (6%)	4 (11%)	3 (4%)	3 (9%)
High school diploma	50 (43%)	16 (46%)	35 (48%)	14 (42%)
Lower than high school diploma	59 (51%)	15 (43%)	35 (48%)	16 (49%)
	χ^2 = 1.46, d.f.=2, p =0.48		χ^2 = 1.15, d.f.=2, p =0.56	
Marital status (n, %)				
Single	114 (97%)	33 (94%)	72 (99%)	33 (100%)
Married	2 (2%)	2 (6%)	1 (1%)	0 (-)
Separated/divorced	1 (1%)	0 (-)	0 (-)	0 (-)
	χ^2 = 1.96, d.f.=2, p =0.37		χ^2 = 0.46, d.f.=1, p =0.49	
Family psychiatric history (n, %)	70 (60%)	22 (63%)	47 (65%)	21 (64%)
	χ^2 = 0.07, d.f.=1, p =0.78		χ^2 = 0.03, d.f.=2, p =0.87	
Family history of schizophrenia (n, %)	23 (20%)	6 (17%)	9 (12%)	3 (9%)
	χ^2 = 0.11, d.f.=1, p =0.74		χ^2 = 0.23, d.f.=1, p =0.62	
Obstetric complications (n, %)	24 (20%)	5 (14%)	17 (23%)	8 (24%)
	χ^2 = 0.67, d.f.=1, p =0.41		χ^2 = 0.01, d.f.=1, p =0.91	
Already in treatment for psychological symptoms (n, %)	59 (51%)	17 (48%)	32 (46%)	13 (39%)
	χ^2 = 0.05, d.f.=1, p =0.81		χ^2 = 0.29, d.f.=1, p =0.58	
Past admissions (n, %)	66 (56%)	27 (77%)	6 (8%)	6 (18%)
	χ^2 = 4.87, d.f.=1, p =0.03		χ^2 = 2.24, d.f.=1, p =0.13	
Exposure to traumatic events (n, %)	16 (14%)	4 (11%)	4 (5%)	7 (21%)
	Fisher's exact test p =0.78		Fisher's exact test p =0.03	
Suicide attempt before enrollment (n, %)	8 (7%)	7 (20%)	5 (7%)	6 (19%)
	χ^2 = 4.98, d.f.=1, p =0.01		Fisher's exact test p =0.08	
Substance use (any) (n, %)	30 (25%)	5 (14%)	17 (23%)	5 (15%)
	χ^2 = 1.96, d.f.=1, p =0.16		χ^2 = 0.98, d.f.=1, p =0.32	
Substance abuse (any) (n, %)	14 (12%)	2 (6%)	3 (4%)	3 (9%)
	Fisher's exact test p =0.36		Fisher's exact test p =0.37	

patients no statistical difference by sex was found in age at enrollment.

In both groups, females were more likely than males to have a college degree, but the difference did not reach the statistically significant threshold (Table 1).

3.1. Reliability of the scales used in the study

In the FEP group, ICC was 0.65 (95%CI: 0.42–0.78) for the ERlraos-CL; 0.80 (0.69–0.87) for the BPRS; 0.61 (0.35–0.80) for the HoNOS. In the UHR group ICC was 0.64 (0.38–0.85) for the ERlraos-CL; 0.81 (0.67–0.89) for the BPRS; 0.71 (0.51–0.86) for the HoNOS.

3.2. Clinical characteristics at entry in the FEP and the UHR groups

In both groups, a family psychiatric history (first/second close relative with a diagnosed mental disorder) was shared by 2/3 of the sample, with no difference by sex. Family history of psychosis within the spectrum of schizophrenia was not statistically more frequent in FEP ($n=29$; 19%) than in UHR ($n=12$; 11%) patients ($\chi^2=2.26$; $p=0.13$), again with no difference by sex in both groups. There were no differences by diagnosis or sex in the history of obstetric complications (Table 1).

FEP patients were more likely than UHR patients to have had a past admission (RR=12.34; 95% C.I.=6.23–24.46). No other statistically significant differences were found between FEP and UHR

patients in terms of exposure to traumatic event, suicide attempt before enrollment, substance use or abuse.

