



Gender differences in childhood trauma in first episode psychosis: Association with symptom severity over two years

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ABSTRACT

Early life adversity is associated with increased risk for psychosis onset and poor clinical outcome. Male compared to female patients often show a more severe course of psychotic illness. The aim of the present study was to investigate gender differences in childhood trauma (CT) and their impact on symptomatic and functional outcome following psychosis onset.

The study included 210 patients (144 men, 66 women) diagnosed with a first-episode of psychosis (FEP). Early adversity was assessed with the Childhood Trauma Questionnaire. Psychotic symptoms and general functioning were rated with the Brief Psychiatric Rating Scale and Global Assessment of Functioning scale at baseline, 12 and 24 months of follow-up in an established early intervention service.

Male patients reported higher rates of physical or emotional neglect, whereas female patients indicated significantly higher rates of emotional abuse. More severe CT was related to higher levels of depression in women and to negative symptoms in men. Distinct CT effects were observed on positive and negative symptom severity and global functioning in male patients at 24 months. Emotional abuse was the strongest predictor of depression in both genders. In male patients only, emotional abuse predicted positive symptom severity and impaired global functioning, whereas emotional neglect predicted more severe negative symptoms.

Our results suggest differences in CT experiences in male and female FEP patients, with a more pronounced impact on longer-term outcome in male patients. The findings support the notion that sex differences in stress vulnerability account for the relatively poor illness course in male psychosis patients.

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1. Introduction

Women and men differ in their risk to develop psychosis across the life-course and in a wide variety of outcome measures of the illness (Baldwin and Srivastava, 2015). Gender and sex differences in schizophrenia and first-episode psychosis (FEP) can be found in many domains and might explain part of the heterogeneity of psychosis. Compared to women, men have a higher incidence rate for psychosis, an earlier age at onset, lower rates of remission, higher relapse rates and lower life expectancy. They show more pronounced deficits in premorbid and social functioning, and more frequently abuse substances. Whereas women experience more symptoms of depression, male patients suffer more frequently from negative psychotic symptoms which in turn greatly affect functioning (for reviews see (Hjorthoj et al., 2017; Ochoa et al., 2012; Thorup et al., 2014)).

There is increasing evidence from large population-based and prospective studies supporting the notion of a causal relationship between the experience of childhood trauma and psychosis risk (Fisher et al., 2013; Misiak et al., 2017). Childhood trauma is associated with more severe clinical symptoms of psychosis (Garcia et al., 2016) as well as consistently higher severity of psychotic experiences and symptoms over time (Trotta et al., 2015). We recently observed that the impact of childhood trauma extends to more limited remission of positive and negative symptoms following the initial onset of psychosis (Pruessner et al., in preparation), which may then have important consequences for longer-term functional outcome and quality of life (Brissos et al., 2011; Cassidy et al., 2010; Emsley et al., 2007; Haro et al., 2014; Haynes et al., 2012; Heering et al., 2015).

Few studies have investigated gender and sex differences in the prevalence of childhood trauma and its consequences on illness parameters in psychosis. A recent study in psychosis found that significantly more female than male patients had experienced childhood trauma or adversity (Sweeney et al., 2015), although another recent study could not confirm this (Garcia et al., 2016). There is consensus, however,

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that women are generally more likely than men to have experienced childhood sexual abuse (Tolin and Foa, 2006). In patients with psychosis, there is some indication that particularly the prevalence of sexual (Fisher et al., 2009; Morgan and Fisher, 2007; Read et al., 2005) and likely physical abuse as well (Fisher et al., 2009; Kelly et al., 2016) are higher in female compared to male patients.

In addition to the different experiences of CT in male and female psychosis patients, these furthermore appear to be differentially expressed in non-psychotic and psychotic health outcomes in male and female patients. For example, male patients with psychotic disorder and with a history of childhood trauma were more likely to have experienced a lifetime history of physical symptoms like cardiovascular problems and pain, whereas female patients with childhood trauma experiences were more prone to show elevated or depressed mood (Sweeney et al., 2015). Another study reported significant correlations of childhood trauma scores with positive and negative psychotic symptoms, depression and poor functioning in female but not in male patients with psychotic disorder (Garcia et al., 2016). In this study, physical and emotional neglect were more clearly associated with the psychopathological profile than childhood abuse (Garcia et al., 2016). In contrast, another study found that physical abuse was associated with psychotic symptoms in female patients only (Kelly et al., 2016).

Previous research has clearly established that male compared to female patients have more adverse outcomes in psychosis. Early life adversity has been shown to be a major risk factor of psychosis and also appears to have consequences for clinical and functional outcome over time. However, few studies have examined the differential effects of childhood trauma on clinical outcomes in male and female patients. Thus, the aim of the present study was to investigate gender differences in childhood trauma and whether the experience of trauma is differentially associated with symptomatic and functional outcome in male and female patients at psychosis onset and 12 and 24 months thereafter. Based on the previous literature, we hypothesized higher rates of abuse in female patients compared to male patients. We furthermore hypothesized that a history of childhood trauma would potentiate gender specific symptoms, i.e. have a differential effect on the presentation of symptoms, with negative symptoms being more severe in male patients and depressive symptoms being more prominent in female patients. Based on recent observations that childhood trauma affects symptomatic severity and functioning over time, we further expected that these associations would be more pronounced at the 24- rather than 12-month follow-up points.

