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GENDER AND FIRST EPISODE PSYCHOSIS

S.S.D. _____

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Gender and First Episode Psychosis
Carla Comacchio
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SUMMARY

La presente tesi di Dottorato si occupa di differenze di genere nei pazienti con esordio di psicosi. Il lavoro si articola in *due sezioni*, ciascuna costituita da una *parte teorica* e da una *parte di ricerca*. Nella prima sezione vengono analizzate le differenze di genere nei primi anni dopo l'insorgenza di psicosi, mentre nella seconda viene studiato l'impatto del genere e degli abusi infantili sull'esordio di psicosi.

Per quel che riguarda la prima sezione - "Differenze di genere nei primi anni dopo l'insorgenza di psicosi" - la parte teorica è costituita da una revisione della letteratura che è stata pubblicata come capitolo nel libro "*Health and Gender. Resilience and Vulnerability Factors For Women's Health in the Contemporary Society*". La parte di ricerca è stata condotta nella cornice dello studio PICOS (Psychosis Incident Cohort Outcome Study) ed è diventata un articolo scientifico sottomesso alla rivista *Archives of Women's Mental Health*. Questo lavoro ha evidenziato che nei primi cinque anni dopo l'insorgenza di psicosi, gli uomini mostrano più sintomi negativi delle donne, mentre le donne presentano maggiori livelli di sintomi depressivi e bisogni di cura insoddisfatti rispetto agli uomini.

Nella seconda sezione - "Impatto del genere e degli abusi infantili sull'esordio di malattia psicotica" - la parte teorica è costituita da una revisione narrativa della letteratura su genere e abusi infantili nella psicosi, che sarà a breve sottomessa alla rivista *Acta Psychiatrica Scandinavica*. La parte di ricerca è stata condotta nel contesto del programma strategico GET UP (Genetics, Endophenotypes, Treatment: Understanding early Psychosis) e ha evidenziato un impatto dei traumi infantili sui sintomi negativi e sui bisogni di cura di entrambi i sessi e sull'età d'esordio solo nelle donne. Questo studio è stato sottomessa in forma di articolo scientifico alla rivista *Schizophrenia Research*.

ABSTRACT

Background

There have been many studies investigating the impact of gender on psychosis but few studies have examined the impact of gender on first episode psychosis (FEP). Although recent studies suggest that at psychosis onset gender appears to affect age of the incidence peak, symptoms presentation and social functioning, these findings are not entirely consistent and it is not known whether and how these gender differences impact on the first years after psychosis onset. Other gender differences include childhood trauma, and adulthood domestic abuse, which are common among psychotic patients, with women being more likely to have been exposed to sexual abuse and physical abuse during their childhood, and adulthood. These may therefore impact on psychopathology, age of onset and needs for care differently in men and women with FEP. The in depth study of gender differences in needs for care of FEP patients may thus highlight important deficiencies in treatment provision, especially in those countries where there is a lack of gender-sensitive services.

Aims

This PhD Thesis aims to:

- 1) explore gender differences in psychopathology, needs for care and insight in a large cohort of FEP patients over 5 years;
- 2) provide a comprehensive summary of the findings on gender and childhood abuse in people with psychosis;
- 3) assess the impact of gender and traumatic experiences (physical and sexual abuse) on psychopathology, age of psychosis onset and needs for care in a large cohort of FEP patients.

Methods

For the aim 1 analyses were conducted within the framework of the PICOS study (Psychosis Incident Cohort Outcome Study). A total of 185 FEP patients have been followed-up for five years after psychosis onset and gender differences have

been explored for psychopathology (PANSS), needs for care (CAN) and insight (SAI-E).

For the aim 2 a narrative review was conducted. Papers concerning the impact of gender and childhood trauma in people with psychosis (to July 2018) were identified using a comprehensive search of PubMed, Web-of-Science, Scopus and Cochrane databases and analysing reference list of relevant papers.

For the aim 3 a total of 444 FEP patients have been recruited within the context of the GET UP trial (Genetics, Endophenotypes, Treatment: Understanding early Psychosis). Symptomatology has been assessed using the PANSS scale, needs for care with the CAN scale and childhood abuse with the CECA-Q scale.

Results

Regarding aim 1, male patients with FEP showed more negative symptoms than females over time, whereas female patients showed higher levels of depressive symptoms than males throughout the study period. In addition, female patients presented more functioning unmet needs for care than males but higher levels of insight into illness than males.

Concerning aim 2, we found that women with psychosis and childhood abuse tend to report more positive and mood symptoms, more suicide attempts and an earlier age of onset compared to men. Conversely, men with psychosis and childhood abuse tend to show more negative symptoms, substance abuse and a poorer cognitive performance compared to women.

As for aim 3, childhood abuse was associated with higher levels of negative symptoms in both men and women, with a reduced the age of onset in women only and little increase in needs for care in both men and women.

Conclusions

This Thesis contributes to the literature on gender differences in psychosis. It may be useful in identifying the different factors that can influence treatment in the first years after psychosis onset. It may also help clinicians to select the best treatment options for men and women with FEP, especially for those who experienced childhood trauma.

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INTRODUCTION

This doctoral thesis focuses on gender differences in people with psychosis. There have been many studies investigating the impact of gender on psychosis, but few studies have examined the impact of gender on first episode psychosis (FEP). However, there is some evidence that at psychosis onset, gender is associated with age of onset [lower for male patients compared to females (Jackson *et al*, 2013)], symptoms [women having more positive symptoms than men; men presenting with more negative and disorganized symptoms than women (Hui *et al*, 2014)], and different needs for care [women showing more unmet needs in the domains of “functioning” (basic education, money, childcare, self-care, looking after the home) (Bertani *et al*, 2012) and “services” (information, telephone use, transport, and benefits) (Ochoa *et al*, 2012) compared to men]. In addition to the paucity of information on gender differences at psychosis onset, even less is known on how gender impacts on the first years after psychosis onset.

Other gender differences include rates of childhood trauma, and adulthood domestic abuse, which are common among all psychotic patients (Bendall *et al*, 2008), but with women being more likely to have been exposed to sexual abuse and physical abuse during their childhood (Alvarez *et al*, 2011), and adulthood (Oram *et al*, 2017). In addition, severe childhood physical and sexual abuse have found to be more strongly associated with psychosis in women than men (Fisher *et al*, 2009). Childhood traumatic experiences appear to be involved in the etiological path leading to the development of psychosis with postulated mechanisms that include the lowering of Brain Derived Neurotrophic Factor (BDNF) levels (Theleritis *et al*, 2014); the over-activation of the Hypothalamus Pituitary Adrenal (HPA) axis (Aas *et al*, 2011); a subclinical pro-inflammatory state (Dennison *et al*, 2012) and metabolic dysregulation (Misiak *et al*, 2015) which have been observed in FEP patients. However, there has been less research on how childhood adversities impact on clinical features of psychosis, and the majority of studies have involved cohorts of chronic adult patients.

There is even less known about the impact of gender and childhood traumatic experiences on FEP patients. Nevertheless, as there is evidence of gender differences in stress reactivity to trauma, there may be a differential impact of childhood abuse on psychopathology, age of psychosis onset and needs for care in First Episode Psychosis (FEP) patients.

Thesis aims

Based on these premises, the three studies that constitute the main body of this thesis aim to overcome the limits of the current research described in Chapter 1 and, more in detail, at the beginning of each dedicated chapter. The studies also aim to respond to three main research objectives (ROs), hereafter presented:

1. Explore gender differences in psychopathology, needs for care and insight in a large cohort of FEP patients over 5 years;
2. Provide a comprehensive summary of the findings on gender and childhood abuse in people with psychosis;
3. Assess the impact of gender and traumatic experiences (physical and sexual abuse) on psychopathology, age of psychosis onset and needs for care in a large cohort of FEP patients.

Structure of the thesis and personal contribution

To address the research aims stated above, this thesis is divided into two main sections, each one with a *theoretical part* and a *research part*. A third section represents the conclusion.

The *first section* is composed of three chapters:

The first chapter provides an overall theoretical framework on gender studies in psychiatry, its relevance, its complexities and the limits of the current research,

whereas the second chapter presents an overview on gender differences in FEP patients. Taken together, the first and the second chapters constitute the *theoretical part* of the present doctoral thesis and are part of a book chapter, where the candidate worked as first author during the doctoral period. The book chapter is called “Towards gender-sensitive mental health services” and is part of “Health and Gender. Resilience and Vulnerability Factors For Women's Health in the Contemporary Society” (Riecher-Rossler & Tarricone, 2018).

Chapter three represents the *research part* and shows the results of a study on gender differences in FEP patients over 5 years that has been conducted by the candidate during the doctoral period. The study has been run within the framework of the Psychosis Incident Cohort Outcome Study (PICOS), a multisite naturalistic research aiming to examine the relative role of clinical, social, genetic, and morpho-functional factors in predicting clinical and social outcomes in a large cohort of FEP patients treated by public mental health services. Information on the PICOS study are provided within the chapter. The study addresses the first aim of the thesis and constitutes a submitted paper, with the candidate as first author (Comacchio et al, 2018).

The *second section* of the thesis is composed of two chapters.

The fourth chapter represents the *theoretical part* and is a narrative review on gender and childhood traumatic experiences in psychosis. The review addresses the second aim of the thesis and constitutes a submitted paper where the candidate worked as first author (Comacchio et al, 2018).

Chapter 5 is the *research part*. It presents a research study on the impact of gender and childhood traumatic experiences in FEP patients and addresses the second aim of the thesis. The study has been conducted within the framework of the research program GET UP (Genetics, Endophenotypes, Treatment: Understanding early Psychosis), and, specifically, within the PIANO (Psychosis: early Intervention and Assessment of Needs and Outcome) trial, a cluster randomized controlled trial which compares the effectiveness of Treatment As Usual (TAU) plus a multi-element psychosocial treatment for patients with FEP and their family members, versus TAU alone, as provided by Italian community mental

health services. Information on the GET UP study are provided within the chapter. The study has been developed and written in cooperation with the Section of Women's Mental Health at the Health Service and Population Research Department of the King's College London, in order to maximise the focus on gender issues. The study addresses the third aim of the thesis and constitutes a submitted paper, with the candidate as first author (Comacchio et al, 2019).

The thesis ends with an overall conclusion (Chap. 6, *third part*), where results presented in the different chapters are integrated and commented, with specific attention to potential practical implication and future research directions.

**Part 1: GENDER DIFFERENCES IN FIRST EPISODE PSYCHOSIS
PATIENTS**

THEORETICAL PART

**TOWARDS GENDER-SENSITIVE MENTAL HEALTH
SERVICES***

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KEY POINTS

- Patterns to care of males and females affected by psychiatric disorders are different and these differences should be taken into account when delivering services and programs;
- Female patients with mood disorders and eating disorders make greater use of psychiatric services compared with males;
- Despite evidence of gender differences in people with FEP there is limited availability of gender-targeted rehabilitation treatments;
- Women-only programs for people with drug abuse and addiction appear to be more effective than Mixed Gender programs for female patients with comorbid psychiatric disorders;
- Women affected by psychiatric disorders in the perinatal period can be successfully treated in specialised services (Mother and Baby Units) without being separated by their offspring.

*published in: “Health and Gender. Resilience and Vulnerability Factors For Women's Health in the Contemporary Society” (A. Riecher-Rossler, I. Tarricone, 2018).

Chapter 1 – Gender studies in psychiatry

1.1 Introduction

The degree of gender equality in a country has been found to be proportional to gender differences in mental health (Seedat *et al*, 2009; val de Velde *et al*, 2013) and this has led to great efforts to include gender-sensitivity in policy making with a specific focus on mental health care delivery and research (WHO, 2004). Despite this, implementation of gender specific interventions is slow (WHC, 2005) and research limited.

This chapter is constituted by two parts: in Part 1 we aim to describe gender differences in mental health service use by summarising findings on the main disorders; in Part 2 we report about the available gender-specific mental health services and programmes.

1.2 Gender differences in mental health service use

1.2.1 Mood disorders

Prevalence of major depression is 5-7% among women in the general population (Hasin *et al*, 2005; Patten *et al*, 2006) and 3-4% among men that however show higher rates of suicide related to mood-disorders than women (Ladouceur, 2011; Oliffe *et al*, 2012, Rutz, 2003). Among individuals affected by depression women are about twice more likely than men to use mental health services (Rhodes *et al*, 2002; Addis *et al*, 2003 ; Burns *et al*, 2000; Ojeda *et al*, 2006; Angst *et al*, 2001; Bertakis *et al*, 2000, Johnson *et al*, 2011; Kovess-Masfety *et al*, 2014) even in the presence of suicidal thoughts (Vasiliadis *et al*, 2013; Gegné *et al*, 2014). This difference can be partly explained by the higher rates of anxiety observed in female patients compared with males, which might be associated with a stronger demand for mental healthcare (Seedat *et al*, 2009; Vesga-Lopez *et al*, 2009; de Graaf *et al*, 2012), by the higher compliance with treatment (Green *et al*, 1999) and symptoms awareness in females patients compared with males (Wang *et al*, 2007; Sevilla-Dedieu *et al*, 2011; Kovess-Masfety *et al*, 2007, Hibbard *et al*, 1987) and also by the fact that male patients tend to show higher rates of self-stigmatisation related to viewing mental illness as a consequence of personal

weakness than females (Olliffe *et al*, 2016; Schomerus *et al*, 2010; Pattyn *et al*, 2015).

1.2.2 First episode psychosis and longitudinal outcome of psychosis

Psychosis affects 1-2% of the general population: its incidence peaks in the early adulthood for both genders and shows a second peak for women in the perimenopausal period (Rabinowitz *et al*, 2007; Jackson *et al*, 2013). Among female patients with FEP, 73% receive a diagnosis of non-affective psychosis and 27% a diagnosis of affective psychosis (Bertani *et al*, 2012) Among male patients with FEP, 86% receive a diagnosis of non-affective psychosis and 14% a diagnosis of affective psychosis. Despite evidence of gender differences in the psychopathological characteristics in FEP patients (Hui *et al*, 2014; Cotton *et al*, 2009; Ochoa *et al*, 2012), little is known about how gender impacts on the response to the specialised treatments in the early phase (Tseliou *et al*, 2017), as the majority of studies have been conducted prior to the introduction of specialist services for young people with psychosis. As proved in the case of depression, male patients with FEP show less motivation to engage with treatment (Cotton *et al*, 2009; Longenecker *et al*, 2010) and greater lack of insight for their illness (Malla *et al*, 2005; Cotton *et al*, 2009) which may delay treatment efficacy, leading to a poorer prognosis (McFarlane *et al*, 1995). Regardless the type of specialised intervention provided, during the first year after psychosis onset, females tend to have higher rates of admission than males. However, males present fewer but longer periods of admission (88.5 days of hospitalization in males vs 76.1 of females) (Thorup *et al*, 2014). This may be due to females' higher levels of insight, which could allow them seeking effective treatment more often and earlier (Karow *et al*, 2008). Another possible explanation is that women tend to have more affective episodes with greater risk for self-harm which may require more frequent hospitalization. (Haro *et al*, 2008). In fact, females with FEP are more likely to experience a psychosocial stressor at the time of psychosis onset (Morgan *et al*, 2008) and subsequently to express more depressive symptoms (Carpenter *et al*, 2007), and fewer negative symptoms than males.

Table 1. Gender differences in First Episode Psychosis (FEP) patients.

