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ORIGINAL RESEARCH

Impact of Childhood Trauma and Adult Separation Anxiety Disorder on Quality of Life in Individuals with Schizophrenia

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Background: Childhood trauma and anxiety disorders are common in individuals with schizophrenia. This study aimed to investigate the effects of childhood trauma and adult separation anxiety disorder on the quality of life of individuals with schizophrenia.

Methods: This cross-sectional study included 111 individuals with schizophrenia and 85 control subjects. The separation anxiety symptom inventory (SASI), adult separation anxiety questionnaire (ASAQ), Positive and Negative Syndrome Scale (PANSS), childhood trauma questionnaire (CTQ), and World Health Organization quality of life questionnaire (WHOQoL-BREF) were administered to the participants.

Results: More individuals with schizophrenia than control subjects were unemployed and single ($p<0.05$). Individuals with schizophrenia scored significantly higher on the SASI, ASAQ, and CTQ ($p<0.05$), whereas the control subjects scored significantly higher on the WHOQoL-BREF ($p<0.05$). ASAQ scores had mild positive correlations with total PANSS and PANSS subscale scores, and moderate positive correlations with total CTQ, CTQ emotional subscale scores, and CTQ physical abuse subscale scores. A negative moderate correlation was found between ASAQ and total WHOQoL-BREF scores. Mediation analysis revealed that CTQ scores significantly affected total WHOQoL-BREF and ASAQ scores. The model pathway for ASAQ scores showed a significant direct and indirect effect of CTQ on the total WHOQoL-BREF scores.

Conclusion: Childhood trauma predicts adult separation anxiety disorder, which partially mediates the impact of childhood trauma on quality of life in individuals with schizophrenia. Therapeutic interventions for adult separation anxiety disorder in individuals with schizophrenia and a history of childhood trauma may help increase their quality of life.

Keywords: schizophrenia, adult separation anxiety disorder, childhood trauma, quality of life

Introduction

Schizophrenia, a well-known psychotic disorder with a prevalence of 0.45% among adults, affects approximately 24 million people worldwide.[1] Childhood trauma, caused by exposure to stressful events before adulthood, is an established risk factor for schizophrenia.[2] Experiencing early trauma, in particular, reveals the symptoms of mood and anxiety disorder in schizophrenia.[3] Approximately 65% of individuals with schizophrenia exhibit anxiety symptoms, and approximately 38% of these individuals fulfill any anxiety disorder criteria. The most common types of anxiety disorders in individuals with schizophrenia are social anxiety disorder, generalized anxiety disorder, and panic disorder.[4]

Models explaining the relationship between psychosis and childhood trauma include dysregulation of affect, dissociation, dysfunctional cognitive schemas, and insecure attachment styles.[5] Bowlby's attachment theory describes the shaping of future relationships by bonding in early childhood and associates previously experienced insecure attachment styles with later-onset separation anxiety.[6] Separation anxiety disorder can be described as exaggerated anxiety manifesting as a disproportionate concern over either actual or anticipated separation from a figure of attachment.[7] Separation

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anxiety disorder is a reported comorbidity in individuals with various psychiatric disorders such as major depressive disorder, bipolar disorder, and attention-deficit/hyperactivity disorder.[8–10]

The relationship between psychotic experiences and childhood trauma is mediated by anxiety and depressive symptoms.[11] Recently, insecure attachment was determined to have a mediating role in the relationship between separation anxiety in adults and the perception of parental rejection in childhood.[12]

Anxiety disorder comorbidity reduces the quality of life in individuals with schizophrenia.[13] Moreover, the prominence of inhibited temperament that emerges in early childhood among individuals with schizophrenia affects anxiety and quality of life later in adulthood.[14] The World Health Organization (WHO) defines health as the absence of any disease and the presence of well-being from the physical, social, and mental perspectives.[15] The concept of quality of life, which encompasses personal satisfaction with life, interpretations of environmental living conditions, and assessments of functioning in life matters, has become a significant part of the medical management of individuals with schizophrenia.[16] In parallel, individuals with schizophrenia, especially those presenting in the acute phase, should be checked for unspecified anxiety disorder.[17] The results of relevant studies indicate that individuals with schizophrenia benefit from targeted interventions for anxiety disorder.[18]