2. Materials and methods

2.1. Study participants

The study included 210 patients (144 men and 66 women, mean age 23.73 ± 4.53 years) diagnosed with a first episode of psychosis. Patients were recruited from the Prevention and Early Intervention Program for Psychosis (PEPP) in Montreal, Canada (Iyer et al., 2015). PEPP is a naturalistic early intervention service for patients experiencing a first episode of psychosis (FEP) based on DSM-IV-TR criteria for affective or non-affective psychosis. Patients must be between 14 and 35 years of age and have an IQ > 70. Patients were not accepted to the program if they had been treated with antipsychotic medication for more than one month prior to admission, suffer from organic brain damage, or their psychotic symptoms were solely drug-induced. All patients signed a consent form approving the use of their data for research purposes, approved by the Research Ethics Board of the Douglas Mental Health University Institute. For minors, additional written informed consent was obtained from a parent or legal guardian.

2.2. Diagnostic and demographic variables

Patients' diagnoses were established with the Structured Clinical Interview for DSM disorders (SCID IV) and were classified into affective

and non-affective psychosis based on the DSM-IV criteria (First et al., 2002). Duration of untreated illness (DUI) and duration of untreated psychosis (DUP) in weeks were determined through the Circumstances of Onset and Relapse Schedule (CORS) (Norman et al., 2004), which is derived from the Interview for Retrospective Assessment of Schizophrenia (IRAOS) (Hafner et al., 1992). Male and female patients in the trauma and non-trauma groups were furthermore described using binary variables for education (high school degree achieved – yes/no), relationship status (in partnership – yes/no) and ethnicity (Caucasian – yes/no). Socioeconomic status of the patient, mother and father (middle class or higher – yes/no) was determined with the Four-Factor Index of Social Status (Hollingshead, 1975). Substance abuse and dependence (yes/no) at baseline were determined with the Drug Use Scale (DUS) (Drake et al., 1996).

2.3. Assessment of childhood trauma

Early life adversity was assessed with the Childhood Trauma Questionnaire (CTQ) (Bernstein and Fink, 1998; Bernstein et al., 2003), a 25-item self-report retrospective measure of abuse and neglect experiences during childhood. Individual items are rated on a five-point Likert scale, and scores of five items each are summed (some items require recoding) to constitute five clinical subscales (physical neglect, emotional neglect, physical abuse, emotional abuse, and sexual abuse). Total scores for abuse and neglect were calculated by adding up the scores for the respective subscales. The sum of all five subscales was used as total trauma rating. Scores for each of the five subscales were categorized into none (or minimal), low (to moderate), moderate (to severe), and severe (to extreme) levels of maltreatment, using cut-off scores based on validation studies in healthy and clinical populations (Bernstein and Fink, 1998). For group comparisons, CTQ total and subscales category scores were further categorized into binary variables indicating low or less trauma as no childhood trauma (N-CT) and moderate to severe trauma levels as childhood trauma (CT).

2.4. Assessment of symptomatic and functional outcome

The severity of psychotic symptoms was assessed with the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) at the time of intake into the FEP program (baseline), and at 12 and 24 months of follow-up. Baseline assessment scores represent the severity of symptoms leading up to the initial episode, follow-up ratings represent symptom severity in the past month. BPRS ratings were obtained on a 7 point-rating scale and allow the determination of separate ratings for positive, negative, depression and mania symptoms based on results from a factor analysis (Kopelowicz et al., 2008). Overall functioning was assessed on a continuum from 0 to 100 with the Global Assessment of Functioning (GAF) scale (American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Washington, DC 1994 (pp. 25–35)). The GAF considers both the severity of mental illness and its effect on psychological, social and occupational functioning. All symptom ratings were conducted by trained research staff.

2.5. Statistical analyses

Childhood trauma scores were positively skewed and thus were log-transformed. *t*-Tests and chi-square tests were conducted to determine gender differences in demographic and clinical variables at baseline and in childhood trauma ratings. Spearman rank correlations were performed separately for male and female patients to assess associations between the total trauma score and clinical symptoms and functioning at baseline, 12 and 24 months of follow-up. Subsequent multiple linear regression analyses with the CTQ subscales as independent factors entered stepwise were conducted to determine which specific trauma experience(s) best predicted symptomatic and functional outcomes. Repeated measures ANOVAs were conducted to determine childhood

Table 1
Sociodemographic and clinical variables in male and female patients.