	Study	Sample size	Females	Males
Diagnosis (NAP vs AP)* %	Bertani <i>et al</i> , 2012	182 F 215 M	73% vs 27%	86% vs 14%
Service engagement (weeks) mean (SD)	Cotton <i>et al</i> , 2009	226 F 435 M	62.6 (35.3)	63.7 (33.6)
Insight (3 pts Likert-scale) mean (SD)	Cotton <i>et al</i> , 2009	226 F 435 M	12.6 (28)	6.9 (30)
Hospitalization (days) mean (SD)	Thorup <i>et al</i> , 2014	231 F 323 M	76.1 (100.5)	88.5 (113.8)
Psychosocial stressors (Diagnostic Interview for Psychosis) %	Morgan <i>et al</i> , 2008	443 F 647 M	55.7%	32.2%

1.2.3 Eating disorders

The prevalence of eating Disorders (EDs) in the general population is 3.5% for women and 1-2% for men (Mccaulaghy *et al*, 2016). EDs are in fact often seen as a “women’s disease” (Hudson *et al*, 2007), with males accounting only for 10% of total ED cases (Muisse *et al*, 2003). EDs are associated with increased general health services utilization (Johnson *et al*, 2001; Lewinsohn *et al*, 2000; Striegel-Moore *et al*, 2004) and patients with undiagnosed EDs appear to be more likely to report higher numbers of primary care visits than patients without ED (Ogg *et al*, 1997; Sansone *et al*, 1997; Johnson *et al*, 2001). It is not clear whether the elevated rate of general services use is due to EDs-related co-morbidity, such as obesity (Reidpath *et al*, 2001; Mond *et al*, 2010; Evans *et al*, 2011; Mond *et al*, 2007) and depression-anxiety (Kraemer *et al*, 2006; Hudson, 2007) or to patients’ attempts to receive care without acknowledging the ED to themselves or healthcare providers (Striegel-Moore *et al*, 2008). Nevertheless, once EDs are diagnosed rates of services use shows an additional increase to both mental health and primary care departments (Striegel-Moore *et al*, 2008). Due to the higher proportion of females affected by EDs compared with males and the gender-stereotypes related to these disorders, the majority of treatments are based on interventions specifically developed for women (NIHCE, 2004). Even though treatment in predominantly female environments has shown to be successful also

for males (Woodside & Kaplan, 1994), male patients appear to be resistant to attend treatment regularly because of stigma and stereotypes (Robinson *et al*, 2012). In addition, evidence has suggested that male patients with EDs are less likely to be diagnosed as having an ED than females despite identical symptoms (Currin *et al*, 2007) and thus less likely to receive adequate treatment (Striegel-Moore *et al*, 2000; Mccaughy *et al*, 2016).

1.2.4 Drug abuse and addiction

Women account for one-third of all substance users (Hepburn, 2002) and the majority of them are of childbearing age (WHO, 2008). Women with substance abuse problems are more likely than men to be identified through contacts with child protective services (Grella & Joshi, 1999) rather than in general health care settings (Brienza & Stein, 2002). Despite the well-known gender differences in addiction behaviours and treatment needs (Hser *et al*, 2003; Green, 2006; Robinson *et al*, 2001), the majority of treatments are not gender-targeted (Grella *et al*, 1999; Oser *et al*, 2009).

Women-only (WO) programs have been developed in the late 80s (Niv *et al*, 2007) to address the barriers that prevent women from entering and staying in treatment (Grella & Greenwell, 2004). Treatment components in WO programs include group discussions of addiction, relapse prevention, anger management, HIV education and job training with a focus on how these issues relate to women's recovery, and group discussions utilize a more supportive and less confrontational approach than Mixed-Gender (MG) programs (Grella *et al*, 1999). The possibility for a substance-abusing mother to be accompanied by her child while on treatment is characteristic of WO specialized treatment. Although some have argued that children in a treatment facility may impact on the mother's ability to attend her program by delaying or adversely affecting her recovery, available evidence suggests that women who are allowed this provision demonstrate higher rates of retention than women who are not (Chen *et al*, 2004). Findings on the effectiveness of WO programs are inconsistent (Greenfield *et al*, 2010; Greenfield *et al*, 2007; Harrison & Asche, 2001; Kaskutas *et al*, 2005) but some evidence indicates that women, especially those with low self-efficacy

(Cummings *et al*, 2010) or high psychiatric symptom severity (Greenfield *et al*, 2008), are less likely to drop out of WO programs (Grella, 1999; Greenfield *et al*, 2007), have better drug outcomes after discharge (Evans *et al*, 2013) and improved criminal justice outcomes (Niv & Hser, 2007; Prendergast *et al*, 2011).

1.2.5 Gender differences in the late period of life

Historically, in the population over 65 years old women have always outnumbered men and this difference persists nowadays despite the decline in males' death rate from other causes (Bahir *et al*, 2010). Psychogeriatric is a discipline that has developed in the last 30 years (Holyrood *et al*, 1997) as a consequence of the rapid ageing of the population and the subsequent increased need for psychiatric care in elderly people. It has been estimated that the number of people over the age of 65 will reach 70 million by the year 2030 making up 20% of the population (Bahir *et al*, 2010). Even if the majority of elderly people attend regular health care visits, they are less likely to use specialized mental services than younger age groups (Holyrood *et al*, 1997) and they tend to seek for psychiatric help in the context of a general medical complaint during a primary care visit (Bahir *et al*, 2010).

Psychogeriatric units (PGU) are acute hospital units that provide inpatient care to elderly people with mental disorders (Dobrothoff *et al*, 2011), but their availability is limited (O'Connor & Melding, 2006; Snowden, 2007). A higher proportion of women is admitted to PGU compared with men (Draper *et al*, 1998; Chui *et al*, 2009; George, 2003), mostly for psychosis-related conditions, and women have longer inpatient stay than men. These findings may be explained by the higher incidence of schizophrenia in older women and by the greater female longevity in the older schizophrenic population (Cohen *et al*, 2000). By contrast, men show higher readmission rates (Dobrothoff *et al*, 2011) and better response to rehabilitative intervention targeted for elderly people with psychiatric disorders (Mueser *et al*, 2010)

1.3 Gender-specific mental health services

1.3.1 Pregnancy and postpartum

Depression in pregnancy occurs in 12% of women (Dennis *et al*, 2013; Cantwell *et al*, 2011) and in the post-partum period 10-20% of women develop a major depressive episode (Friedman *et al*, 2009; O’Hara & Wisner, 2014) and 0.1-0.2% of women a psychotic episode (O’Hara & Wisner 2014; Sit *et al*, 2006; Blackmore *et al*, 2013). Post-partum is also associated with an increased risk of developing bipolar or post-traumatic stress disorder (Munk-Olsen *et al*, 2014) and with relapse and exacerbation of any pre-existing psychiatric condition (Freidman *et al*, 2011; Brockington *et al*, 2006). Mental disorders in pregnancy and postpartum are associated with a range of adverse outcomes, both for the mother and for the baby (Davalos *et al*, 2012; Friedman *et al*, 2009; Farr *et al*, 2013; Staehelin *et al*, 2013; Beebe *et al*, 2008). However, the perinatal period represents a good chance for mental health professionals, as women are more open to advice and support (Goodman *et al*, 2009; Miller *et al*, 2009). Mother and Baby Units (MBUs) have been developed in the late 50s (Main, 1958) to respond to needs of women affected by psychiatric disorders in the perinatal period. MBUs are specialized services in which women can be admitted without being separated from their child – generally under the age of 12 months. Despite the higher rates of patients’ preference for treatment in MBUs rather than in acute general wards without their baby and the higher levels of patients’ satisfaction (Neil *et al*, 2006, Antonysamy *et al*, 2009; Glangeaud-Freudenthal *et al*, 2014), MBUs are not widespread (Cazas and Glangeaud-Freudenthal, 2004, Glangeaud-Freudenthal *et al*, 2014). Figure 1 provides an overview of their localization worldwide. Specialized interventions for mental disorders in the perinatal period are associated with positive outcomes, both for the mothers and for the babies (Kahn *et al*, 2002; Minkowitz *et al*, 2005; Cazas and Glangeaud-Freudenthal, 2004; Salmon *et al*, 2004; Wilson *et a.*, 2004; Nair *et al*, 2010), which implies that all women suffering from psychiatric perinatal conditions should have access to this kind of specialised care.

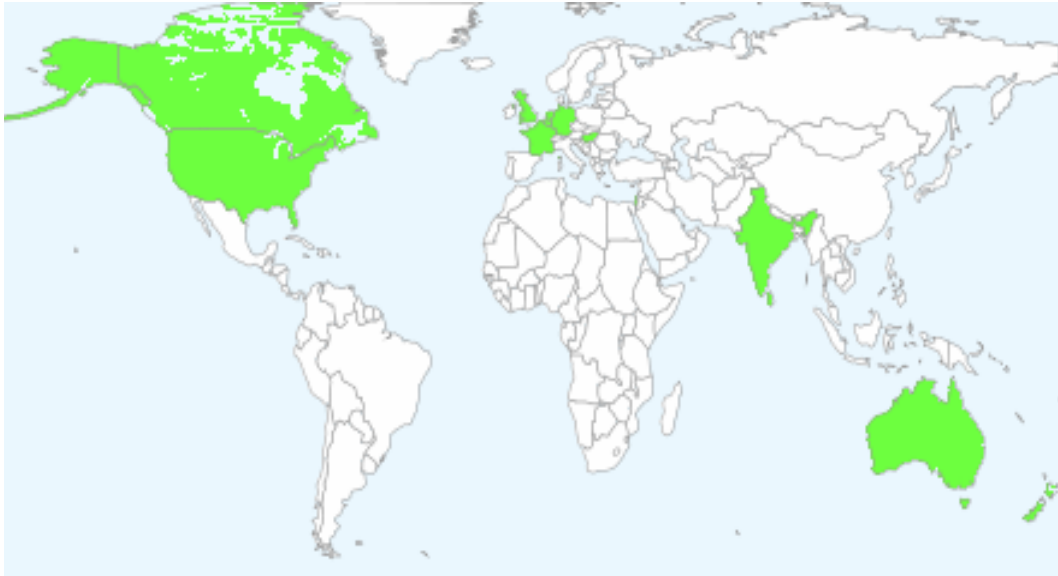


Figure 1. Distribution of MBUs worldwide. MBUs are present in UK, France, Germany, Belgium, Luxembourg, Netherlands, Hungary, USA, Canada, Australia, New Zealand, India, Israel, Sri Lanka (Cazas and Glangeaud-Freudenthal, 2004; Glangeaud-Freudenthal *et al*, 2014).

1.4 Conclusion

For long time men and women affected by mental disorders have been seen as a homogeneous group, with similar characteristics, needs for care and outcomes (Vlassoff & Garcia Moreno, 2002; WHO, 2006). However, men and women differ in relation to prevalence, impact of biological, psychological and social factors and course of illness (Judd *et al*, 2009) and these differences have to be carefully taken into account when planning patient-tailored interventions (McCormack *et al*, 2010).

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Chapter 2 – Gender differences in First Episode Psychosis patients

2.1 Age of onset

The incidence of psychosis has its peak in the early adulthood for men, while it shows a double peak for women, the first in the early adulthood few years later than the one of men and the second in the peri-menopausal period, thus suggesting that oestrogens may play a neuroprotective role in the aetiology of the disorder (Jackson *et al*, 2013).

2.2 Psychopathology

Levels and characteristics of psychopathology at psychosis onset are also associated with gender differences: a number of studies reported a greater prevalence of positive symptoms in women and more negative and disorganized symptoms in men (Preston *et al*, 2002; Thorup *et al*, 2007; Hui *et al*, 2014). In addition, male patients with FEP tend to present lower levels of insight into illness than females (McEvoy *et al*, 2006; Parellada *et al*, 2011), and lack of insight has been linked to an increased severity in psychopathology (Smith *et al*, 2000; McEvoy *et al*, 2006; Parellada *et al*, 2009).

2.3 Needs for care

Despite the evidence of an impact of gender on psychosis, mental health services have been criticized as failing to respond to gender-sensitive issues (Grossman *et al*, 2006) and, even when they try to, there seem to be a gender-bias in needs satisfaction, with males improving more than females in a wide range of domains over time (Grossman *et al*, 2006). A study conducted in Italy on a cohort of FEP patients (Bertani *et al*, 2012) found that despite their greater level of social impairment, males reported fewer unmet needs in the functioning domain than females did. Author suggested that this could be due to an increased tolerance and support from families that may be more likely to accept and cope with underperforming males (Bimbi *et al*, 2003).

2.4 Hospitalization

In the first year following psychosis onset female patients tend to have higher rates of admission than males, who show fewer but longer periods of admission (Thorup *et al*, 2014). This may be due to females' higher levels of insight, which could allow them seeking effective treatment earlier and more frequently than males (Fonagy *et al*, 2002). Another possible explanation for females' higher rates of hospitalization is that they tend to have more affective episodes with greater risk for self-harm which may require more frequent hospitalization (Liotti *et al*, 2010). One main difference between males and females with FEP concerns the access to mental health services. It has been found that males are nearly five times more likely to make first contact with the emergency department (Archie *et al*, 2009) and less likely to be admitted voluntarily compared to females (Temmingh & Oosthuizen, 2008). Gender differences in pathways to care between males and females may account for gender differences observed in the DUP, which is longer for males (Barajas *et al*. 2015; Cascio *et al*. 2012). Given that DUP has shown to be significantly associated with several clinical and social outcomes of psychosis (Malla *et al.*, 2014) bearing in mind gender differences in pathways to care for FEP patients could help implementing early diagnosis.

2.5 Compliance to treatment

Male patients with FEP appear to be less likely to be compliant with treatments than females. This may be related to males' higher rates of substance abuse at psychosis onset (Thorup *et al*, 2014), which is known to worsen symptomatology and reduce the effectiveness of treatments. On the other hand, females with FEP show more help-seeking behaviours and a more positive attitude towards taking medication than males, which results in higher compliance to treatment (Galdas *et al*, 2005). Lastly, it has been suggested that higher rates of females' access to social network and social support (Gayer-Anderson *et al*, 2015) may account for the discrepancy in treatment compliance between males and females (Thorup *et al*, 2014).

2.6 Response to treatment

Early intervention programs for FEP patients are varied and they generally include psychotherapy, customized psychopharmacological treatment, social skills training, case management and family network and they have proved to be effective in improving the outcome of these patients, at least over the short run (Ruggeri *et al*, 2015). Despite the body of evidence concerning gender differences in people with psychosis, little is known on how gender impacts on the response to these specialized programs for the early stages of psychosis (Tseliou *et al*, 2017), as the majority of studies on gender differences in FEP patients have been conducted prior to the introduction of specialized services for young people with psychosis. However, the identification of gender differences in the course of psychotic disorders still remains essential for the development of targeted treatments (Thorup *et al*, 2007; Koster *et al*, 2008; Bertani *et al*, 2012). Male patients with FEP tend to show less motivation to engage with treatment (Longenecker *et al*, 2010) and a greater lack of insight for their illness (Malla *et al*, 2005), which may delay treatment efficacy, leading to a poorer prognosis (McFarlane *et al*, 1995). A recent study found no difference in terms of level of symptomatology between the sexes at 1-year follow up after the end of a specialised intervention for FEP patients, while gender differences were detected with regard to social and vocational functioning with men scoring lower than women (Thorup *et al*, 2014). Of notice, the majority of findings concerning the impact of gender on treatment outcome come from well resourced, research-funded services and it is unclear whether similar results would be obtained from a naturalistic study in routine care (Tseliou *et al*, 2017). Psychopharmacological guidelines for FEP patients recommend the administration of gender-targeted doses of antipsychotic medication, due to different body mass between males and females (NICE, 2015). However, Thorup *et al*, (2014) and Koster *et al*. (2008) found that females and males receive similar doses of antipsychotic medication. Taking into account gender differences when prescribing antipsychotic medication to FEP patients is also very important because their side-effects have a different impact in the two genders, with females being more susceptible to weight gain, QT-prolongation and hyperprolactinemia and males in greater risk of metabolic changes and cardiovascular problems (Haack *et al*, 2009).