In FEP patients a past admission was more frequent among females (RR=2.60; 95% C.I.=1.09–6.22), as was a history of suicide attempt before enrollment (RR=3.31; 1.10–9.91). In UHR patients, females were more likely than males to have been exposed to a traumatic event (RR=4.64; 1.25–17.2).

None of these differences survived the false discovery rate correction.

3.3. Sex differences in DUI and DUP

No statistically significant differences were found in DUI by diagnosis, sex or diagnosis by sex interaction (Table 2).

When the analysis was limited to the FEP patients, both DUI (Hedges's $g=0.40$; 0.02–0.78) and DUP (Hedges's $g=0.53$; 0.14–0.91) were shorter in females than in males.

3.4. Sex differences in severity of symptoms and level of functioning at presentation

At presentation FEP patients were more severe than UHR patients on the ERlraos and the BPRS, and had a lower level of functioning on the GAF (Table 2).

There was no diagnosis by sex interaction on severity of symptoms or level of functioning at presentation. FEP patients

Table 2
Clinical characteristics of the patients enrolled in treatment: first-episode psychosis. All data mean (S.D.), or no. (%).

Variables of interest	First-episode patients		High-risk patients		Two-way ANOVA		
	Males No.=117	Females No.=35	Males No.=73	Females No.=33	By diagnosis	By sex	Diagnosis by sex
Duration of untreated illness (months)	30.1 (25.3)	20.4 (21.0)	32.2 (21.9)	30.6 (23.7)	$F=3.31, p=0.07$	$F=2.79, p=0.09$	$F=1.43, p=0.23$
Duration of untreated psychosis (days)	165.6 (213.0)	64.7 (81.9)	–	–	–	$F=7.47, p=0.007$	–
Clinical characteristics at enrollment							
ERlraos	26.1 (8.5)	25.8 (7.5)	18.1 (8.6)	21.2 (6.8)	$F=31.24, p<0.001$	$F=4.90, p=0.03$	$F=1.29, p=0.25$
HoNOS	14.8 (6.4)	14.8 (6.3)	12.6 (4.8)	13.3 (6.2)	$F=3.00, p=0.08$	$F=1.20, p=0.27$	$F=0.01, p=0.90$
BPRS	52.6 (16.9)	56.8 (22.1)	45.4 (12.2)	44.3 (9.2)	$F=5.55, p=0.02$	$F=0.71, p=0.39$	$F=0.44, p=0.50$
GAF	45.3 (10.4)	45.6 (14.3)	52.7 (9.6)	51.3 (8.6)	$F=15.26, p<0.001$	$F=0.09, p=0.76$	$F=0.25, p=0.62$

showed no age-by-sex interaction on severity of symptoms or level of functioning at presentation (data not shown).

4. Discussion

In a sample of 152 patients with first-episode schizophrenia enrolled in a defined catchment area in northern Italy, we found that males outnumbered females, apparently confirming the reported greater incidence of schizophrenia in males (Aleman et al., 2003; McGrath et al., 2008; Cascio et al., 2012). As a matter of fact in the high-risk group, too, males outnumbered females.

In the FEP group, females turned to a specialized center for the early detection and early treatment of psychosis at an older age than males; nevertheless, they had shorter DUI and DUP than males. No differences by sex in DUI were found in the UHR sample.

At presentation, males and females did not differ in terms of symptoms severity or level of functioning. Overall, differences by sex were modest in both the FEP and the UHR samples.

4.1. Sex differences in FEP patients

In our sample, women with first-episode schizophrenia had shorter DUI and DUP than males, but did not differ from men as far as severity of symptoms and level of functioning at presentation were concerned. Changes in the provision of health-care and the settlement of community-based mental health services in Italy may have influenced DUI and DUP of female patients, but did not change the differences in incidence rates by sex.

4.2. Age of onset in FEP and UHR patients

Male FEP patients were younger at presentation than female FEP patients, but this difference did not extend to UHR patients. In all likelihood, the factors that are related to sex differences in age of onset of schizophrenia are specific to the full-blown psychosis and are less evident in the prodromal phases. Precipitating factors, such as stress and substance use and abuse might contribute to explaining sex differences in age of onset of schizophrenia. Possible mediators (e.g., family psychiatric history, and obstetric complications) did not differ by sex in this study.