	N all (m/w)	Total	Men	Women	Statistic	p-Value
Demographic information						
Gender, N (%)			146 (68.87)	66 (31.13)		
Age, mean (SD)	210 (144/66)	23.73 (4.526)	23.72 (4.42)	23.75 (4.79)	$t = -0.056$.955
SES patient, <slower middle class, N (%)	163 (109/54)	104 (63.4)	74 (57.3)	30 (55.6)	$\chi^2 = 2.379$.123
SES mother, <slower middle class, N (%)	97 (69/28)	32 (33.0)	23 (33.3)	9 (32.1)	$\chi^2 = 0.013$.910
SES father, <slower middle class, N (%)	95 (65/30)	29 (30.5)	20 (30.8)	9 (30)	$\chi^2 = 0.006$.940
Education, >high school, N (%)	205 (141/64)	141 (68.9)	94 (67.4)	47 (72.3)	$\chi^2 = 0.551$.458
Relationship status, single, N (%)	210 (145/66)	190 (90.5)	132 (91.7)	58 (87.9)	$\chi^2 = 0.754$.385
Ethnicity, Caucasian, N (%)	203 (139/64)	124 (61.1)	85 (61.2)	39 (60.9)	$\chi^2 = 0.001$.977
Substance abuse and dependence, N (%)	208 (142/66)	111 (53.4)	90 (63.4)	21 (31.8)	$\chi^2 = 18.04$.000
Clinical characteristics at baseline						
Non-affective/affective psychosis, N (%)	206 (141/65)	147/59 (71.4/28.6)	99/42 (70.2/29.8)	48/17 (73.8/26.2)	$\chi^2 = 0.287$.592
DUP, in weeks, median (SD) ^a	179 (127/52)	18.57 (115.0)	19.57 (129.9)	15.57 (62.5)	$t = 0.765$.446
DUI, in weeks, median (SD) ^a	184 (129/55)	255.3 (268.6)	242.6 (259.2)	282.0 (289.2)	$t = -1.546$.124
BPRS – total, mean (SD)	194 (131/63)	65.31 (13.88)	66.23 (13.9)	63.41 (13.8)	$t = 1.327$.187
BPRS – positive symptoms, mean (SD)	202 (138/64)	25.67 (6.35)	26.11 (6.66)	24.70 (6.06)	$t = 1.457$.142
BPRS – negative symptoms, mean (SD)	202 (138/64)	6.648 (3.34)	6.841 (3.34)	6.234 (3.32)	$t = 1.205$.280
BPRS – mania symptoms, mean (SD)	202 (138/64)	15.55 (5.29)	13.16 (5.55)	11.25 (4.43)	$t = 2.417$.017
BPRS – depression, mean (SD)	202 (138/64)	11.98 (4.66)	11.46 (4.51)	13.11 (4.83)	$t = -2.370$.019
GAF, mean (SD)	209 (143/66)	30.06 (8.88)	29.43 (8.71)	31.44 (9.16)	$t = -1.528$.128

SES – Socioeconomic status; DUP – Duration of untreated psychosis; DUI – Duration of untreated illness; BPRS – Brief Psychiatric Rating Scale; GAF – Global Assessment of Functioning.

^a Statistics based on log transformed data.

trauma effects on the course of psychotic symptoms (positive, negative, depressive) and global functioning over time (baseline, 12 and 24 months) separately for male and female patients. Clinical or sociodemographic variables at baseline that were found to be significantly different between males and females were included as covariates in subsequent analyses.

3. Results

3.1. Gender differences in demographic and clinical variables at baseline

Table 1 shows differences in sociodemographic and baseline clinical variables between male and female patients. Male compared to female patients had significantly higher rates of substance abuse and dependence ($\chi^2 = 18.04$; $p < .001$) and showed more severe mania symptoms ($t = 2.42$; $p = .017$). In contrast, female patients showed more severe symptoms of depression than male patients ($t = -2.37$; $p = .019$). Substance abuse and dependence as well as depression and mania at baseline were included as covariates in subsequent analyses where appropriate. Demographic differences between patients with and without trauma will be presented in a separate paper (Pruessner et al., manuscript in preparation).

3.2. Gender differences in childhood trauma experiences

A total of 114 patients (54.3%) had experienced any form of moderate to severe childhood trauma. Table 2 provides details on gender differences in all trauma subscales and totals. The adjusted alpha level for these analyses after Bonferroni correction was 0.006 (0.05/8).

Table 2
Childhood trauma experiences in male and female first-episode psychosis patients.