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RESEARCH PART

Gender and 5-years course of First Episode Psychosis patients: focus on clinical and social variables*

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ABSTRACT

Purpose: The majority of studies on gender and psychosis have focused on gender differences at illness onset or in the long-term outcome, whereas little is known on the impact of gender on the first years after psychosis onset.

Methods: A total of 185 First Episode Psychosis (FEP) patients have been followed-up for five years after psychosis onset and gender differences have been explored for psychopathology (PANSS), needs for care (CAN) and insight (SAI-E).

Results: Male patients have showed more negative symptoms than females over time, whereas female patients have showed higher levels of depressive symptoms than males throughout the study period. In addition, female patients have presented more functioning unmet needs for care than males but higher levels of insight into illness than males.

Conclusion: Rehabilitation programmes for FEP patients should be gender-targeted as gender has proved to impact the course of the very first years following psychosis onset.

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Chapter 3 – Gender and 5-years course of First Episode Psychosis patients: focus on clinical and social variables

3.1 Study design

The Psychosis Incident Cohort Outcome Study (PICOS) is a multisite naturalistic research aiming to examine the relative role of clinical, social, genetic, and morpho-functional factors in predicting clinical and social outcomes in a large cohort (n=397) of FEP patients treated by public mental health services located in the Veneto region (Bertani *et al.* 2012; Lasalvia *et al.* 2012). All psychiatric facilities located in the regional area covered by PICOS were asked to refer to the research team all potential cases of psychosis at first service contact over a three-year period (1st January 2005-31st December 2007). Patients were assessed at baseline (T0), after one (T1), two (T2) and five years (T5). Inclusion criteria were: (1) age 15-54 years; (2) residence in the Veneto Region; (3) presence of (a) at least one of the following symptoms: hallucinations, delusions, qualitative speech disorder, qualitative psychomotor disorder, bizarre or grossly inappropriate behavior, or (b) at least two of the following symptoms: loss of interest, initiative and drive, social withdrawal, episodic severe excitement, purposeless destructiveness, overwhelming fear, marked self-neglect; (4) first lifetime contact with any mental health service located in PICOS area during the study period occasioned by symptoms enumerated in (3). Exclusion criteria were: (1) prior treatment with an antipsychotic agent for more than 3 months; (2) mental disorders due to a general medical condition; (3) moderate to severe mental retardation. The formal best-estimate research diagnosis was made 6 months after inception and only patients with a confirmed ICD-10 diagnosis of psychosis (F1x.4; F1x.5; F1x.7; F20–29; F30.2, F31.2, F31.5, F31.6, F32.3, F33.3) were finally included in the study.

3.2 Aim

The aim of the present research was to assess the impact of gender on clinical and social course over 5 years in a large cohort of FEP patients receiving community-based mental health care. On the basis of the existent literature, we hypothesized

that: 1) female patients would show more positive symptoms, less negative symptoms and less general psychopathology symptoms than males; 2) female patients would show higher levels of unmet needs for care than males; 3) female patients would show higher levels of insight into illness than males.

3.3 Measures

The Positive and Negative Syndrome Scale (PANSS; Kay *et al.* 1987) was used to evaluate severity of psychotic symptoms. The PANSS scale is a widely used assessment scale consisting of 30 items that cover positive symptoms, negative symptoms and general psychopathology; each item is rated on a Likert-type severity scale ranging from 1 (absent) to 7 (extreme). The European version of the Camberwell Assessment of Needs (CAN-EU) was used to measure the number of present needs of subjects per area and the number of unmet needs (McCrone *et al.* 2000). This interview comprises 22 items grouped into five conceptual domains; health (physical health, psychotic symptoms, drugs, alcohol, safety to self, safety to others, psychological distress); basic needs (accommodation, food, and daytime activities); social needs (sexual expression, social networks, and intimate relationships); service needs (information, telephone, transport, benefits) and functioning (basic education, money, childcare, self-care, looking after the home). Each item is rated on a scale of three conditions: 0 = no problem, 1 = absent or moderate problem due to the person receiving ongoing interventions (met need), 2 = actual serious problem and no interventions received (unmet need). Insight was assessed using the Schedule for the Assessment of Insight (SAI) in its expanded version (SAI-E; Kemp & David, 1996). The scale is based on a concept of insight that includes three distinct dimensions that are: 1) awareness of mental illness; 2) ability to relabel unusual mental events (e.g. hallucinations) as pathological; and 3) treatment compliance, both expressed and observed. It consists of 11 items, with a standardized mode of rating of the items by the interviewer. Items 1–6, 10, and 11 are rated from 0 to 2, while items 7–9 are rated from 0 to 4, with higher scores indicating better insight. All the items are summed to reach a total score, ranging from 0 to 28 (David, 1990).

3.4 Statistical analyses

Mean scores, χ^2 test and t-test were used to describe the sample's basic socio-demographic characteristics as appropriate. Linear mixed models (for each outcome) with gender, time, and gender-by-time interactions were performed: a significant gender-by-time interaction indicates that the change over time differed between males and females, whereas the main effect of sex but no significant interaction with time suggests that the rate of change over the five-year follow-up was the same for males and females. Analyses were performed using SPSS 23.0 for Windows and Stata 13.0 at 0.05 significance level.

3.5 Results

3.5.1 Composition of the sample

A total of 397 patients were assessed at baseline, 215 (54%) males and 182 (46%) females. Gender differences on socio-demographic and clinical characteristics at baseline are described in detail elsewhere (Bertani et al. 2012). Following the overall PICOS design (Lasalvia et al, 2012) patients recruited at baseline have been stratified into three cohorts according to the length of their follow-up (see Figure 1). Short-term follow-up cohort is composed of patients (n=58) who completed the 1-year follow-up assessment only. Medium-term follow-up cohort is composed of patients (n=89) who completed the 1- and 2-year follow-up assessment and/or the 2-year follow-up assessment only. Long-term follow-up cohort is composed of patients (n=185) who completed the 1-, the 2- and the 5- follow-up assessment and/or the 1- and the 5-years follow-up assessment only, the 2- and/or the 5-years follow-up assessment only and/or the 5-year follow-up assessment only. For the present study only patients in the long-term follow-up cohort were included in the analysis. Gender differences in socio-demographic characteristics of the long-term follow-up cohort patients are described in detail in Table 1.

Fig. 1 PICOS cohorts according to patients' follow-up length

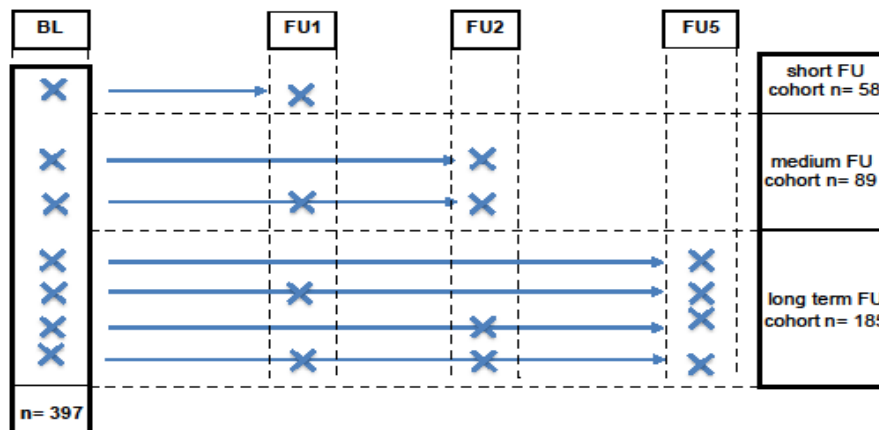


Table 1 Sociodemographic characteristics of patients in the long-term follow-up cohort

	M n=103 (55.7%)	F n=82 (44.3%)
Age, mean (sd)	(41 missing) 36.53 (9.54)	(24 missing) 37.22 (10.14)
Education	(2 missing)	(10 missing)
High (secondary school, university)	52 (51.5%)	38 (52.8%)
Low (primary, middle-school)	49 (48.5%)	34 (47.2%)
Marital status	(10 missing)	(12 missing)
Unmarried	74 (79.6%)*	39 (55.7%)*
Married	15 (16.1%)*	23 (32.9%)*
Widowed, separated, divorced	4 (4.3%)*	8 (11.4%)*
Living condition	(3 missing)	(8 missing)
Alone	10 (10.0%)	8 (10.8%)
Partner/ children	11 (19.0%)*	33 (44.6%)*
Other relatives	71 (71.0%)*	33 (44.6%)*
Working status	(5 missing)	(10 missing)
Employed	41 (41.8%)	30 (41.7%)
Unemployed	38 (41.8%)	23 (33.3%)
Housewife, student, retired	19 (16.3%)	19 (23.6%)
Nationality	(0 missing)	(0 missing)
Italian	96 (93.2%)	67 (81.7%)
Other	7 (6.9%)	15 (18.4%)

Note: * $p < 0.05$ (χ^2 test)

3.5.2 Psychopathology

Positive and general psychopathology scales showed a significant time effect only, with positive and general psychopathology symptoms improving over time for both males and females (Figure 3, e-f). By contrast, Negative scale showed a

significant time and gender effect, with females showing a greater reduction in negative symptoms than males over time (Figure 2, a). When analysing individual items composing the Negative scale, we found a significant gender and time effect for “depression”, “blunted affect”, “emotional withdrawal”, “passive social withdrawal” and “poor impulse control”. Concerning “depression”, female patients scored persistently worse than males throughout the years and there was a trend in the increase in depressive symptoms levels on the medium-term (Figure 2, b). Conversely, male patients scored worse than females over time for “blunted affect”, “emotional withdrawal”, “passive social withdrawal” and “poor impulse control” (Figure 3, g-h and Figure 4, i-j).

Fig. 2 Clockwise: a) PANSS negative symptoms scale’s scores over time. Significant time and gender effect. b) PANSS “depression” scores over time. Significant time and gender effect. c) CAN “functioning unmet needs” scores over time. Significant time and gender effect. d) SAI-E “insight into illness” scores over time. Significant time and gender effect

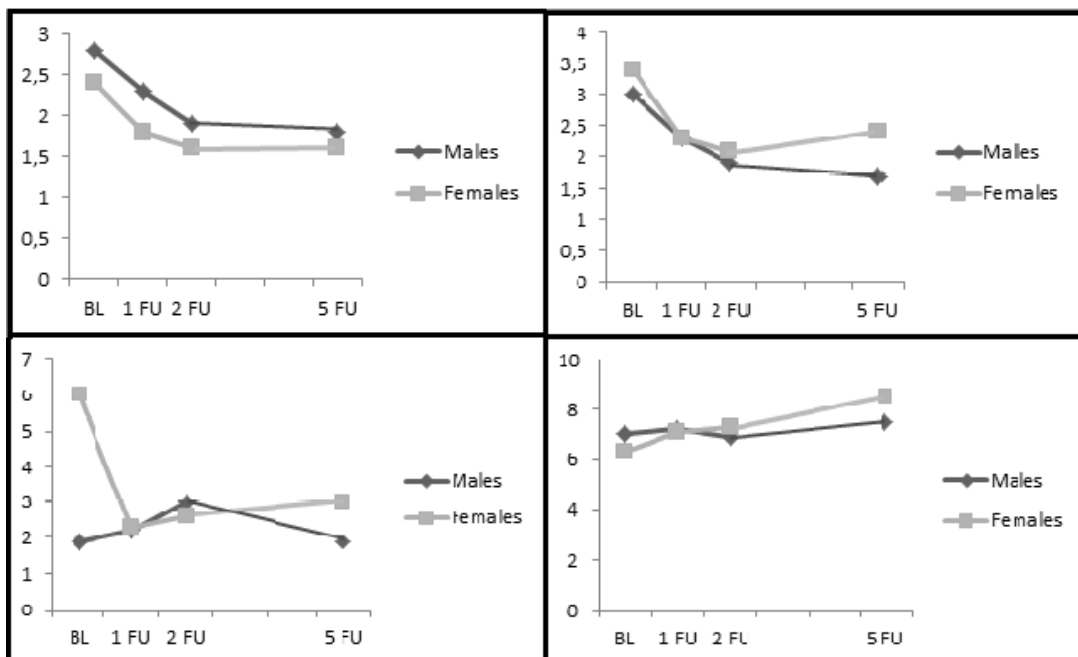


Fig. 3 Clockwise: e) PANSS positive scale’s scores over time. Significant time effect. f) PANSS general symptomatology scale’s scores over time. Significant time effect. g) PANSS “blunted affect” scores over time. Significant time and gender effect. h) PANSS “emotional withdrawal” scores over time. Significant time and gender effect

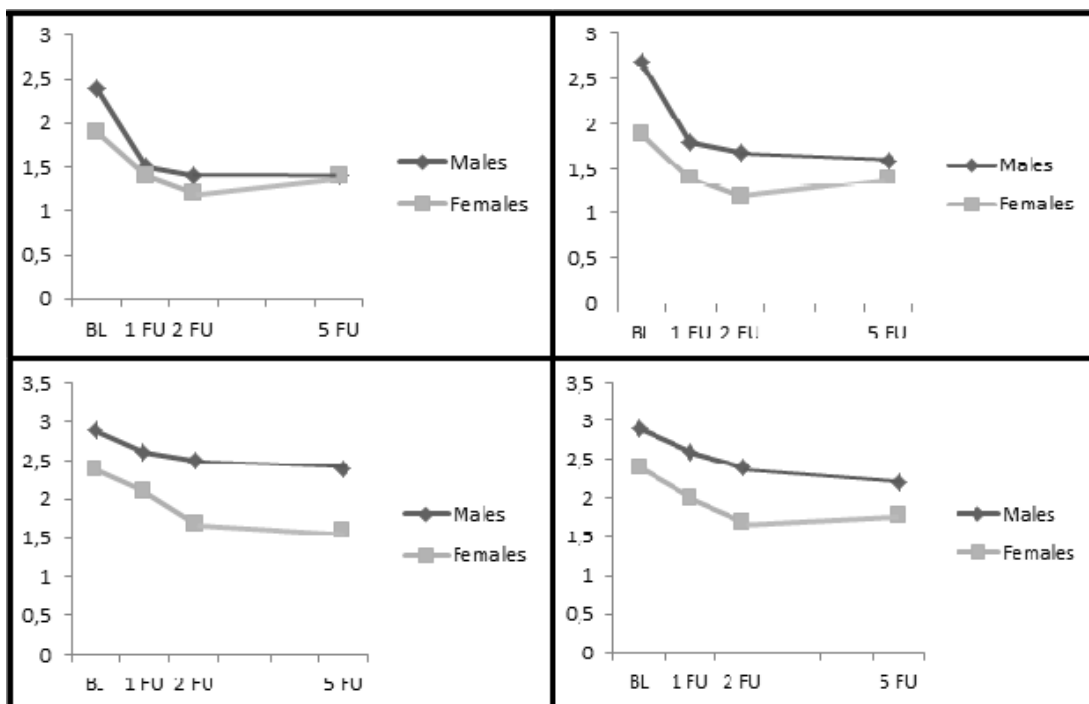
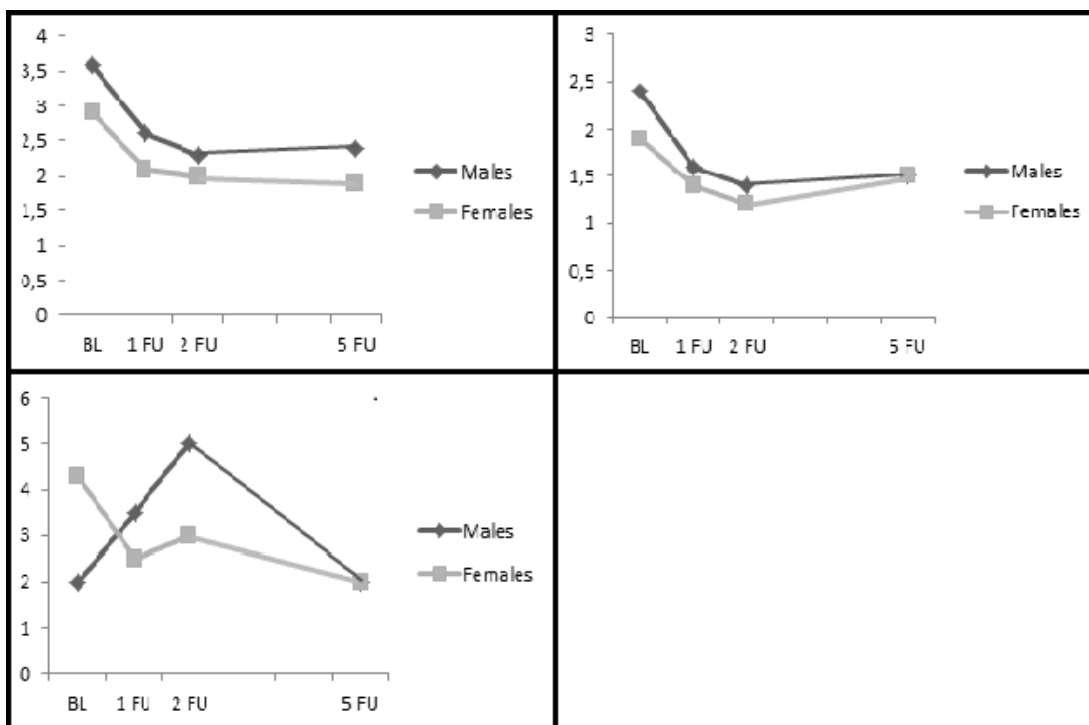