Previously, the diagnosis of separation anxiety disorder was limited to childhood and adolescence; however, the extension of timing for the onset of symptoms into adulthood, prolongation of the duration of symptoms to a minimum of six months, and modification of attachment figures to include children, spouse, and significant others has resulted in the categorization of adult separation anxiety disorder as a separate disorder in the Diagnostic and Statistical Manual of Mental Disorders, version 5 (DSM-5).[7] A systematic review of 332 studies aimed to identify individuals at ultra-high risk for psychosis by investigating psychiatric comorbidities, including anxiety disorders. However, none of these studies have addressed adult separation anxiety disorder.[19] Similarly, in another study that addressed comorbidities in schizophrenia, only obsessive-compulsive disorder, panic disorder, agoraphobia, social anxiety disorder, substance use disorder, and major depressive disorder were considered, and not adult separation anxiety disorder.[20,21]

Only a handful of studies have addressed adult separation anxiety disorder comorbidity, compared to a considerable number of studies on anxiety disorder comorbidity in individuals with schizophrenia; this may be attributed to the relatively recent inclusion of adult separation anxiety disorder in the DSM-5, the presence of only a few separation anxiety disorder studies, or the overshadowing of adult separation anxiety disorder by symptoms of other well-known disorders.[20,22]

In light of the literature on childhood trauma and anxiety disorder comorbidity in psychotic disorders, this study hypothesized that childhood trauma could predict adult separation anxiety disorder and negatively affect the quality of life in individuals with schizophrenia. To our knowledge, this hypothesis has not been tested before. Therefore, our study aimed to assess the role of childhood trauma in adult separation anxiety disorder and determine the effects thereof on the quality of life of individuals with schizophrenia to guide the development of new approaches for treating separation anxiety disorder in individuals with schizophrenia, in addition to classical antipsychotic drugs.

Material and Method

This cross-sectional study was conducted with adult individuals with schizophrenia in outpatient clinics at the Cukurova University Medical School in Adana, Turkey. The institutional ethics committee approved the study protocol as a non-interventional trial (#96-30, February 14, 2020). Signed informed consent forms were obtained from all participants. The study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Study Groups

The study population comprised 18–65-year-old individuals diagnosed with schizophrenia according to the DSM-5 criteria.[7] Individuals with schizophrenia hospitalized within three months preceding enrollment and whose pharmacotherapy was modified within four weeks prior to the study were excluded. We did not include individuals with schizophrenia whose Positive and Negative Syndrome Scale (PANSS) scores were >3 based on the definition of remitted schizophrenia suggested by Andreasen et al.[23] All individuals with schizophrenia were on second-generation antipsychotic monotherapy (olanzapine, risperidone, quetiapine, or aripiprazole), with a daily antipsychotic dose of 487.9 ± 243.9 mg chlorpromazine equivalents. The

mean chlorpromazine equivalents were calculated according to Woods.[24] Individuals with schizophrenia who were evaluated for insight and attitude towards their diagnosis were grouped into six categories. Accordingly, individuals in total denial made up the first group, individuals in partial denial who declined to receive help made up the second group, individuals cognizant of their condition who blamed external conditions made up the third group, and individuals who were considering the presence of an unknown causative factor for their condition made up the fourth group, individuals who acknowledged their symptoms but could not make use of this level of cognizance in daily life made up the fifth group, and individuals who were aware of their emotions/thoughts and were able to manage them made up the sixth group.[25] Individuals in the first and second groups were also excluded.

