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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.

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; Könnecke 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 (Kovasznay 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 analysizing 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;