Fig. 4 Clockwise: i) PANSS “passive social withdrawal” scores over time. Significant time and gender effect. j) PANSS “poor impulse control” scores over time. Significant time and gender effect. k) CAN “basic unmet needs” scores over time. Significant time and gender effect



3.5.3 Needs for care

A significant time and gender effect for “basic” and “functioning” unmet needs was found. Concerning “basic” unmet needs female patients scored worse than males at baseline and showed a progressive reduction in “basic” unmet needs over time, whereas male patients showed an increase in their levels of “basic” unmet needs from baseline to 2-year follow-up, and then a progressive decline in their “basic” unmet needs over time (Figure 4, k). With regard to “functioning” unmet needs, female patients scored worse than males throughout the years (Figure 2, c).

3.5.4 Insight into illness

A significant time and gender effect concerning “insight into illness” was found, with female patients scoring worse than males at baseline but improving more than males over time (Figure 2, d).

3.6 Discussion

Concerning psychopathology, no gender effect was detected with regard to positive symptoms and general psychopathology, thus partly disconfirming our first hypothesis. This is in contrast with Thorup and colleagues (2007), who found higher levels of positive symptoms in female patients compared to males, but it is in line with previous studies showing no gender differences in positive and general psychopathology symptoms in patients with FEP (Barajas *et al*, 2007; Hui *et al*, 2014). Nevertheless, we did find a gender and time effect for negative symptoms, with male patients exhibiting more negative symptoms than females throughout the study. This is consistent with the majority of findings that point at a higher presence of negative symptoms in male patients with FEP compared to females (Thorup *et al*, 2007; Kohler *et al*, 2009; Chang *et al*, 2012). In our sample, female patients showed higher levels of depression than males over time and, interestingly, even an increase in the levels of their depressive symptoms on the medium term. Other studies have found higher levels of depression in female patients with psychosis than males (Grossman *et al*, 2008; Koster *et al*, 2008; Cotton *et al*, 2009), but this is the first study identifying the real course of depressive symptoms over time for males and females patients with FEP.

With regard to needs for care, we found a significant gender and time effect for “basic” and “functioning” unmet needs, thus confirming our second hypothesis. Ochoa and colleagues (2012) reported that male patients with psychosis have more “basic” and “functioning” unmet needs than females, whereas female patients present more “service” unmet needs than males. This is partly in contrast with our findings, as CAN scores of unmet needs for care showed higher levels of “functioning” unmet needs in females compared to males throughout the study period. However, our result is consistent with our previous study (Bertani *et al*, 2012), which found a higher presence of “functioning” unmet needs for care in female patients compared to males, despite their better premorbid functioning and their lower social disability. The explanation for this result was sought in the familiar environment, as Italian families appear to be more likely to accept and cope with underperforming males (Bimbi, 2003) and to provide to male patients greater support in everyday activities than to females. However, in the light of the present finding other factors should be taken into consideration: the lack of a gender perspective in the Italian public mental health services may lead clinicians to be unaware of gender differences in needs for care of people with FEP and to replicate the behavioral patterns of FEP patients’ families, thus hyper-investing in the rehabilitation programs of males and underestimating the needs of females.

In our sample, we found a significant gender and time effect for the “insight into illness”, with female patients showing a greater improvement of insight over time in their insight levels compared to males. This confirms our third hypothesis and is consistent with previous studies reporting higher levels of insight into illness in female patients with psychosis than males (McEvoy *et al*, 2006; Karow *et al*, 2008). In addition, the greater levels of depression all along the study course in female patients compared to males may have contributed to the higher levels of insight in female patients than males, as there is a the directly proportional relationship between depression and insight (Mintz *et al*, 2003).

The present study has several clinical implications: first, male patients with FEP should be carefully monitored for negative symptoms and specific treatment like cognitive-behavioral therapy (CBT) or cognitive-remediation therapy (CRT) should be provided in order to minimize the impact of negative symptoms in everyday life and to reduce the long-term effect of negative symptoms. Second, male patients with FEP should be enquired regularly about their beliefs concerning their psychiatric disorder and helped to acquire a better understanding of their condition. Dedicated psychotherapeutic interventions may be considered in order to increase insight into illness. Third, female patients with FEP should be assessed for depression periodically and depressive symptoms treated with CBT or antidepressants according to their severity. Fourth, female patients with FEP should be frequently asked about their specific needs for care. The degree of support provided by families of female patients with FEP in daily activities should be explored and patients should be helped in finding a good balance between support and autonomy. When needed, female patients with FEP may be helped in negotiating additional help from their families or from psychiatric services.

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Part 2: GENDER AND CHILDHOOD TRAUMATIC EXPERIENCES IN PSYCHOSIS AND FIRST EPISODE PSYCHOSIS PATIENTS

THEORETICAL PART

Childhood traumatic experiences in psychotic patients: a literature review*

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ABSTRACT

Introduction: Childhood abuse is common occurrence among people with psychosis, particularly among women, and it is associated with poor illness outcomes. A modulating effect of gender in the association between childhood abuse and psychosis has been hypothesized, but evidence is scarce and it has never been put into a congruent frame.

Methods: Research articles on the impact of gender and childhood trauma in people with psychosis (to July 2018) were identified using a comprehensive electronic search of PubMed, Web-of-Science, Scopus and Cochrane databases and analysing reference list of relevant papers. A narrative synthesis was used to summarise results.

Results: A different pattern between women and men emerged from the literature search. Specifically, psychotic women who had been abused during childhood report more positive and mood symptoms at illness onset, more suicide attempts and earlier age of onset compared to men. Conversely, psychotic men who had been abused during childhood show more negative symptoms, substance use and a poorer cognitive performance compared to women.

Conclusion: Some, but not all, gender differences in people with psychosis and childhood abuse appear to reflect general gender differences in psychosis. We

recommend clinicians to carefully investigate early experiences of abuse in their patients and to provide them adequate treatment according to gender.

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Chapter 4 – Gender and childhood traumatic experiences in psychosis: a narrative review

4.1 Introduction

Childhood abuse is associated with a myriad of negative sequelae, such as depression (Amado *et al*, 2015), Post-Traumatic Stress Disorder (Carey *et al*, 2008), suicidality (Devries *et al*, 2014), eating disorders (Monteleone *et al*, 2019) and drug abuse (Meshesha *et al*, 2019). Childhood abuse is frequent among people with psychosis (Morgan *et al*, 2007), affecting 28%-73% of them (Bendall *et al*, 2008). Exposure to trauma during childhood is associated with a 2.8-fold increased risk of developing psychosis in adulthood (Varese *et al*, 2012) and the odds of developing the disorder is higher in people exposed to multiple and more severe experiences of abuse compared to not exposed (Shevlin *et al*, 2008). Childhood abuse is associated with a less favorable course of illness, with higher rates of psychotic symptoms (Gallagher *et al*, 2013), substance abuse (Bendall *et al*, 2012), comorbid physical disorders (Sweeney *et al*, 2015), cognitive deficits (Lysaker *et al*, 2001), earlier and more frequent hospitalizations (Newmann *et al*, 1998) and poorer rehabilitation outcomes (Lysaker *et al*, 2004) in people exposed compared to non-exposed.

However, not every people exposed to childhood abuse will develop psychosis in adulthood and gender has been claimed to moderate strength and features of this association for a number of reasons. First, women with psychosis are more likely to have been exposed to sexual abuse (Fisher *et al*, 2009; Heins *et al*, 2011) and physical abuse (Alvarez *et al*, 2011) during their childhood compared to men. Second, women tend to report greater perceived threat (Olf *et al*, 2007) and subjective distress (O'Hare *et al*, 2006) after a traumatic event and a greater negative appraisal of trauma than men (Sherrer *et al*, 2011). Third, females appear more prone than males to internalizing difficulties and this may explain their likeliness of becoming suspicious of other people's intentions and develop paranoid delusions, whereas males seem to respond to difficulties by exhibiting externalizing behaviors, which are linked to aggression and conduct disorders (Fisher *et al*, 2009). Fourth, there is evidence that childhood abuse selectively

affects neuroendocrine transmission in females, with women exposed to childhood abuse showing hypothalamic-pituitary-adrenal axis and autonomic nervous system hyperreactivity, presumably due to CRF hypersecretion, compared to non-exposed. (de Bellis *et al*, 1994; Heim *et al*, 2000). Despite this, most studies on childhood abuse in people with psychosis have not stratified results for gender and have simply provided cumulated data for males and females.

Given the difficulty to find information on the impact of gender and childhood abuse in people with psychosis, the present paper aims to: (1) review research conducted in this field; (2) compare gender differences in people with psychosis with and without childhood abuse and with the general population; and (3) to identify specific areas for development of gender targeted-intervention in people with psychosis who had experienced childhood trauma.

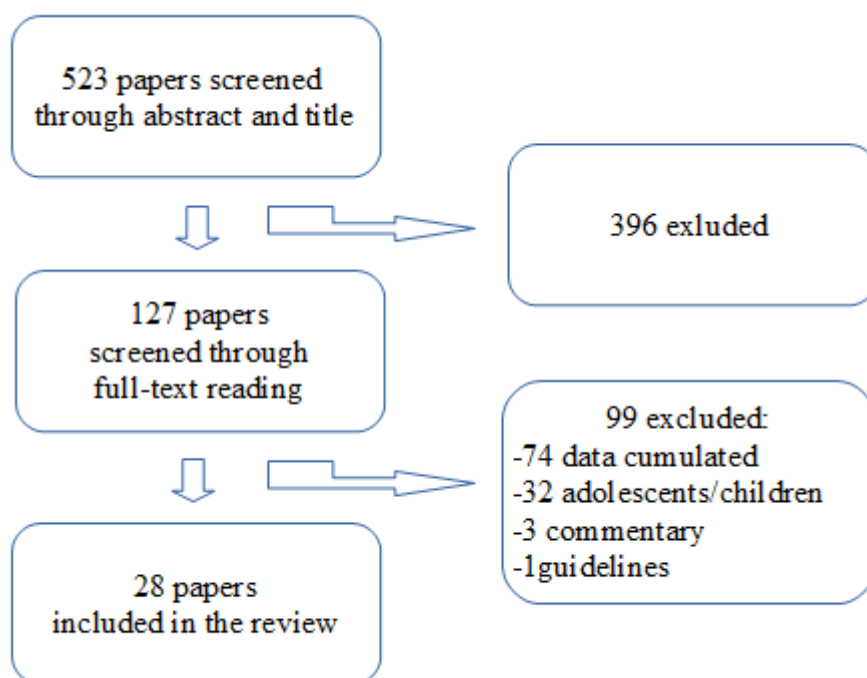
4.2 Methods

PubMed, Web-of-Science, Scopus and Cochrane databases were searched for potentially relevant articles. The search employed a combination of the following terms: “gender”, “sex”, “psychosis”, “first episode psychosis”, “schizophrenia”, “childhood trauma”, “childhood abuse”, “sexual abuse”, “physical abuse”. We accepted only original papers published in English in peer-reviewed journals. Articles were screened through title and abstract and we considered for inclusion articles on childhood abuse in psychotic or schizophrenic patients. After full text reading, only papers that provided information for both sexes separately or for either male or female-only patients were included. We excluded papers on children and adolescents and ultra high-risk patients because our focus was psychosis or first episode psychosis. We also excluded papers providing commentary or proposed guidelines. Further resources were identified through manual searches of the reference section of the articles selected for inclusion (Figure 1).

4.3 Results

The search was conducted on July 12th 2018. Based on the inclusion and the exclusion criteria a total of 127 articles have been selected for inclusion. After full text reading, 28 papers have been included in the present review (Figure 1). All articles included have been published between 2001 and 2018. Three papers were systematic reviews, sixteen were cohort studies and eight were case-control studies. For clarity, results have been grouped into 14 sections according to the outcome targeted by papers. A summary of the main findings of the articles included is presented in Table 1. Three papers were systematic reviews, sixteen were cohort studies, eight were case-control studies and one was a RCT (Comacchio *et al*, 2019) (see Table 1). Two studies involved FEP patients (Misiak *et al*, 2016; Aas *et al*, 2016) and six schizophrenic patients (Lysaker *et al*, 2005; Schafer *et al*, 2006; Andrianarisoa *et al*, 2017; Ruby *et al*, 2015; Fuller-Thomson *et al*, 2016; Haaramans *et al*, 2018). All other papers involved psychotic patients in general. Two studies were women-only (Schafer *et al*, 2006; Aakre *et al*, 2014) and one was men-only (Lysaker *et al*, 2005).

Figure 1. Flow chart.