Childhood trauma experience	Total (N = 210)	Men (N = 144)	Women (N = 66)	Statistic	p-Value
Physical neglect, N (%)	53 (25.2)	44 (30.6)	9 (13.6)	$\chi^2 = 6.866$.009
Physical abuse, N (%)	46 (21.9)	34 (23.6)	12 (18.2)	$\chi^2 = 0.780$.377
Emotional neglect, N (%)	54 (25.7)	43 (29.9)	11 (16.7)	$\chi^2 = 4.125$.042
Emotional abuse, N (%)	51 (24.3)	27 (18.8)	24 (36.4)	$\chi^2 = 7.636$.006
Sexual abuse, N (%)	40 (19.0)	24 (16.7)	16 (24.2)	$\chi^2 = 1.684$.194
Abuse total, N (%)	87 (41.4)	58 (40.3)	29 (43.9)	$\chi^2 = 0.250$.617
Neglect total, N (%)	76 (36.2)	63 (43.8)	13 (19.7)	$\chi^2 = 10.34$.001
Trauma total, N (%)	114 (54.3)	84 (58.3)	30 (45.5)	$\chi^2 = 3.025$.082

Significantly more male than female patients reported moderate to severe neglect experiences ($\chi^2 = 10.34$; $p < .001$), whereas women were significantly more likely to report moderate to severe emotional abuse compared to men ($\chi^2 = 7.64$; $p = .006$). Physical and sexual abuse were not different between men and women (all $p > .19$). Fig. 1 illustrates the gender differences in CT.

3.3. Gender differences in BPRS symptoms at follow-up

Symptom data were available for 202 patients (138 men, 64 women) at baseline, 173 patients (119 men, 54 women) at 12 months and for 134 patients (95 men, 39 women) at 24 months of follow-up. At 12 months, we observed more severe negative and manic symptoms in male compared to female patients at trend level ($t(171) = 1.65$, $p = .10$ and $t(145.5) = 1.90$, $p = .059$; respectively), but no other gender differences were observed in other symptom categories or in global functioning (all $p > .34$). At 24 months of follow-up, male patients had significantly higher levels of positive ($t(93.9) = 2.07$; $p = .041$), negative ($t(106.1) = 2.32$; $p = .022$) and manic symptoms ($t(93.9) = 2.05$; $p = .043$) and reduced global functioning ($t(87.5) = 2.43$; $p = .017$) compared to female patients. However, these results did not survive Bonferroni corrections ($0.5/8 = 0.006$).

3.4. Associations of childhood trauma with clinical outcome

Table 3 shows the association between severity of total childhood trauma and clinical outcome at all three time points. Both, the higher total symptom severity and the poor global functioning observed in men at 24 months of follow-up were significantly associated with

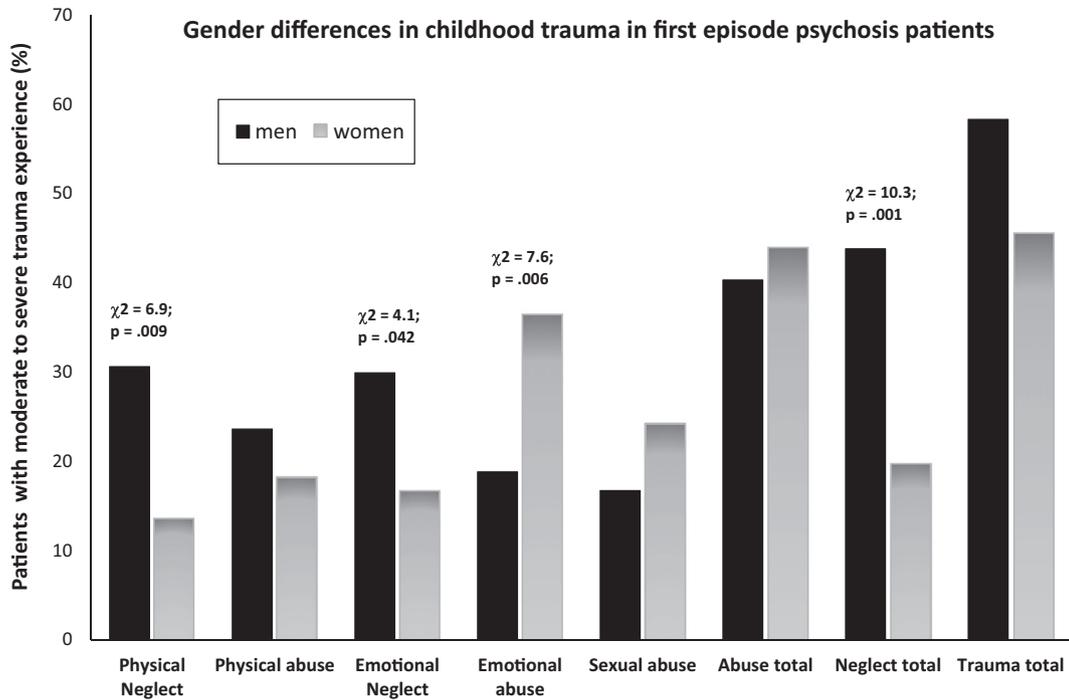


Fig. 1. Gender differences in childhood trauma in first episode psychosis patients.

higher total scores of CT ($\rho = 0.33$; $p < .001$ and $\rho = -0.29$; $p = .004$; respectively). These associations survived Bonferroni correction for multiple comparisons (adjusted $\alpha = 0.05/12 = 0.004$). Follow-up analyses showed that most clinical outcome measures at 24 months in males were affected by CT, including positive ($\rho = 0.32$; $p = .024$), negative ($\rho = 0.25$; $p = .015$) and depressive symptom severity ($\rho = 0.25$; $p = .014$). In contrast, associations between CT and outcome measures at the other time points were more selective. At baseline, the severity of total CT was correlated with negative symptoms in men ($\rho = 0.18$; $p = .034$) and with depressive symptoms in women ($\rho = 0.28$; $p = .024$). At 12 months of follow-up, childhood trauma was related to depressive symptom severity in both male ($\rho = 0.19$, $p = .036$) and female ($\rho = 0.37$, $p = .006$) patients.