To rule out dementia and mild cognitive disorder, the cognitive functions of the remaining individuals were assessed via a Mini-Mental State Examination (MMSE).[26] Accordingly, we excluded 11 individuals with schizophrenia since they had MMSE scores below 28.[27] To avoid the confounding effects of comorbid mental disorders, we excluded five individuals with schizophrenia with comorbid major depressive disorder, five with generalized anxiety disorder, and four with obsessive-compulsive disorder. Finally, participants with an educational status less than elementary school were excluded. We randomly included 85 volunteers from hospital employees and their relatives who were literate, had no previous psychiatric complaints, and reported not having psychiatric disorders as a control group. Consequently, we conducted a study with 111 individuals with schizophrenia and 85 control subjects.

Power Analysis

A review of the literature revealed no similar studies that could have been used as a reference to determine the minimum sample size. Therefore, a pilot study was conducted with 18 individuals with schizophrenia. The resultant power analysis indicated that at least 108 individuals were needed to test the significance of the model under the conditions of 90% power and 5% type I error. The analysis of the data collected from the overall patient group resulted in 99% power and 5% type I error, indicating that a sample size of 111 individuals was more than sufficient for the study. Power analysis was performed using the "power mediation" software available in the R software package.[28]

Procedure

The first author interviewed all participants in two consecutive sessions for approximately 90 minutes. The first session focused on sociodemographic variables such as age, sex, marital status, literacy, place of residence, and employment status. The second interview comprised a diagnosis of schizophrenia and separation anxiety disorder.

Assessment Tools

Adult Separation Anxiety Questionnaire (ASAQ)

The ASAQ is a 27-item self-report questionnaire that evaluates the symptoms of adult separation anxiety disorder according to DSM-IV criteria.[29] Each item is assigned a score between 0 and 3, with higher scores indicating a higher probability of separation anxiety disorder. In a Turkish validity and reliability study, a score of 25 or higher was considered adequate for an adult separation anxiety disorder diagnosis.[30]

Separation Anxiety Symptom Inventory (SASI)

The SASI is a 15-item, 4-point Likert-type self-report scale that evaluates childhood separation anxiety symptoms in adults. The SASI has three subscales: separation anxiety (seven items), fear of separation from family members (five items), and school phobia (three items). The sensitivity and specificity of the SASI were 83% and 76%, respectively, and the cut-off score was determined to be 12. The validity and reliability of the Turkish version have been established.[30,31]

Structured Clinical Interview for Separation Anxiety Symptoms (SCI–Separation Anxiety Symptoms)

SCI–separation anxiety symptoms is a 16-item scale developed to identify adult separation anxiety symptoms using DSM-IV-based symptoms of childhood separation anxiety disorder to adulthood. It comprises two parts, each with eight items. The first part retrospectively evaluates childhood separation anxiety symptoms, whereas the second evaluates current adulthood symptoms. Childhood separation anxiety disorder or adult separation anxiety disorder diagnoses of individuals determined to have at least three of the eight symptoms are verified. Cronbach's alpha values of the childhood

and adulthood parts of the SCI–separation anxiety symptoms are 0.56 be 0.57, respectively. Dirioz et al verified the validity and reliability of SCI–separation anxiety symptoms.[32,33]

World Health Organization Quality of Health Scale-Short Form (WHOQoL-BREF)

The WHO defines health quality as "an individual's perception of his/her position in life in the context of the culture and value systems in which he/she lives and concerning his/her goals, expectations, standards, and concerns". The WHOQoL-BREF comprises physical, psychological, social relations, and environment subscales. The validity and reliability of the Turkish version of the WHOQoL-BREF have been established.[34]

Panss

The PANSS was developed to assess positive and negative symptoms and general psychopathology in individuals with schizophrenia.[35] A validity and reliability study of the Turkish version revealed that Cronbach's alpha values are 0.75, 0.77, and 0.71 for positive symptoms, negative symptoms, and 0.71 for general psychopathology, respectively.[36]

Childhood Trauma Questionnaire (CTQ)-28

The CTQ is a self-report scale with two versions.[37] The more extended version contains 53 items, whereas the shorter version contains 28. The shorter version, the CTQ-28, evaluates physical neglect, emotional neglect, physical abuse, emotional abuse, and sexual abuse. The Cronbach alpha value of the Turkish version of the CTQ-28 is 0.93.[38]