Author(s) and year	Type of study	Sample size	Main findings
EPIDEMIOLOGY			
Read et al, 2005	Systematic review	-	Prevalence of childhood abuse 59% in males and 69% in females
Morgan and Fisher, 2007	Systematic review	-	Prevalence of childhood abuse 18% in males and 26% in females
Bonoldi et al, 2013	Systematic review	-	Prevalence of self-reported childhood abuse 39% and 26% for physical abuse and sexual abuse respectively in both sexes
PSYCHOPATHOLOGY			
Comacchio et al, 2019	RCT	444	Childhood abuse was linked to higher levels of negative symptoms in both men and women. Childhood physical abuse lowered the age of psychosis onset in women only.
Pruessner et al, 2018	Cohort	210	Childhood abuse correlated with higher levels of negative symptoms in men and to higher levels of depressive symptoms in women.
Sweeney et	Cohort	402	Male patients with childhood traumatic

al, 2015			experiences showed more anhedonia, subjective thought disorder compared to women. Childhood abuse was linked to higher levels of depressive and elevated mood symptoms in both sexes.
Shah et al, 2014	Cohort	1825	Male patients with childhood traumatic experiences showed more anxiety symptoms compared to women.
Kocsi-Bogar et al, 2017	Cohort	102	Childhood trauma predicted more frequent hospitalizations only in men.
Heins et al, 2011	Case-control	757	No gender difference in positive symptoms in people exposed to childhood traumatic experiences.
Kelly et al, 2016	Cohort	80	Childhood physical abuse was associated with higher levels of psychotic and depressive symptoms in women but not in men.
Misiak et al, 2016	Cohort	94	Childhood sexual abuse was associated with higher levels of auditory-verbal hallucinations in females but not in males.
Lysaker et al, 2005	Cohort	56	Patients with a history of childhood sexual abuse had significantly higher levels of dissociation, intrusive experiences, and state and trait anxiety than non-abused.
Garcia et al, 2016	Cohort	79	Childhood emotional neglect correlated with greater severity in positive, negative, general psychopathology and depressive symptoms only in women.
Aas et al, 2016	Case-control	360	No correlation between emotional neglect and impaired functioning in woman.
Schafer et al, 2006	Cohort	30	Childhood physical neglect was linked to higher levels of PANSS total scores at admission only in women.
Braehler et al, 2013	Case-control	171	Childhood physical neglect was associated with higher levels of dissociation in male patients.
Haug et al, 2015	Cohort	55	Emotional abuse, emotional neglect and physical neglect were linked to higher levels of depression in women.
SOCIAL FUNCTIONING			
Andrianarisoa et al, 2017	Cohort	544	Poor quality of life, which is related to levels of social support, was predicted by childhood abuse and male gender.

Gayer-Anderson et al, 2015	Case-control	472	Women with childhood physical abuse were four times more likely to be diagnosed as psychotic if they had not received emotional or practical support in adulthood and six times more likely to be diagnosed as psychotic if they had a small number of significant relationships in adulthood .
COGNITIVE FUNCTIONING			
Lysaker et al, 2004	Case-control	56	No impact of gender on neurocognition in people exposed to childhood adversities.
Ruby et al, 2015	Cohort	28	Female gender and a history of childhood trauma were associated with better performance on verbal fluency, verbal memory, attention, delayed memory, general memory and full-scale and verbal IQ scores.
Aas et al, 2011	Case-control	276	A history of childhood abuse was associated with poorer verbal intelligence, language, attention, concentration and mental speed, executive function and working memory only in male patients.
SUICIDE RISK			
Fuller-Thomson et al 2016	Cohort	22559	Women with schizophrenia and childhood abuse had four times the odds of suicide attempts than men.
Amr et al, 2016	Case-control	135	Male gender and a history of childhood sexual and physical abuse predicted higher levels of impulsive behaviours.
Lejoyeux et al, 2013	Cohort	100	Male gender and a history of childhood sexual and physical abuse predicted higher rates of aggressive behaviours.
SUBSTANCE ABUSE			
Rey et al, 2017	Cohort	240	Childhood abuse and male gender were associated with severe nicotine dependence.

Aakre et al, 2014	Cohort	117	Early traumatic experiences were more common in women with psychosis and comorbid substance abuse than in women with depression and comorbid substance abuse or women with substance abuse alone.
OTHER			
Haarmans et al, 2018	Case-control	92	Childhood sexual abuse was associated with gender-role strain in the non-clinical sample only.

4.3.1. Epidemiology

Three systematic reviews conducted so far reported data on the prevalence of childhood abuse in men and women with psychosis. The first systematic review on childhood abuse and psychosis was carried out by Read and colleagues (2005). They estimated the weighted average prevalence of either physical or sexual abuse by 59% in males and 69% in females, and the prevalence of both types of abuse by 19% in males and 36% in females. Specifically, the weighted average prevalence of reported childhood physical abuse was 50% for males and 48% for females, whereas for childhood sexual abuse the weighted average prevalence was 28% for males and 48% for females. Morgan and Fisher (2007) re-examined the literature addressed by Read *et al* (2005) by applying more stringent inclusion criteria. After excluding articles based on child and adolescent or mixed-diagnosis samples, the prevalence of either physical or sexual abuse resulted lowered at 50% for both genders and the prevalence of both types at 18% for males and 26% for females. The prevalence of physical abuse resulted at 35% for males and at 35% for females, whereas the prevalence of childhood sexual abuse resulted at 28% for males and at 42% for females. More recently, Bonoldi and colleagues (2013) conducted a systematic review on the prevalence of self-reported childhood abuse in retrospective studies on people with psychosis and found a prevalence of childhood physical abuse at 38.8% and a prevalence of childhood sexual abuse at 26.3% for both sexes. They also found that gender had a significant modulating effect on childhood sexual abuse, thus suggesting that studies with higher

proportions of females were more likely to report higher rates of abuse, whereas gender did not seem to influence childhood physical abuse.

4.3.2. Psychopathology, age of onset and childhood trauma

In men, childhood traumatic experiences have been correlated with negative symptoms ($p=0.18$; $p=0.034$) (Pruessner *et al*, 2018), and male patients with childhood traumatic experiences have shown more anhedonia ($\chi^2=8.44$, $df=1$, $p=0.004$), subjective thought disorder ($\chi^2=3.87$, $df=1$, $p=0.049$) (Sweeney *et al*, 2015) and anxiety (OR 1.8 95% CI 1.3–2.5) (Shah *et al*, 2014) compared to females. Childhood trauma has found to predict more frequent hospitalizations only in men ($R^2=0.55$) (Kocsi-Bogar *et al*, 2017). In women, childhood traumatic experiences have been linked to depressive mood symptoms ($p=0.28$; $p=0.024$ Pruessner *et al*, 2018; $\chi^2=5.59$, $df=1$, $p=0.018$ Sweeney *et al*, 2015), elevated mood symptoms ($\chi^2=4.30$, $df=1$, $p=0.038$ Sweeney *et al*, 2015) and higher rates of premorbid personality disorder (OR 1.8 95% CI 1.03–3.1 Shah *et al*, 2014) compared to men. However, two studies found no gender difference in positive symptoms in people exposed to childhood traumatic experiences (Heins *et al*, 2011; Kocsi-Bogar *et al*, 2017). Childhood physical abuse has found to predict earlier age at onset ($R^2=0.23$ Kocsi-Bogar *et al*, 2017; $p<0.001$ Comacchio *et al*, 2019) in women only.

4.3.3. Psychopathology, age of onset and childhood physical abuse

Childhood physical abuse has been associated with higher levels of psychotic symptoms ($F=4.03$, $df=1.76$, $p=0.048$) (Kelly *et al*, 2016), negative symptoms ($p<0.001$ Comacchio *et al*, 2019) and depressive symptoms ($F=4.23$ $df=1.76$ $p=0.04$ Kelly *et al*, 2016; $\beta=0.308$ $p=0.014$ Pruesner *et al*, 2018) in women but not in men.

4.3.4. Psychopathology and childhood sexual abuse

Childhood sexual abuse has been associated with auditory-verbal hallucinations in females but not in males ($B=0.394$, $t=2.501$, $p=0.017$ vs $B=0.123$, $t=0.880$, $p=0.383$) in FEP patients (Misiak *et al*, 2016). However, in a small case control

study involving schizophrenic male patients those with a history of childhood sexual abuse had significantly higher levels of dissociation (mean 12.67, SD 5.50, $p < 0.001$), intrusive experiences (mean 13.29, SD 6.60, $p < 0.001$), and state (mean 47.14, SD 14.14, $p < 0.001$) and trait (mean 54.14, SD 9.16, $p < 0.01$) anxiety than non-abused (Lysaker *et al*, 2005). Childhood sexual abuse has found to be a predictor of higher levels of negative symptoms in both men and women ($p = 0.001$; Comacchio *et al*, 2019) and of depression only in women ($\beta = -0.44$; $p = 0.002$; Pruessner *et al*, 2018).

4.3.5. Psychopathology and childhood emotional abuse

Childhood emotional abuse has found to be a predictor of positive symptoms ($\beta = 0.29$; $R^2 = 0.09$; $F(1,93) = 8.99$; $p = 0.003$), depression ($\beta = 0.25$; $R^2 = 0.062$; $F(1,93) = 6.15$; $p = 0.015$) and global functioning ($\beta = -0.33$; $R^2 = 0.11$; $F(1,93) = 10.98$; $p = 0.001$) in men and of depression in women ($\beta = 0.56$; $p = 0.001$) (Pruessner *et al*, 2018).

4.3.6. Psychopathology and childhood emotional neglect

Garcia and colleagues (2016) found a correlation between childhood emotional neglect and a greater severity in positive ($\rho = 0.498$; $p < 0.01$), negative ($\rho = 0.378$; $p < 0.05$), general psychopathology ($\rho = 0.403$; $p < 0.05$) and depressive symptoms ($\rho = 0.481$; $p < 0.01$) only in women. The same study revealed a correlation between emotional neglect and impaired functioning in woman ($\rho = -0.497$; $p < 0.05$), but this finding was not replicated in a case control study on FEP patients (Aas *et al*, 2016). Nevertheless, emotional neglect has found to predicted negative symptoms only in men ($\beta = 0.28$; $R^2 = 0.078$; $F(1,93) = 7.89$; $p = 0.006$) (Pruessner *et al*, 2018).

4.3.7. Psychopathology and childhood physical neglect

A small cohort study found a link between childhood physical neglect and PANSS total scores at admission ($\tilde{r} = 0.35$; $p = 0.039$), but not at discharge, only in women (Schafer *et al*, 2006).

4.3.8. Dissociation

Childhood physical neglect has found to be associated with high levels of dissociation in male patients with either FEP and chronic psychosis, but not in females ($r=0.345$, $p<0.001$) (Braehler *et al*, 2013). However, Schafer and colleagues (2006) in a small sample of female schizophrenic inpatients found that childhood physical neglect was significantly correlated with dissociative symptoms at admission ($\rho=0.58$; $p= 0.023$), but not at discharge. In the same sample, emotional abuse was significantly correlated with high levels of dissociation both at admission ($\rho=0.55$; $p= 0.034$) and at discharge ($\rho=0.34$; $p= 0.032$). Severe forms of dissociation may involve Anomalous Self-Experiences (ASEs) (Sass *et al*, 2013), that are described as subtle forms of depersonalization, anomalous experiences of cognition and stream of consciousness, self-alienation, pervasive difficulties in grasping familiar and taken-for-granted meanings, unusual bodily feelings, permeability or complete loss of the self-world boundary, in addition to existential reorientation (Parnas *et al*, 2005). In a sample of FEP patients emotional neglect was linked to higher levels of ASEs in women ($\rho=0.551$ $p=0.004$) but not in men. In the same sample, emotional abuse ($\rho=0.586$ $p=0.001$), emotional neglect ($\rho=0.693$ $p=0.001$) and physical neglect ($\rho=0.525$ $p=0.005$) were linked to higher levels of depression in women but not in men (Haug *et al*, 2015).

4.3.9. Social functioning

In a recent case-control study (Gayer-Anderson *et al*, 2015) women with childhood physical abuse were four times more likely to be diagnosed as psychotic if they had not received emotional (OR 4.04, 95 % CI 1.47–11.09) or practical (OR 4.90, 95 % CI 1.65–14.57) support in adulthood and six times more likely to be diagnosed as psychotic if they had a small number of significant relationships in adulthood (OR 6.14, 95 % CI 1.80–21.00) compared to women without childhood physical abuse. Similar associations were found for childhood sexual abuse (OR 4.41, 95 % CI 1.60–12.16) for emotional support; OR 3.31, 95 % CI 1.11–9.87 for a small number of significant relationships), whereas no clear association was identified for men exposed and non-exposed to childhood abuse. Women with psychosis and a history of childhood trauma have found to be more

likely to be married or in a *de facto* relationship than males (OR 4.89 95% CI 1.2–19.2 $p=0.02$) (Sweeney *et al*, 2015). However, a large population-based study run in Australia (Shah *et al*, 2014) showed that female patients with a history of childhood abuse were less likely to have someone to rely on in times of need compared to males (OR 0.5 95% CI 0.3–0.8). Lastly, poor quality of life, which is related to levels of social support, was predicted by childhood abuse ($\beta=-0.21$, $p<0.0001$) and male gender ($\beta = -0.16$, $p<0.0001$) in a cohort study of schizophrenic patients (Andrianarisoa *et al*, 2017).

4.3.10. Cognitive functioning

The impact of gender and childhood adversities on cognition in psychotic patients has yielded to mixed results: two studies failed to identify an impact of gender on neurocognition in people exposed to childhood adversities (Lysaker *et al*, 2004; Garcia *et al*, 2016), whereas female gender and a history of childhood trauma have found to be associated with better performance on verbal fluency ($r=0.852$; $N=7$; $p=0.015$), verbal memory ($r=0.766$; $N=7$; $p=0.045$), attention ($r=0.880$; $N=7$; $p=0.009$), delayed memory ($r=0.779$; $N=7$; $p=0.039$), general memory ($r=0.806$; $N=7$; $p=0.029$) and full-scale ($r=0.822$; $N=7$; $p=0.023$) and verbal IQ scores ($r=0.837$; $N=7$; $p=0.019$) in a small cohort study of schizophrenic patients (Ruby *et al*, 2015). Consistently, a case control study on FEP patients revealed that a history of childhood abuse was associated with poor verbal intelligence (mean=0.10; SD=0.8; $p =0.002$), language (mean=0.04; SD=0.7; $p =0.031$), attention, concentration and mental speed (mean=0.09; SD=0.8; $p =0.011$), executive function and working memory (mean=0.07; SD=0.8; $p=0.028$) only in male patients (Aas *et al*, 2011).

4.3.11. Suicide risk

The impact of gender and childhood abuse on suicidality and related behaviours has been tested in samples of schizophrenic patients. Fuller-Thomson and colleagues (2016) in a community-based study found that women with schizophrenia and childhood abuse had four times the odds of suicide attempts than men (OR = 4.59; 95% CI =1.21, 17.35) and 24% of the variability in suicide

attempts was explained by a history of childhood traumatic experiences ($R^2=0.24$). Concerning related behaviours, male gender and a history of childhood sexual and physical abuse have found to predict impulsive ($\beta=14.930$; $SE=3.696$ $p<0.001$) (Amr *et al*, 2016) and aggressive behaviours ($OR = 3.6$; $95\% CI=1.1-11.7$; $p=0.03$) (Lejoyeux *et al*, 2013).

4.3.12. Substance abuse

In psychotic patients, childhood abuse and male gender have found to be associated with increased alcohol intake ($\rho= 0.331$; $p<0.05$) (Garcia *et al*, 2016) and severe nicotine dependence ($OR = 4.5$; $95\% CI 1.5-13.7$; $p=0.009$) (Rey *et al*, 2017). In a cohort study on psychiatric women, early traumatic experiences were reported to be more common in women with psychosis and comorbid substance abuse than in women with depression and comorbid substance abuse or women with substance abuse alone ($\chi^2=13.64$; $p=0.001$) (Aakre *et al*, 2014).