Subsequent multiple linear regression analyses in men and in women employing all five CTQ variables as independent factors, which were allowed to enter in a stepwise fashion, and all four BPRS domains as separate dependent variables were conducted. In male patients, emotional abuse was the only significant predictor for positive symptoms ($\beta = 0.29$; $R^2 = 0.09$; $F(1,93) = 8.99$; $p = .003$),

depression ($\beta = 0.25$; $R^2 = 0.062$; $F(1,93) = 6.15$; $p = .015$) and global functioning ($\beta = -0.33$; $R^2 = 0.11$; $F(1,93) = 10.98$; $p = .001$) at 24 months of follow-up whereas emotional neglect predicted negative symptoms ($\beta = 0.28$; $R^2 = 0.078$; $F(1,93) = 7.89$; $p = .006$). In women, depression at 12 months of follow-up was predicted by emotional abuse ($\beta = 0.56$; $p < .001$), sexual abuse ($\beta = -0.44$; $p = .002$) and physical abuse ($\beta = 0.308$; $p = .014$). The overall model fit for women was $R^2 = 0.36$; $F(3,50) = 9.32$; $p < .001$.

3.5. Effects of trauma on the course of symptomatic outcome over 24 months

Complete data on symptom severity and functioning over all three assessment points were available for 120 patients (85 men, 35 women). Of those, 47 men (55.3%) and 15 women (42.9%) reported a history of childhood trauma. All symptoms and functioning scores significantly improved over time in both men and women (all $p < .001$), but improvement rates were not significantly different between men and women. Measures of substance abuse and dependence, depression

Table 3

Spearman correlations between total childhood trauma and symptomatic and functional outcome at baseline and 12 and 24 months of follow-up.

		CTQ total					
		Baseline		12 months		24 months	
		Male (N = 138)	Female (N = 64)	Male (N = 119)	Female (N = 54)	Male (N = 95)	Female (N = 39)
Positive symptoms	rho	-0.124	0.082	0.049	0.097	0.232	0.016
	p-Value	.148	.519	.595	.487	.024	.921
Negative symptoms	rho	0.180	-0.215	0.104	0.024	0.249	0.089
	p-Value	.034	.088	.262	.864	.015	.591
Manic symptoms	rho	0.002	0.061	0.174	0.319	0.182	0.063
	p-Value	.986	.633	.059	.019	.078	.703
Depressive symptoms	rho	0.139	0.283	0.192	0.371	0.251	0.289
	p-Value	.104	.024	.037	.006	.014	.075
BPRS total	rho	-0.049	0.040	0.161	0.273	0.330	0.120
	p-Value	.577	.756	.084	.051	.001	.472
GAF	rho	0.068	0.038	-0.088	-0.077	-0.290	0.084
	p-Value	.419	.763	.344	.583	.004	.616

and mania at baseline had been included as covariates in these analyses. Fig. 2 shows trauma effects on symptom severity and functioning separately for men and women. Considering all three assessment times, a history of CT was associated with more severe positive symptoms in both men and women ($F = 4.89, p = .030$ and $F = 5.91, p = .021$; respectively). However, the effect of trauma on negative symptoms was only significant in male patients ($F = 6.08; p = .016$), whereas the

effect on depression was only significant in women ($F = 6.82, p = .013$). With respect to global functioning, we observed a trauma by time effect in male ($F = 3.45; p = .034$) but not female patients ($p > .80$) (Fig. 3). When 'substance abuse and dependence' was included as a covariate in these analyses, the results were still mostly significant (positive symptoms: $F = 3.70, p = .058$ in men and $F = 5.80, p = .022$ in women; negative symptoms in men: $F = 5.12; p = .026$;