4.3. Clinical implications of the findings

Sample size is a determinant of the retrieval of statistical differences. We had a very small group of females in both samples under examination, and we might have lost some significant result due to the small sample size. Nevertheless we found confirmation of most findings reported in past studies, which corroborated the validity of this study.

Past studies had already reported that females receive initial inpatient and outpatient treatment at an older age than males (Angermeyer and Kuhn, 1988; Flor-Henry, 1990; Hafner et al., 1998; Tang et al., 2007; Zhang et al., 2012), probably a reflection of the well-known smoother onset of schizophrenia in women (Hafner and an der Heiden, 1999). This smoother course of the disorder associated to a later onset of the frank episode of psychosis was attributed to the protective effects of estrogens in women (Reicher-Rossler et al., 1994; Seeman and Lang, 1990; Kulkarni et al., 2012). An older age of onset also allows the development of social skills and experience, and favors better coping with the difficulties and problems generated by the disorder and its consequences. Alternatively it was suggested, but it is not proven yet, that “a first break at a later age may suggest greater internal resiliency or greater resistance to psychopathology” (Grossman et al., 2008, p. 527). Both biological and social factors may contribute to late onset and better course of schizophrenia in females than in males (Grossman et al., 2006, 2008; McGlashan and Bardenstein, 1990; Palacios-Araus et al., 1995).

It should be borne in mind that the sample included patients within a strict age range (17–30 years old), while people with substance dependence were excluded since the Italian law provides that they be treated in the Department of Drug Abuse. As a consequence, this study excluded those females for whom psychosis had set in after 30 years of age, and the males with a more severe course of the disorder. This may explain the large preponderance of males in both clinical samples and the lack of important clinical differences by sex.

The use and abuse of illicit drugs were reported as a risk factor for the onset of schizophrenia (Bühler et al., 2002), because they mainly act as a precipitating factor in subjects vulnerable to schizophrenia. In our sample, more males than females had a history of substance abuse before the onset of psychosis (but again, we did not reach statistical significance due to sample size). Exposure to traumatic events was statistically more likely in UHR female patients than in males. Despite the limitations due to sample size by sex in this study, the sex differences in sensitivity to substance abuse, and stress as a precipitating factor for psychosis (Gracie et al., 2007; Scott et al., 2007), might be worthy of further investigation.

4.4. Limitations of the study

The limited sample size by sex and the strict age range were already mentioned as limitations of this study. Moreover, some of the variables (e.g., DUI/DUP) were not measured with standardized instruments, although this limitation is common to past studies on the topic (Cascio et al., 2012). The sample was based on consecutive admissions to the two early intervention centers

operating in Northern Italy. We cannot say how this sample is representative of the population of all FEP and UHR cases accessing Italian psychiatric services because there is no study on this topic in Italy. High geographic variability in terms of facilities distribution, coordination standards, knowledge transfer and computerization was reported in Italy (de Girolamo et al., 2007a, 2007b). This organizational variability corresponds to a wide variability across geographical areas of help-seekers with first-episode psychosis (Preti and Miotto, 2000). This organizational and epidemiological variability limits the generalizability of the findings of this study.

5. Conclusion

In a sample including 152 patients diagnosed with FEP and 106 patients diagnosed as UHR, differences by sex were modest or absent under many variables that were classified as typical of schizophrenia in the past. The limited number of women in both samples, and the exclusion of people who were older than 30 and of substance-dependent subjects may have reduced the extent of sex-related differences in this study. The changes in the provision of healthcare implemented in Italy might have also reduced the extent of sex-related differences in schizophrenia compared to the past, by decreasing the negative impact of the disorder on males. Regarding the UHR group, the lack of differences by sex in the investigated variables is congruent with the findings of past studies (Johnstone et al., 2005; Willhite et al., 2008; Lemos-Giráldez et al., 2009; Ziermans et al., 2011; Rössler et al., 2012). Sex differences of the precipitating factor for psychosis might be worthy of further investigation.

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