4.3.13. Physical health

Sweeney *et al* (2015) in a cohort study found that more males with a history of childhood abuse reported chronic pain ($\chi^2 = 5.2$, $df = 1$, $p = 0.022$), cardiovascular disease/stroke ($\chi^2 = 7.9$, $df = 1$, $p = 0.005$), headaches/migraines ($\chi^2 = 10.0$, $df = 1$, $p = 0.001$), arthritis ($\chi^2 = 4.7$, $df = 1$, $p = 0.031$) and epilepsy ($\chi^2 = 5.3$, $df = 1$, $p = 0.021$) than males without childhood abuse. By contrast more females with childhood abuse than without reported chronic pain ($\chi^2 = 9.8$, $df = 1$, $p = 0.002$) and headaches/migraines ($\chi^2 = 6.2$, $df = 1$, $p = 0.012$). However, this result was not replicated by Shah and colleagues (2014), who did not find an impact of gender and childhood abuse on Body Mass Index (BMI) and metabolic syndrome in a cross-sectional survey.

4.3.14. Needs for care

Childhood abuse had little impact on needs for care other than unmet functioning (basic education, money, childcare, self-care, looking after home) and service (information, telephone use, transport and benefits), which showed higher levels in both men and women exposed to childhood traumatic experiences in a cohort

of FEP patients ($p=0.02$ for service needs and $p=0.005$ for functioning needs; Comacchio *et al*, 2019).

4.3.15. Other

In a small case control study childhood sexual abuse has found to be associated with gender-role strain in the non-clinical sample only (Pearson $r = 0.35$, $p < 0.05$) (Haarmans *et al*, 2018). Gender-role strain is defined as the negative psychological consequences, such as low self-esteem and depression (Zamarripa *et al*, 2003), experienced when individuals try to live up to internalized gender-role stereotypes and norms (Pleck, 1981) and it has been found that non-psychiatric women with childhood sexual abuse experienced greater feminine self- discrepancy than non-abused women (Krause and Roth, 2011). Haarmans and colleagues (2018) hypothesized a stronger association between childhood sexual abuse and gender-role strain in the clinical group compared to controls, as a consequence of the higher rates of childhood sexual abuse in psychotic women and suggested that their unexpected result could be due to the low within-group variance or to the effect of revictimization in adulthood and psychosis-related vulnerability in women.

4.5 Discussion

The present paper provides a comprehensive overview on the impact of childhood traumatic experiences in men and women with psychosis. As far as we know, this is the first review ever published to fully address this specific issue.

We found that prevalence of childhood sexual abuse are higher in women with psychosis compared to men, whereas there seem to be no, or little, gender difference for childhood physical abuse. Childhood abuse rates in non-clinical samples are 2-3 time higher in women compared to men (Stoltenborgh *et al*, 2011; Afifi *et al*, 2014). In the last few years the number of studies investigating the role of traumatic experiences, especially those occurred in the early years of life, in the development of psychiatric disorders has rapidly grown (Carr *et al*, 2013). The definition of childhood trauma comprises eight main dimensions: physical abuse,

sexual abuse, psychological abuse, witnessing interpersonal violence, physical neglect, emotional neglect, significant separations from caregivers and loss of caregiver (Roy *et al*, 2004). This broad definition of childhood trauma, has implied a large variety in the conceptualization that researchers have used based in their studies, making it difficult to understand the real extent of trauma presence in their samples (Vergano *et al*, 2015). Even measurement tools used to detect childhood trauma vary massively across studies, making it difficult to compare results of the existing literature (Sahin *et al*, 2013). However, recent literature shows adequate consistency on childhood physical and sexual abuse rates.

We also found that psychotic women who had been abused during their childhood show more positive and mood symptoms both at illness onset and during the illness course compared to men. Specifically, all types of abuse appear to be associated with positive and depressive symptoms in women, except emotional abuse that has found to be associated with psychotic symptoms only in men. Conversely, psychotic men who had been abused during their childhood present with more negative, anxiety and dissociative symptoms compared to women. Particularly, in men childhood sexual abuse showed an association with anxiety and emotional neglect with negative symptoms. Impaired global functioning was linked to emotional abuse in men and to emotional neglect in women. However, recent population-based studies reported that men with psychosis tend to show more negative symptoms compared to women and that women tend to display more positive and mood symptoms than men (Koster *et al*, 2008; Hui *et al*, 2016; Comacchio *et al*, 2019). Unfortunately, none of these studies have controlled results for childhood abuse, so we do not know whether these gender differences are due to childhood trauma or are simple gender differences in psychosis manifestation. To our knowledge, only one study has found an association with anxiety symptoms and male gender in people with psychosis (Brebion *et al*, 2013) but results were not controlled for childhood trauma, so we can speculate that the higher levels of anxiety in male patients exposed to childhood sexual abuse compared to females may be a true effect of childhood trauma. This may be

explained by cultural factors related to rape, that have been proposed to have a stronger impact on men compared to women (Shevlin *et al*, 2007).

Concerning age at onset, we found that childhood physical abuse was a predictor of an earlier age at onset only in women. In psychosis, mean age at onset is significantly and consistently higher in women compared to men (Eranti *et al*, 2013; Riecher-Rossler *et al*, 2018). Two studies have found a positive association between earlier age of psychosis onset and childhood psychological abuse (Li *et al*, 2015; Alvarez *et al*, 2011), but neither examined the effect of gender. Hacıoglu and colleagues (2014), in a sample of female patients with schizophrenia, found that patients with a history of childhood sexual abuse were significantly younger than those without. Only one study has focused on how childhood trauma interacts with gender on age of psychosis onset (Kocsis-Bogar *et al*, 2018) and found that childhood physical abuse predicted an earlier age at psychosis onset only for female patients. As a possible explanation, we can speculate that gender-specific protective factors in women, but not in men, such as better premorbid adjustment (Addington *et al*, 2003), higher levels of insight (Parellada *et al*, 2011) and shorter duration of untreated psychosis (Cascio *et al*, 2012), may be outweighed by the consequences of childhood abuse, but further research is needed to clarify this aspect.

Our findings seem to indicate that women with psychosis and childhood abuse are less likely to receive social support despite being more likely to be married or in a relationship than men. Social support, defined as the combination of social networks, perceived social support and enacted support (Barrera, 1986), has been claimed to act as a moderating factor between early adversities and later development of psychosis (Gayer-Anderson *et al*, 2015). Nevertheless, childhood trauma can disrupt the acquisition of interpersonal relatedness skills, including the desire for affiliation, and lead to difficulty with social functioning in adulthood (Stain *et al*, 2014), thus the relationship between childhood adversities and social functioning is controversial. In non-clinical samples, childhood traumatic experiences have found to affect the capacity to form positive relationships (Van

der Kolk, 2005) and to predict lower levels of social support in adulthood (Joa *et al*, 2008), with no acknowledge gender differences. Being married or having a partner does not necessarily imply living in a supportive environment, as 21% of women with chronic mental illnesses report being victims of recent intimate partner violence (Khalifeh *et al*, 2015). Childhood abuse is positively correlated with adulthood intimate partner violence, as childhood abused women show a significant tendency to choose potentially abusive partners in adulthood (Herrero *et al*, 2018). In childhood abused victims, secure attachment is disrupted and, for some women, this may drive the selection of partners to the rapid satisfaction of psychological and social needs (Banducci *et al*, 2017), which may explain the increased likeliness of women with psychosis and childhood abuse to be in a relationship. This in no way implies any responsibility on the part of the potential victim of abuse, though stresses the importance of investigating intimate partner violence in women with psychosis and childhood abuse by their clinicians (Khalifeh *et al*, 2015).

Women with psychosis and childhood abuse seem to show a better cognitive performance than men in the domains of verbal intelligence, attention and general and working memory. Despite studies indicating a better cognitive performance in female healthy subjects undergoing psychosocial stress compared to males (Wolf *et al*, 2001), there is no clear evidence for gender differences in cognitive performance in non-clinical samples of people exposed to childhood abuse (Perez and Widom, 1994). However, similar gender differences in neurocognition have been found in non-clinical samples (Ittig *et al*, 2015) and in samples of psychotic patients (Hoff *et al*, 1998; Bozikas *et al*, 2010) in studies that did not control for childhood abuse. It has been hypothesized that gender differences in neurocognition might not be disease-specific (Riechler-Rossler *et al*, 2018) and our findings make it unlikely that childhood abuse may act as a modulator or as a moderator in this area.

Women with psychosis and childhood abuse appear at higher risk of attempting suicide compared to men. Suicidality is frequently reported among victims of

childhood abuse in the general population (Brodsky et al, 2001), with a stronger effect on women than on men (Liu *et al*, 2017). Suicidality is also very frequent among people with psychosis: it has been estimated that one in every twenty individuals affected with psychosis will commit suicide (Palmer *et al*, 2005) and women with psychosis seem to be at a greater risk compared to men (Canuso and Pandina, 2007).

Our review indicates that childhood trauma impacts on substance abuse more in men than in women with psychosis. People with psychosis show high levels of substance abuse, some of which are known to increase the risk for psychosis or at least to act as a trigger in vulnerable individuals (Riecher-Rossler *et al*, 2018). Men with psychosis tend to consume more cannabis (Koskinen *et al*, 2010), alcohol, cocaine and hallucinogens than women (Ochoa *et al*, 2012). It has been suggested that childhood abuse and cannabis use may have a cumulative effect in the risk of developing psychosis (Harley *et al*, 2010; Konings *et al*, 2011). In non-clinical samples men show higher rates of substance abuse compared to women (Khan *et al*, 2013), though women with childhood abuse have shown higher levels of substance abuse compared to men (Young-Wolff *et al*, 2012). Therefore, although it seems that childhood trauma does not modulate substance abuse in people with psychosis, further research may help disentangle the impact of gender and childhood trauma on substance abuse in the general population.

Both men and women with psychosis and childhood abuse report more chronic pain and headache compared to non-abused. In addition men with psychosis and childhood abuse present more cardiovascular disease/stroke, epilepsy and arthritis compared to non-abused. A positive association between childhood traumatic experiences and poor physical health outcomes has been found in non-clinical samples (Goodwin and Stein, 2004) without any significant gender difference (Springer *et al*, 2007). Cardiovascular disease, the leading cause of death in high and middle-income countries (Mozaffarian *et al*, 2016), is exceedingly prevalent in people with psychosis because of the high prevalence of risk factors (Galletly *et al*, 2012). One acknowledge and non-modifiable risk factor for cardiovascular

disease, both in general and psychiatric samples, is male gender (Connolly *et al*, 2005), and childhood abuse does not seem to affect the association between gender and cardiovascular disease in either populations. Conversely, chronic pain is more common in women than men in the general population (Tyrer *et al*, 1989) and in psychiatric settings (Chaturvedi, 1986), therefore we can speculate that childhood abuse may be linked to some forms of somatization only in men. Reasons for that require further investigation.

4.6 Conclusions

A different pattern between women and men emerged from the literature search. Specifically, psychotic women who had been abused during childhood report more positive and mood symptoms at illness onset, more suicide attempts and earlier age of onset compared to men. Conversely, psychotic men who had been abused during childhood show more negative symptoms, substance use and a poorer cognitive performance compared to women. It seems that some, but not all, gender differences in people with psychosis and childhood abuse reflect general differences between men and women with psychosis.

4.7 References

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properties of an instrument for measuring early relational trauma. *Frontiers in Psychology* 2015; **6**.

121. **Wolf RS.** Support groups for older victims of domestic violence. *J Women Aging* 2001; **13**(4): 71-83.
122. **Young-Wolff KC, Kendler KS, Prescott CA.** Interactive effects of childhood maltreatment and recent stressful life events on alcohol consumption in adulthood. *J Stud Alcohol Drugs* 2012; **73**(4): 559-69.
123. **Zamarripa VG.** International trauma and disaster management. *Crit Care Nurs Clin North Am* 2003; **15**(2): 275-81. Table 1. Summary of reviewed articles, stratified by thematic area

RESEARCH PART

The impact of gender and childhood abuse on age of psychosis onset, psychopathology and needs for care in First Episode Psychosis patients*

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ABSTRACT

Gender is associated with several features of psychotic disorders, including age of illness onset, symptomatology, a higher prevalence of history of childhood sexual abuse (CSA) and needs for care. Childhood sexual abuse is associated with adverse mental health consequences but as there is a gender difference in stress reactivity, there may be a differential impact of CSA on psychopathology, age of psychosis onset and needs for care in First Episode Psychosis (FEP) patients. We hypothesized that a history of abuse would be associated with lowering of age of onset, more severe psychotic symptoms and more unmet needs in women but not men. A total of 444 FEP patients have been recruited within the context of the GET UP trial. Symptomatology has been assessed using the PANSS scale, needs for care with the CAN scale and childhood abuse with the CECA-Q scale. Childhood sexual abuse was more frequent among female patients [22.6% in women vs 11.6% in men (OR=0.45, $p<0.01$)], whereas there was no gender difference in the prevalence of childhood physical abuse (29.0% in women vs 31.7% in men).

Childhood abuse was associated with higher levels of negative symptoms in both men and women, with a reduced the age of onset in women only and little increase in needs for care in both men and women. Our results seem to suggest that childhood sexual abuse in female FEP patients may be linked to a form of psychosis whose presentation is similar to that considered the typical “male” presentation of psychosis (earlier age of onset, higher levels negative symptoms).

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Chapter 5 – The impact of gender and childhood abuse on age of psychosis onset, psychopathology and needs for care in First Episode Psychosis patients

5.1 Study design

The present research represents a secondary development of the GET UP (Genetics, Endophenotypes, Treatment: Understanding early Psychosis) PIANO (Psychosis: early Intervention and Assessment of Needs and Outcome) trial. The GET UP PIANO trial has a pragmatic cluster randomized controlled design, which compares the effectiveness of Treatment As Usual (TAU) plus a multi-element psychosocial treatment for patients with FEP and their family members, versus TAU alone, as provided by Italian community mental health services. Based on the WHO 10-country study (Jablensky *et al*, 1992), the inclusion criteria to ascertain FEP were as follows: (1) age 18–54 years, (2) residence in catchment areas (Veneto and Emilia Romagna regions and cities of Milan, Florence and Bolzano), (3) presence of at least one of the following: hallucinations, delusions, qualitative speech disorder, qualitative psychomotor disorder, bizarre, or grossly inappropriate behaviour, or two of the following: loss of interest, initiative, and drive; social withdrawal; episodic severe excitement; purposeless destructiveness; overwhelming fear; or marked self-neglect, (4) first lifetime contact with Mental Health Services, prompted by these symptoms. Exclusion criteria were: (1) antipsychotic medication (>3 months) prescribed for an identical or similar mental disorder; (2) mental disorders due to general medical condition; (3) moderate-severe mental retardation per a clinical functional assessment; and (4) psychiatric diagnosis other than International Classification of Diseases (ICD)-10 for psychosis. A detailed description of the GET UP PIANO trial is available elsewhere (Ruggeri *et al*, 2015).

5.2 Aim

The present study therefore aims to 1) explore gender differences in psychopathology, age of onset and needs for care in a large cohort of FEP patients; and 2) assess the impact of gender and traumatic experiences (physical and sexual abuse) on psychopathology, age of psychosis onset and needs for care.