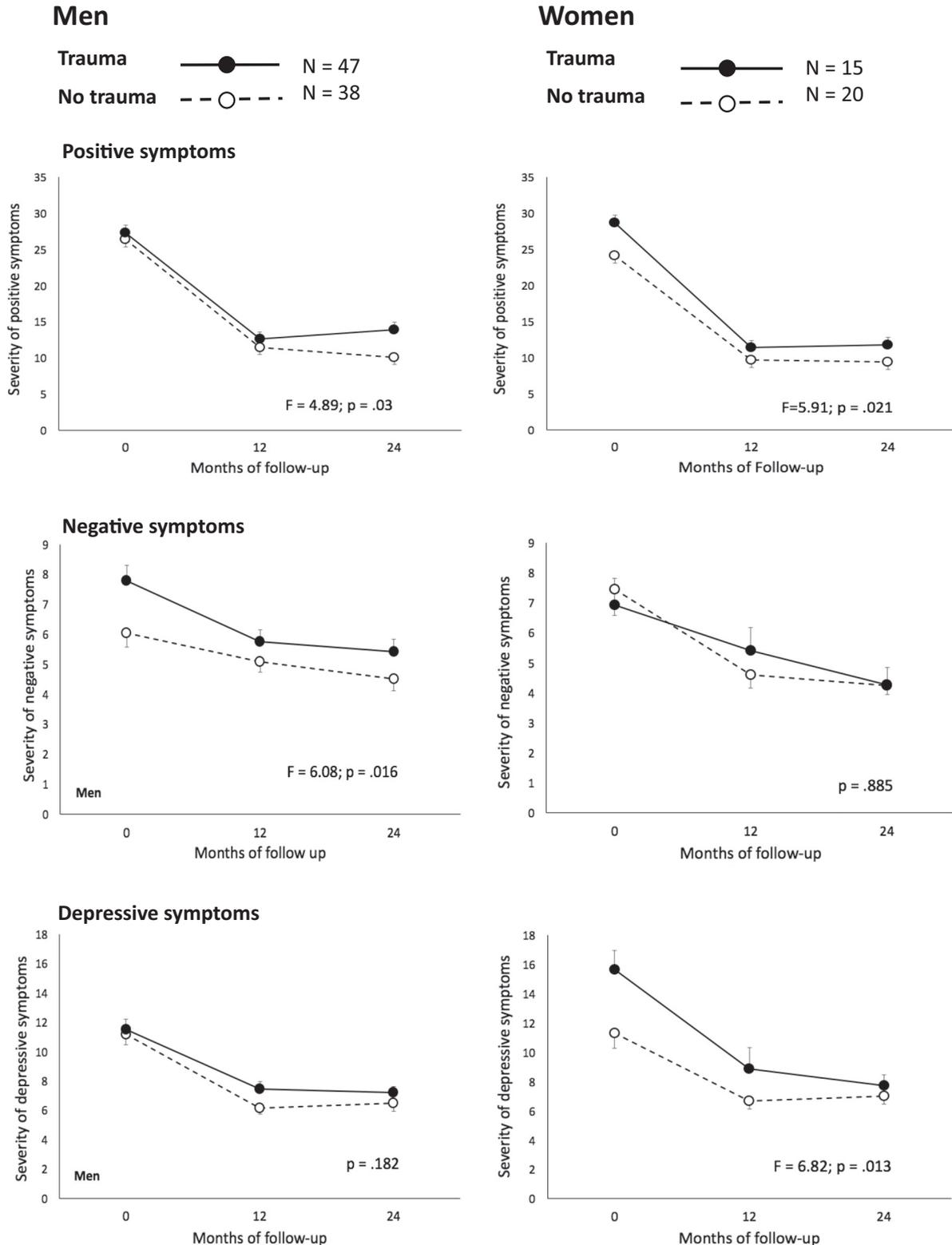


Fig. 2. Intra-individual course of symptoms over 24 months of follow-up in male and female patients.

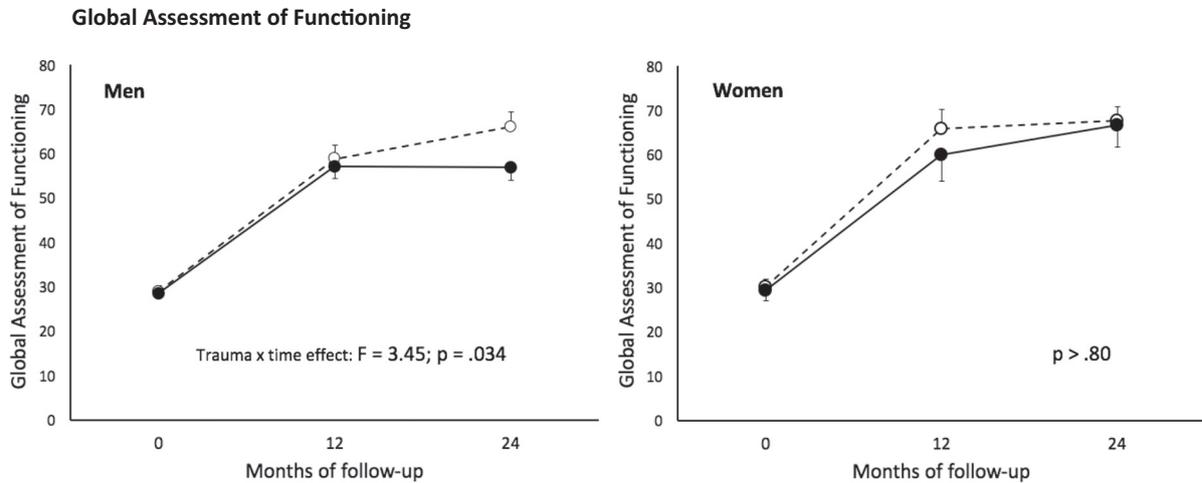


Fig. 3. Intra-individual course of global functioning over 24 months of follow-up in male and female patients.

depression in women: $F = 6.57$; $p = .015$; global functioning in men: $F = 3.01$; $p = .052$). However, the ANOVA analyses did not survive correction for multiple comparisons ($p = .05/8 = .006$).

4. Discussion

The present study observed gender differences in self-reported childhood trauma in first episode psychosis patients and demonstrated a differential impact of stressful early life experiences in men and women on symptom severity over the first two years of FEP clinical follow-up.

Male patients reported higher rates of physical or emotional neglect compared to female patients, whereas women showed significantly higher rates of emotional abuse than men. At first glance, these findings appear to contradict previous research showing higher rates of sexual and physical abuse in female patients (Fisher et al., 2009). However, the study design is not directly comparable with the present study. Whereas Fisher et al. looked at childhood trauma in male and female patients compared with same sex control subjects, the present study compared male and female patients directly. Thus, it is still possible that a larger proportion of female patients compared to female controls have experienced childhood sexual abuse.

Not finding gender differences in sexual and physical abuse could also be related to the different rates of childhood trauma in our study compared to previous studies. The rate of sexual abuse in the current study was 24.2% in women and 16.7% in men, which is clearly lower than the weighted average for the prevalence of sexual abuse reported in the review by Morgan and Fisher in 2007 (Morgan and Fisher, 2007), which was 42% in females and 28% in male patients. In line with this discrepancy, the total trauma rate in the present study is 54.3%, whereas the rate in other studies ranged from 91% (Stumbo et al., 2015) over 75% (Duhig et al., 2015), to 73% (Schalinski et al., 2015), and 71% (Trotta et al., 2016). It is likely that these inconsistencies with previous studies are a consequence of methodological differences and that previous studies have included mild forms of childhood trauma in their ratings, whereas in the current study, only moderate to severe ratings warranted a rating of childhood trauma.

The findings confirmed previous reports of higher rates of depression in women with psychotic disorder during the acute illness phase (Ochoa et al., 2012; Thorup et al., 2014). However, we did not observe a gender difference in negative symptoms at baseline, which might be related to the generally erratic illness presentation during the acute phase of psychosis. The most pronounced gender differences in clinical outcome were observed after two years of follow-up, when symptom severity and functioning have generally improved. Here, male compared to female patients showed more severe positive, negative and

manic symptoms as well as reduced global functioning. The relatively higher symptomatic burden and functional consequences in males at two years of follow-up may be indicative of reduced recovery rates and represent an early indicator of the relatively poorer long-term prognosis in male compared to female patients (Hjorthoj et al., 2017).

Looking at the course of clinical symptoms over 24 months, all clinical measures improved over time, suggesting that all patients benefited from the specialized early intervention program they were receiving services from (Iyer et al., 2015). However, the course of symptoms appeared to be modulated by the experience of childhood trauma and gender. While a history of childhood trauma was generally associated with more severe positive symptoms in both genders, it was specifically related with more severe negative symptoms in male patients and with more depressive symptoms in female patients, suggesting that CT amplifies the well-known sex specific expression of symptoms (Ochoa et al., 2012; Thorup et al., 2014). With respect to general functioning, the significant time by trauma effect in male patients suggests that functioning does not further improve in male trauma victims between 12 and 24 months of follow-up. Indeed, childhood trauma was particularly associated with more severe psychotic symptoms in male patients at 24 months of follow-up. However, since these results did not survive corrections for multiple comparisons, they should not be over-interpreted.

Results of the regression analyses demonstrate the power of emotional abuse and neglect to predict symptom severity. It was emotional abuse which had the strongest predictive value for depression, positive symptoms and global functioning, and it was emotional neglect, which best predicted negative symptoms in male patients at two years of follow-up. Interestingly, many studies of childhood maltreatment fail to include assessments of emotional abuse and neglect (Kelly et al., 2016; Morgan and Fisher, 2007). In fact, those studies that did look at emotional maltreatment often found it to be highly predictive of functioning in psychotic patients. For example, our results here echo previous findings in healthy controls, demonstrating that emotional abuse was associated with higher levels of subclinical psychopathology (Samplin et al., 2013). In two studies by our own group we found that emotional abuse had the strongest association with dissociative symptom severity in schizophrenia patients (Braehler et al., 2013; Holowka et al., 2003). In another study, emotional neglect and abuse were the trauma experiences that were most clearly associated with more severe symptoms in female patients with psychotic disorder (Garcia et al., 2016). Thus, the current study adds to the body of literature supporting the importance of emotional maltreatment during the childhood of schizophrenia patients.

The particular impact of childhood trauma on longer-term symptom severity and functioning in male patients possibly reflects higher stress vulnerability in men. Such increased vulnerability could be related to

sex differences in neurodevelopmental processes (Abel et al., 2010), poor premorbid adjustment (Norman et al., 2005), deficits in cognitive and social functioning (Vaskinn et al., 2011), reduced emotional expressiveness (Kring and Gordon, 1998), and higher rates of substance abuse in men (Drake and Wallach, 1989). These early deficits in male patients might raise the risk of neglect by caregivers, resulting in high trauma scores. They could furthermore be precursors of negative symptoms in men and likely potentiate over time due to complex interactions with the poor clinical presentation of male patients.