Given that both severe physical and sexual abuse appear to be associated with psychosis in female patients, that childhood sexual abuse is more frequently experienced by girls and that childhood sexual abuse has been reported to be associated with some features of psychosis at illness onset, our primary hypothesis was that women with FEP, compared with men, would have had higher levels of positive and negative symptoms and lower age of illness onset in people exposed to childhood sexual abuse. Due to the or the lack of information on the impact of gender and childhood abuse on needs for care of both chronic and FEP patients, for the formulation of our secondary hypothesis we relied on studies assessing gender differences in needs for care in FEP patients, and thus we hypothesized that women with FEP, compared with men, would have had more unmet needs for care in the services and functioning domains in people exposed either physical or sexual abuse in their childhood.

5.3 Measures

Symptomatology has been assessed using the Positive and Negative Syndrome Scale (PANSS), a widely used assessment scale consisting of 30 items that covers positive symptoms, negative symptoms and general psychopathology; each item is rated on a Likert-type severity scale ranging from 1 (absent) to 7 (extreme) (Kay *et al*, 1997). The European version of the Camberwell Assessment of Needs (CAN-EU) has been used to measure the number of present needs of subjects per area and the number of unmet needs. This interview comprises 22 items grouped into five conceptual domains: health (psychotic symptoms, drugs, alcohol, safety to self, safety to others, psychological distress, and physical health); basic (accommodation, food, and daytime activities); social (sexual expression, social networks, and intimate relationships); service (information, telephone use, transport, and benefits) and functioning (basic education, money, childcare, self-care, looking after the home). Each item is rated on a scale of three conditions: 0 = no problem, 1 = absent or moderate problem due to the person receiving ongoing interventions (met need), 2 = actual serious problem and no interventions received (unmet need) (McCrone *et al*, 2000). Age at psychosis onset has been collected via case register. Information on childhood trauma has been collected at

baseline using the Childhood Experience of Care and Abuse-Questionnaire (CECA-Q), a measure of sexual abuse, parental physical abuse and lack of parental care (neglect and antipathy) occurred before the age of 17. It takes the form of a semi-structured interview, which aims to reflect objective features of early life experience with probing questions to ascertain details of context and time-sequence of experience (Bifulco *et al*, 2005).

5.4 Statistical analysis

Categorical variables were evaluated by Chi-square test or Fisher's exact test (for 2x2 tables). Continuous variables were analyzed by t test (2 independent groups), ANOVA with Bonferroni post-hoc comparisons (more than 2 independent groups) or paired t test (repeated measures). Results were not adjusted for demographic variables (marital status, education and employment) because they could act both as direct and as reverse causal factors. All tests were bilateral at $p < 0.05$. Analyses were performed by SPSS 22.0 for Windows.

5.5 Results

5.5.1 Composition of the sample

444 FEP patients were assessed at baseline, 260 males and 184 females. The groups did not differ in socio-demographic characteristics, except marital and working status (males were more frequently unmarried and unemployed than females) (Table 1).

Table 1. Gender differences in socio-demographic characteristics

	Females (n=184)	Males (n=260)	p-value Chi-square, Fisher or t test
Age at onset, mean (SD)	33.4 (10.2)	27.9 (8.5)	<0.001
Educational level, n (%)	(12 missing)	(10 missing)	
Low (primary-middle school)	69 (40.1%)	94 (37.6%)	0.61
High (secondary school, university)	103 (59.9%)	156 (62.4%)	
Marital status, n (%)	(11 missing)	(13 missing)	
Unmarried	102 (59.0%)	211 (85.4%)	<0.001
Married	54 (31.2%)	26 (10.5%)	
Widowed, separated, divorced	17 (9.8%)	10 (4.1%)	
Working status, n (%)	(10 missing)	(5 missing)	
Employed	60 (34.5%)	99 (38.8%)	0.03

Unemployed	51 (29.3%)	93 (36.5%)	
Housewife, student, retired, other	63 (36.1%)	63 (24.7%)	
Nationality, n (%)	(1 missing)	(4 missing)	
Italy	163 (88.6%)	227 (87.3%)	0.76
Other	21 (11.4%)	33 (12.7%)	
Diagnosis, n (%)			
Non affective psychosis	139 (75.5%)	207 (79.6%)	0.35
Affective psychosis	45 (24.5%)	53 (20.4%)	

5.5.2 Childhood traumatic experiences

Sociodemographic characteristics of CECA-Q completers and CECA-Q non-completers are presented in Table 2. There was no difference between female completers and non-completers, whereas male completers were less likely to be married, widowed/separated/divorced and more likely to be Italian than male non-completers.

Childhood physical abuse was reported by 30.6% (N=103) of patients, with similar rates for males and females (29.0% (N=40) of females and 31.7% (N=63) of males). Sexual abuse was reported by 16.2% (N=53) of patients, 22.6% (N=31) in women, 11.6% (N=22) in men (OR=0.45, $p<0.01$). (Table 3).

Table 2. Gender differences in childhood abuse (CECA-Q)

N (%)	Females (n=150)	Males (n=206)	OR	p-value Fisher test
Physical abuse	40 (29.0%) 12 missing	63 (31.7%) 7 missing	1.12	0.60
Sexual abuse	31 (22.6%) 13 missing	22 (11.6%) 16 missing	0.45	0.009

Table 3. Gender differences in socio-demographic characteristics by CECA-Q completers

	CECA-Q completers		CECA-Q non-completers		p-value Chi-square or t-test	Bonferroni post-hoc
	Females (n=150)	Males (n=206)	Females (n=34)	Males (n=54)		
Age at onset, mean (SD)	32.72 (10.31)	27.65 (8.59)	36.24 (9.53)	28.88 (8.22)	<0.001	F comp > M comp F non-comp > M comp F non-comp > M non comp
Educational level, n (%)	(3 missing)	(6 missing)	(9 missing)	(4 missing)	0.55	
Low (prim-middle school)	57 (38.8%)	72 (36.0%)	12 (48.8%)	22 (44.0%)		-
High (sec school, college)	90 (61.2%)	128 (64.0%)	13 (52.0%)	28 (56.0%)		-
Marital status, n (%)	(5 missing)	(9 missing)	(6 missing)	(4 missing)	<0.001	
Unmarried	85 (58.6%)	172 (87.3%)	17 (60.7%)	39 (78.0%)		- M non-comp > M comp
Married	46 (31.7%)	19 (9.6%)	8 (28.6%)	7 (14.0%)		M non-comp > M comp
Widow, separat, divorc	14 (9.7%)	6 (3.0%)	3 (10.7%)	4 (8.0%)		
Working status, n (%)	(6 missing)	(3 missing)	(4 missing)	(2 missing)	0.52	
Employed	50 (34.7%)	80 (39.4%)	10 (33.3%)	19 (36.5%)		-
Unemployed	42 (29.2%)	71 (35.0%)	9 (30.0%)	22 (42.3%)		-
Housewife, stud, retir	52 (36.1%)	52 (25.6%)	11 (36.7%)	11 (21.2%)		-
Nationality, n (%)	(1 missing)	(3 missing)	-	(1 missing)	0.03	
Italy	133 (89.3%)	186 (91.6%)	30 (88.2%)	41 (77.4%)		M comp > M non-comp
Other	16 (10.7%)	17 (8.4%)	4 (11.8%)	12 (22.6%)		M non-comp > M comp
Diagnosis n (%)					0.36	
Non-affective psychosis	111 (74.0%)	161 (78.2%)	28 (82.4%)	46 (85.2%)		-
Affective psychosis	39 (26.0%)	45 (21.8%)	6 (17.6%)	8 (14.8%)		-

5.5.3 Psychopathology

There were some gender differences in PANSS subscales. For positive symptoms, female patients showed higher levels of excitement compared to males, whereas male patients showed higher levels of grandiosity compared to females. Male patients showed higher levels of negative symptoms than females in the PANSS negative subscale total and in the items of blunted affect, emotional withdrawal, passive/apathetic social withdrawal, difficulty in abstract thinking and lack of spontaneity. General psychopathology scale revealed higher levels of guilt feelings in females compared to males and higher levels of poor impulse control in male patients than females (Table 4).

The impact of gender and childhood traumatic experiences on psychopathology is presented in Table 5. There were no gender differences in positive symptoms for patients (male or female) with or without a history of physical abuse; however, for negative symptoms, physical abuse was associated with higher levels of symptoms in both men and women. Similarly, while there were no differences for positive symptoms for CSA by gender, CSA was associated with higher levels of negative symptoms for both men and women.

Table 4. Gender differences in psychopathology (PANSS)

Mean (SD)	Females (n=184)	Males (n=260)	p-value t test
Total	2.29 (0.65) 1 missing	2.40 (0.69)	0.07
Positive sub-scale	2.27 (0.86) 2 missing	2.27 (0.89)	0.98
Delusions	3.39 (1.92) 2 missing	3.37 (1.85) 2 missing	0.90
Conceptual disorganization	2.00 (1.22) 3 missing	1.96 (1.35) 3 missing	0.73
Hallucinatory behaviour	2.12 (1.65) 3 missing	2.07 (1.64) 2 missing	0.79
Excitement	1.78 (1.24) 3 missing	1.53 (1.01) 3 missing	0.02*
Grandiosity	1.50 (1.03) 4 missing	1.76 (1.38) 5 missing	0.02*
Suspiciousness/persecution	3.40 (1.79) 2 missing	3.29 (1.76)	0.51
Hostility	1.64 (1.02) 3 missing	1.85 (1.33) 3 missing	0.07
Negative sub-scale	2.28 (1.01)	2.70 (1.18)	<0.001*

	2 missing	1 missing	
Blunted affect	2.39 (1.48) 3 missing	3.04 (1.59) 4 missing	<0.001*
Emotional withdrawal	2.62 (1.56) 2 missing	3.12 (1.69) 3 missing	0.001*
Poor rapport	1.76 (1.18) 2 missing	1.86 (1.38) 2 missing	0.40
Passive/apathetic social withdrawal	2.82 (1.73) 6 missing	3.37 (1.78) 1 missing	0.001*
Difficulty in abstract thinking	2.13 (1.34) 8 missing	2.47 (1.42) 13 missing	0.01*
Lack of spontaneity	1.99 (1.43) 3 missing	2.54 (1.68) 2 missing	<0.001*
Stereotyped thinking	2.20 (1.42) 3 missing	2.40 (1.48) 6 missing	0.17
General psychopathology scale	2.29 (0.66) 1 missing	2.34 (0.56)	0.44
Somatic concern	2.39 (2.68) 4 missing	2.07 (1.59) 5 missing	0.12
Anxiety	3.58 (1.38) 1 missing	3.55 (1.61) 4 missing	0.82
Guilt feelings*	2.44 (1.50) 3 missing	2.07 (1.35) 1 missing	0.01*
Tension	2.12 (1.25) 2 missing	2.34 (1.39) 2 missing	0.09
Mannerisms and posturing	1.26 (0.80) 6 missing	1.25 (0.81) 3 missing	0.87
Depression	3.17 (1.50) 2 missing	3.20 (1.55) 1 missing	0.82
Motor retardation	1.80 (1.17) 3 missing	2.00 (1.26) 3 missing	0.09
Uncooperativeness	1.55 (1.00) 2 missing	1.58 (1.14) 3 missing	0.81
Unusual thought content	2.44 (1.55) 1 missing	2.50 (1.61) 2 missing	0.73
Disorientation	1.32 (0.76) 4 missing	1.44 (0.87) 5 missing	0.14
Poor attention	1.61 (0.99) 4 missing	1.67 (1.06) 3 missing	0.59
Lack of judgment and insight	3.52 (1.72) 3 missing	3.83 (1.66) 1 missing	0.06
Disturbance of volition	1.73 (1.08) 5 missing	1.86 (1.30) 5 missing	0.27
Poor impulse control*	1.65 (1.06)* 4 missing	1.88 (1.25)* 3 missing	0.049*
Preoccupation	2.68 (1.46) 5 missing	2.77 (1.44) 4 missing	0.52
Active social avoidance	3.12 (1.98) 4 missing	3.35 (1.90) 3 missing	0.21

Table 5. Gender differences in psychopathology by childhood abuse (PANSS).

	Physical abuse		No physical abuse			
Mean (sd)	Females (n=40)	Males (n=63)	Females (n=98)	Males (n=136)	p-value ANOVA	Bonferroni post-hoc
PANSS positive scale	2.30 (0.84)	2.42 (0.82)	2.23 (0.83)	2.18 (0.68)	0.25	-
PANSS negative scale	2.40 (0.96)	2.66 (0.98)	2.16 (1.01)	2.59 (1.14)	<0.01	M PA > F no PA M no PA > F no PA
PANSS gen psych scale	2.32 (0.65)	2.37 (0.52)	2.17 (0.63)	2.29 (0.61)	0.20	-
PANSS total	2.33 (0.63)	2.45 (0.51)	2.18 (0.63)	2.33 (0.64)	0.05	M PA > F no PA
	Sexual abuse		No sexual abuse			
Mean (sd)	Females (n=31)	Males (n=22)	Females (n=106)	Males (n=168)	p-value ANOVA	Bonferroni post-hoc
PANSS positive scale	2.30 (0.79)	2.44 (0.78)	2.23 (0.84)	2.24 (0.83)	0.70	-
PANSS negative scale	2.37 (0.84)	2.80 (1.08)	2.20 (1.03)	2.58 (1.10)	0.01	M no SA > F no SA
PANSS gen psych scale	2.39 (0.64)	2.42 (0.77)	2.18 (0.63)	2.30 (0.56)	0.14	-
PANSS total	2.36 (0.58)	2.51 (0.70)	2.20 (0.64)	2.35 (0.60)	0.08	-

5.5.4 Age of onset

Age at psychosis onset was 27.9 years for males and 33.4 for females (Table 1). Physical abuse and sexual abuse reduced the age of onset in women only. (Table 6).

Table 6. Gender differences in age of psychosis onset by childhood abuse

	Physical abuse		No physical abuse			
Mean (sd)	Females (n=40)	Males (n=63)	Females (n=98)	Males (n=136)	p-value ANOVA	Bonferroni post-hoc
Age at onset	31.4 (9.7)	27.5 (8.0)	33.5 (10.8)	27.5 (8.8)	<0.001	F PA > M PA F no PA > M no PA F no PA > M PA
	Sexual abuse		No sexual abuse			
Mean (sd)	Females (n=31)	Males (n=22)	Females (n=106)	Males (n=168)	p-value ANOVA	Bonferroni post-hoc
Age at onset	30.9 (9.5)	29.7 (9.1)	33.0 (10.5)	27.2 (8.5)	<0.001	F no SA > M no SA

5.5.5 Needs for care

Female patients showed higher levels of total (mean=4.73 (SD= 2.89) vs mean=2.44 (SD=2.77)), met (mean=2.38 (SD=2.00) vs mean=2.27 (SD=1.92))

and unmet ((mean=2.35 (SD= 2.29) vs mean=2.01 (SD=2.08)) needs for care compared to males, though these differences were not statistically significant (Table 7). Abuse had little impact on needs for care other than unmet functioning and service, which showed higher levels in both men and women. (Table 8).