Indications for higher stress vulnerability in men also stem from research related to the neural diathesis-stress model of schizophrenia (Pruessner et al., 2017), evident in attenuated Hypothalamus-Pituitary-Adrenal (HPA) Axis reactivity (Pruessner et al., 2008; Pruessner et al., 2013) and reduced hippocampal volume (Adriano et al., 2012; Pruessner et al., 2015) in male compared to female patients with psychotic disorders. In this context, it has been proposed that higher levels of estrogen constitute a protective effect in women that modulate the hormonal response to stress (Handa and Weiser, 2014) and thus could explain the relatively poor illness course in men (Hafner, 2003).

Childhood adversity has been associated with reduced hippocampal volume (Teicher et al., 2012), but studies on sex differences in this relationship have been inconclusive (Teicher et al., 2003). Similarly, early life adversity in the form of poor parenting experiences has been associated with a blunted HPA axis response in FEP patients, but further research is needed to confirm sex differences in this relationship (Pruessner et al., 2013). Interestingly, emotional abuse again appears to be at the core of the associations with neurobiological stress markers, being associated with reduced hippocampal volume in male healthy adults (Samplin et al., 2013) and predicting lower morning cortisol in chronic schizophrenia patients (Braehler et al., 2005).

Another well-known risk factor for poor clinical and functional outcome is a long duration of untreated psychosis (DUP) (Alvarez et al., 2011; Cechnicki et al., 2014; Ito et al., 2015; Malla et al., 2002). Indeed, previous research has shown that a longer DUP is related to childhood trauma (Haahr et al., 2016; Haug et al., 2017). However, since the present study and others (Cascio et al., 2012) did not find evidence for sex differences in DUP, it is unlikely that DUP plays a role in the observed sex differences in symptomatic and functional outcome.

Limitations of the study include a missing control group and the relatively small number of female compared to male patients. The latter might account for a lower statistical power to detect female specific effects, especially at 24 months of follow-up and for longitudinal analyses. Some of our results, especially those including longitudinal analyses, did not survive Bonferroni corrections for multiple comparisons, so that our conclusions are not fully supported by the presented statistics. However, we believe that our findings nonetheless represent valuable hypotheses for future research in this area. Another point that is frequently criticized is the retrospective nature of the CTQ assessment. However, a recent study could not substantiate concerns of any bias due to current psychopathology (Fisher et al., 2011).

Our findings have implications for the development of psychosocial interventions to address the childhood trauma experience in psychosis patients. Indeed, it is possible that the lack of a specific diagnostic and therapeutic approach targeting trauma experiences in our program has contributed to the observed relationship between childhood adversity and symptomatic and functional outcome. Such an approach ideally includes a routine assessment of early life adversity, particularly emotional abuse and neglect, which should then be addressed in the context of psychosocial interventions with the goal to strengthen personal resources and protective factors to offset and better cope with the experience. Many potent psychosocial interventions such as cognitive behavioral therapy, family therapy and peer support are integrated in early intervention programs for psychosis, such as PEPP (Iyer et al., 2015) and could be adjusted accordingly. Given the particular impact of childhood adversity on longer-term outcome particularly in male patients, better engagement of this vulnerable group is needed, and

prolonged early intervention services should be offered to improve long-term functional outcome and quality of life (Malla et al., 2017).

In summary, our findings suggest that male and female psychosis patients have different early life adversity experiences and that these experiences express themselves in different illness trajectories. Childhood trauma effects on symptomatic and functional outcome of psychosis were most apparent in male patients at two years of follow-up, which is possibly a consequence of accumulating and mutually reinforcing sex and gender specific psychological and neurobiological factors over time. Our findings furthermore suggest that specifically emotional abuse and neglect experiences account for the relatively poor prognosis in male patients. Additional research is needed to confirm the gender specific effects of CT history on the course of psychotic illness beyond two years. Therapeutic efforts should be directed towards addressing adverse childhood experiences during the early phases of the illness, aiming to decrease their long-term impact on the illness course.

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The funding sources had no role in study design, in the collection, analysis and interpretation of data, in the writing of the report, and in the decision to submit the paper for publication.

Contributors

Marita Pruessner contributed to study design, data collection, analysis, interpretation and writing of the manuscript. Suzanne King contributed to recruitment of patients for childhood trauma assessment, the interpretation of results and to the writing of the manuscript. Nadia Vracotas and Shereza Abadi contributed to data collection for childhood trauma and clinical symptoms. Ashok Malla contributed to subject recruitment. Srividya Iyer, Jai Shah and Ridha Joobar contributed to interpretation of data and writing of the manuscript. All authors have read and approved the final version of the manuscript.

Conflict of interest

None of the authors have any conflicts of interest to declare.

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