Table 7. Gender differences in needs for care (CAN)

Mean (SD)	Females (n=184)	Males (n=260)	<i>p</i> -values t-test
CAN total	4.73 (2.89) 21 missing	2.44 (2.77) 35 missing	0.10
• Health	1.78 (1.05) 25 missing	1.82 (1.12) 44 missing	0.70
• Basic	0.68 (0.83) 23 missing	0.66 (0.86) 41 missing	0.83
• Social	1.10 (1.08) 26 missing	0.98 (1.04) 44 missing	0.31
• Services	0.64 (0.65) 25 missing	0.47 (0.57) 43 missing	0.01*
• Functioning	0.55 (0.89) 29 missing	0.41 (0.75) 55 missing	0.12
CAN met	2.38 (2.00) 32 missing	2.27 (1.92) 57 missing	0.60
• Health	0.92 (0.91) 25 missing	0.93 (0.97) 44 missing	0.94
• Basic	0.40 (0.66) 23 missing	0.36 (0.62) 41 missing	0.53
• Social	0.37 (0.69) 26 missing	0.39 (0.67) 44 missing	0.76
• Services	0.31 (0.53) 25 missing	0.27 (0.46) 43 missing	0.43
• Functioning	0.39 (0.76) 29 missing	0.30 (0.63) 55 missing	0.25
CAN unmet	2.35 (2.29) 32 missing	2.01 (2.08) 57 missing	0.15
• Health	0.86 (1.01) 25 missing	0.90 (0.99) 44 missing	0.73
• Basic	0.28 (0.58) 23 missing	0.30 (0.58) 41 missing	0.72
• Social	0.73 (0.99) 26 missing	0.59 (0.93) 44 missing	0.18
• Services	0.33 (0.53) 25 missing	0.20 (0.44) 43 missing	0.01*
• Functioning	0.16 (0.43) 29 missing	0.11 (0.36) 55 missing	0.24

Table 8. Gender differences in needs of care by childhood abuse (CAN)

	Physical abuse		No physical abuse			
Mean (SD)	Females (n=40)	Males (n=63)	Females (n=98)	Males (n=136)	p-value ANOVA	Bonferroni post-hoc
CAN tot	5.21 (2.44)	4.59 (2.60)	4.53 (3.17)	4.27 (2.83)	0.35	-
CAN met	2.23 (1.73)	2.56 (1.83)	2.54 (2.09)	2.31 (2.00)	0.72	-
CAN unmet	2.77 (2.18)	1.96 (1.82)	2.00 (2.27)	2.00 (2.12)	0.24	-
CAN unmet services	0.35 (0.63)	0.17 (0.38)	0.27 (0.47)	0.18 (0.44)	0.14	-
CAN unmet functioning	0.26 (0.51)	0.18 (0.39)	0.07 (0.27)	0.07 (0.34)	0.02	F PA > M no PA
	Sexual abuse		No sexual abuse			
Mean (SD)	Females (n=31)	Males (n=22)	Females (n=106)	Males (n=168)	p-value ANOVA	Bonferroni post-hoc
CAN tot	5.37 (2.33)	4.14 (2.80)	4.64 (3.07)	4.38 (2.78)	0.30	-
CAN met	2.50 (2.05)	2.20 (2.19)	2.48 (2.01)	2.48 (1.94)	0.95	-
CAN unmet	2.86 (2.49)	2.00 (1.75)	2.11 (2.17)	1.89 (2.02)	0.17	-
CAN unmet services	0.47 (0.63)	0.33 (0.48)	0.23 (0.47)	0.16 (0.41)	0.005	F SA > M no SA
CAN unmet functioning	0.24 (0.51)	0.10 (0.30)	0.10 (0.31)	0.11 (0.37)	0.29	-

5.6 Discussion

We found that gender and childhood abuse impacted on some outcome measures of interest. We detected high rates of childhood physical and sexual abuse, with sexual abuse more frequently disclosed by women than men. Both types of abuse were associated with differences in psychopathology, with physical abuse associated with higher levels of negative symptoms in both men and women, and sexual abuse associated with higher levels of negative symptoms for both men and women (though men still had a higher level of negative symptoms). Physical abuse and sexual abuse were associated with a lower age of onset in women but not men and both types of abuse had little impact on increased needs for care in either men and women (though their needs for care around abuse were not measured), but female patients showed higher levels of total and unmet service needs than males. Overall these findings suggest that childhood abuse is associated with a more “male” (lower age of onset, higher negative symptoms) presentation of FEP in women.

Our findings for FEP patients are largely consistent with research in more chronic patients though with some notable differences. Our first hypothesis was only

partly confirmed as we did not find a stronger impact of childhood sexual abuse on positive symptoms for female patients compared to males unlike Misiak and colleagues (2016), who found that childhood sexual abuse predicted higher levels of auditory-verbal hallucinations in female patients. Nevertheless, in line with our hypothesis, we found that childhood sexual and physical abuse were associated with higher levels of negative symptoms in both males and females. The association between childhood sexual abuse and severity of negative symptoms in FEP patients has been previously noted (Burns *et al*, 2010), but gender effects have not been previously examined. In our sample, males and females with childhood abuse showed similar levels of negative symptoms thus the present study revealed that the tendency of male patients towards showing higher levels of negative symptoms compared to females at psychosis onset (Hui *et al*, 2014) disappears when the trauma variable is included in the analysis, as a result of the increase in negative symptoms reported by female patients with a history of both physical and sexual abuse during childhood.

Our findings have face validity as we report similar levels of childhood physical abuse as previous reports. A critical review of the literature on childhood abuse rates in people with psychosis (Morgan and Fisher, 2007) reported a prevalence of physical abuse at 35% for both sexes. However, our rates of childhood sexual abuse were lower than their reports of 42% for females and at 28% for males (compared with 22.6% for females vs 11.6% for males in this study). The reliability of self-reports in adulthood of childhood traumatic events has often been questioned (Schafer *et al*, 2012) because the shift from a concrete construct to a theoretical construct in reporting early experiences of abuse allows for the distortion that time, memory, emotions, denial, and other factors put on the events and their recall to remain part of the abstraction (Hulme, 2004). Nevertheless, Fisher *et al*. (2011) compared the similarity of abuse ratings obtained using different measures of childhood adversity (CECA-Q PBI scales and independent clinical case notes) found that reports of childhood abuse were similar when obtained by different assessment methods. It has also been noted that for research purposes the variable “childhood trauma” often requires a dichotomization

(present/absent) and this makes it difficult to understand the real extent of trauma presence in their samples (Vergano *et al*, 2015).

Age at psychosis onset was higher for females compared to males (33.4 *vs* 27.9), in line with other studies that indicate an average 1-5 years difference in age of psychosis onset between sexes (Eranti *et al*, 2013). Childhood physical and sexual abuse reduced the age of onset in female patients only. Moreover, gender difference in age of psychosis onset lost its significance as soon as trauma variables were included in the analysis. Our result confirms our first hypothesis and adds information to the work by Kocsis-Bogar (2018), run on a sample of chronic psychotic patients, who found that childhood physical abuse, but not sexual abuse, acted as a predictor of earlier age of psychosis onset for females only. As a possible explanation, we can speculate that gender-specific protective factors in women, but not in men, such as better premorbid adjustment (Addington *et al*, 2003), higher levels of insight (Parellada *et al*. 2011) and shorter duration of untreated psychosis (Cascio *et al*, 2012), may be outweighed by the consequences of childhood abuse.

Service needs were higher in females compared to males, both total and unmet, consistently with other findings reporting women with psychosis as having more services needs than men (Ochoa *et al*, 2012). Our second hypothesis on the impact of gender and childhood abuse on needs for care was then confirmed but, given that the present paper is the first one investigating this aspect in FEP patients, we cannot make proper comparison with other studies. However, gender differences in needs for care in FEP patients have been reported, with female patients showing more service (Ochoa *et al*, 2012) and functioning (Bertani *et al*, 2012) unmet needs than males, and childhood abuse does not seem to add a significant impact on them. However, this result should be considered in the light of some socio-cultural factors, as Latin families appear to be more likely to accept and cope with underperforming males (Bimbi, 2003) and to provide them greater support in everyday activities. The lack of a gender perspective in the Italian public mental health services may lead clinicians to be unaware of gender-specific

issues and to replicate those behavioral patterns of FEP patients' families, thus hyper-investing in the rehabilitation programs of males and underestimating the needs of females with psychotic disorders.

5.7 Strengths and limitations

Strengths of the present study include the large sample size, the community-based study design, high levels of retention, and no significant differences in demographic variables between completers and non-completers (Ruggeri *et al*, 2015). Although the GET-UP study was not intended to address gender differences, its design ensures a good representativeness of all patients in its area and overcomes the problem of gender differences in help-seeking behaviours (Walker & Levine, 1993). Community-based study designs are considered the gold standard for describing true gender differences (Riecher-Rossler *et al*, 2018). However, despite all the efforts made by the researchers to ensure the representativeness of the sample, we cannot rule out the possibility of selection bias, since most patients were recruited within the public sector and may be possible that patients receiving care from the private sector could have been missed. However, previous research has shown that only a negligible fraction of psychotic patients in Italy are treated in private hospitals or practice alone and that it is a standard practice for general practitioners to refer all psychosis cases to public mental health services (Amaddeo *et al*, 2001). In addition, a leakage study has been conducted to guarantee the completeness of the recruitment procedure and to identify any missed cases (Ruggeri *et al*, 2015). In addition to test our hypotheses the age limit set in the GET-UP study (18-54) is potentially problematic. Women display a second peak in the incidence of psychosis in the perimenopausal period (Jackson *et al*, 2013), and studies with the upper age limit at 60 years show the same cumulative rates of psychosis for both gender (Riecher-Rossler, 2009), in contrast with studies in which the upper age limit is lower that showed a higher incidence of psychosis in men compared to women (Riecher-Rossler *et al*, 2017). It is therefore possible that a proportion of late-onset psychotic women may have been missed by the GET-UP study. Another possible source of bias is misclassification, as psychosis at onset shows a significant

diagnostic instability (Cotton *et al*, 2009). All patients referred to the GET-UP study team have been administered, within 15 days from first contact with Mental Health Services, the Screening Schedule for Psychosis (SSP) (Jablensky *et al*, 1992) and, for those who met the inclusion criteria and accepted to participate in the study, diagnostic accuracy was confirmed at 9-month follow-up using the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) (Wing *et al*, 1990). Needs for care have been assessed using the standard version of the CAN, which is not gender-sensitive (Ramsay *et al*, 2001). We were not able to examine the number of mothers or pregnant women in our sample (pregnancy was not an exclusion criteria in the GET-UP study protocol), but it is known that over 60% of women with severe mental illnesses are mothers (Howard *et al*, 2001) and they have specific, complex needs, including needs around CSA and domestic violence and abuse, contraception and different domains of childcare that are not detected adequately by generic assessment tools (Howard & Hunt, 2008). Therefore, it is extremely likely that actual needs for care in female patients in our sample are higher and more diversified than those detected. Future studies could use a validated and more specific assessment tool such as the CAN-M which provides a more comprehensive picture of needs for care of women with severe mental illnesses who are pregnant or mothers (Howard & Hunt, 2008). NICE guidelines (2012) recommend discussing contraception and optimisation of physical and mental health in potential future pregnancies at all stages of care, thus an adequate assessment of needs for care in this area appears crucial. Other gendered needs include comorbid substance abuse (Riecher-Rossler *et al*, 2018) - men show high rates of cannabis (Crocker & Tibbo, 2017), alcohol, cocaine and hallucinogens (Ochoa *et al*, 2012) abuse compared to women. Unfortunately, we were not able to control for cannabis abuse, which has been found to decrease the age of psychosis onset in both sexes (Di Forti *et al*, 2014).

Finally, patients in the GET-UP trial have been assessed after clinical stabilization (defined as a condition allowing the patient to collaborate at least in a brief examination) and this may have different implications for males and females with FEP. Women with FEP, compared to men, show higher levels of insight into

illness (Karow *et al*, 2008), have greater risk of self-harm (Haro *et al*, 2008) and express more depressive symptoms (Carpenter *et al*, 2007) and for these reasons tend to seek effective treatment more often and earlier than men. Lastly, due to the lack of resources, the present study has not considered the impact of medication. Despite psychopharmacological guidelines for FEP patients recommend gender-targeted treatments (NICE, 2015) patients with psychosis tend to receive similar doses of antipsychotics (Thorup *et al*, 2014; Koster *et al*, 2008). Quantification of side-effects, which are different for males and females (Haack *et al*, 2009), was not stratified by gender in the GET-UP trial (Ruggeri *et al*, 2015) and a future development of the present study could involve an analysis of the dose of the antipsychotic drugs prescribed by gender.

5.8 Conclusions

The investigation of gender differences in people with psychosis is important because it is likely to increase the understanding of the etiological pathway leading to the development of psychosis. Personalization of treatment for people with psychosis is an important goal and taking gender into account is likely to make a big difference, as it is for other fields of medicine. Our results seem to suggest that childhood sexual abuse in female FEP patients may be linked to a form of psychosis whose presentation is characterized by earlier age of onset and higher levels negative symptoms, but additional research is needed to conform this. However, the impact of gender and childhood abuse on psychopathology, age of onset and needs for care appears to be small and further research, is needed to disentangle whether these small differences are due to the lack of gender-sensitive assessment tools or simply reflect a lack of gender difference in itself.

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Part 3: CONCLUSION

Chapter 6 – Take home message and conclusion

The three studies described in this Doctoral Thesis provide important insights to the current literature on gender differences in people with psychosis, with interesting implications for clinicians, researchers and health policy-makers.

The research study presented in Chapter 3 attempts to answer to the first research aim *explore gender differences in psychopathology, needs for care and insight in a large cohort of FEP patients over 5 years* using linear mixed models with gender, time, and gender-by-time interactions. We found that male patients with FEP tend to show higher levels of negative symptoms than females throughout the years. Conversely, female patients with FEP appear to show higher levels of depressive symptoms, unmet needs for care and insight throughout the years compared to males. Thus, it seems that some, but not all, gender differences observed at psychosis onset, tend to remain stable in the first years of illness. Most studies on the medium- and long-term outcome of psychotic patients did not take into account illness fluctuations over time and only provided cross sectional information on levels of psychopathology and functioning. However, the evolution of psychosis over time is not just a baseline-to-follow-up difference in symptoms' severity and a specific focus on symptoms' course can help clinicians providing individualized and patient-centered treatments. To our knowledge, this is the first study addressing the impact of gender on clinical and social course of FEP patients over the medium-run.

One of the most important differences between males and females with psychosis are the rates of childhood traumatic experiences, which are higher for females compared to males. The narrative review presented in Chapter 4 attempts to answer to the second research aim *provide a comprehensive summary of the findings on gender and childhood abuse in people with psychosis*. We found that some, but not all, gender differences in people with psychosis and childhood abuse appear to reflect general gender differences in psychosis. Gender and childhood abuse seem to impact on psychopathology, age of onset and social

support, whereas they seem to have little or no impact on neurocognition, suicidality and substance abuse.

The study presented in Chapter 5 of the present Thesis attempts to answer to the third research aim *assess the impact of gender and traumatic experiences (physical and sexual abuse) on psychopathology, age of psychosis onset and needs for care in a large cohort of FEP patients*. Our results seem to suggest that childhood sexual abuse in female FEP patients may be linked to a form of psychosis whose presentation is similar to that is considered the typical “male” presentation of psychosis (earlier age of onset, higher levels negative symptoms), but additional research is needed to conform this. However, the impact of gender and childhood abuse on psychopathology, age of onset and needs for care appears to be small and further research, is needed to disentangle whether these small differences are due to the lack of gender-sensitive assessment tools or simply reflect a lack of gender difference in itself.

The investigation of gender differences in people with psychosis is important because it is likely to increase the understanding of the etiological pathway leading to the development of psychosis. On the basis of the impact of childhood abuse in psychosis, we recommend clinicians to carefully investigate early experiences of abuse in their patients and to provide them adequate treatment according to gender. Personalization of treatment for people with psychosis is an important goal and taking gender into account is likely to make a big difference, as it is for other fields of medicine. Further research is needed on the implementation of gender-tailored mental health services and programs for young people with FEP and their cost-effectiveness should be explored.