Separation Anxiety Disorder Diagnosis

Individuals who fulfilled the DSM-5 criteria for separation anxiety disorder had three of the adult separation symptoms listed among the SCI–separation anxiety symptoms at the minimum and scored at least 25 on the ASAQ were diagnosed with adult separation anxiety disorder. Conversely, individuals who fulfilled the diagnostic criteria for separation anxiety disorder outlined in the DSM-5 had at least three positive childhood separation anxiety disorder symptoms (fewer than three adult symptoms, if present) and scored at least 12 on the SASI were diagnosed with childhood separation anxiety disorder. Individuals who fulfilled the criteria for both adult and childhood separation anxiety disorder were evaluated in the adult separation anxiety disorder category.

Statistical Analysis

The Shapiro–Wilk, Kolmogorov–Smirnov, and Anderson-Darling tests were used to determine whether the numerical data conformed to a normal distribution. The numerical variables were expressed as mean, standard deviation, median, and maximum-minimum values. We used the independent samples *t*-test when the numerical data were normally distributed, and the Mann–Whitney *U*-test otherwise. The differences between categorical variables in the study groups were compared using Pearson's chi-squared test. Differences between the groups were evaluated using the Bonferroni-Holm correction test for multiple comparisons. Univariate and multiple regression models were used to analyze the parameters that affected the WHOQoL-BREF-TR.

The mediating role of adult separation anxiety disorder in the relationship between childhood trauma and the quality of life of individuals with schizophrenia was evaluated using mediation analysis. The robust maximum likelihood parameter estimation method was used in the path analysis of continuous variables, including the WHOQoL-BREF-TR psychological subscale score as the intrinsic variable, the CTQ total score as the extrinsic variable, and the SASI and ASAQ scores as the mediators. The predictive power of the extrinsic variable for the intrinsic variable was tested first, without including the basic model (mediator variable). Second, direct and indirect effects were tested by adding the mediator variable in the analyses. The Jamovi 2.0.0.0 (Jamovi Project, version 2.0.0.0, retrieved from https://www.jamovi.org) and JASP 0.15 (Jeffreys's Amazing Statistics Program, version 0.15, retrieved from https://jasp-stats.org) programs were used for the statistical analyses, and the PATH analysis software available in the MPLUS 7.4 software package was used for mediation analyses. Probability (p) values ≤ 0.05 indicated statistical significance.

Results

The patient group comprised 111 individuals with schizophrenia and the control group comprised 85 healthy individuals. The groups did not differ significantly in terms of mean age, sex, literacy rate, and place of residence (p>0.05). The groups differed significantly by marital status, as the rate of single individuals was significantly higher than that of control subjects who were single (p<0.001). Additionally, the groups differed in terms of employment status, as the number of employed individuals was significantly lower than that of the employed control subjects (p<0.001). Table 1 presents the distribution of the demographic characteristics of the groups.

Comorbidity of adult separation anxiety disorder was present in 64 individuals diagnosed with schizophrenia. Individuals with and without adult separation anxiety disorder comorbidity were similar in terms of clinical features such as age of onset, number of hospitalizations, family history of psychiatric disorders, electroconvulsive therapy (ECT) administration, educational status, marital status, employment status, alcohol use, substance use, CTQ total, and subgroup scores. The group with adult separation anxiety disorder comorbidity had significantly higher PANSS total (p=0.002), PANSS positive (p=0.003), PANSS negative (p=0.010), PANSS general psychopathology (p=0.001) scores, and suicide attempt history (p=0.01) (Table 2).

As for the clinical characteristics, the proportion of individuals with schizophrenia who were positive for SCI-childhood separation anxiety symptoms was significantly higher than that of the control subjects (p<0.001). The mean ASAQ score of individuals with schizophrenia was significantly higher than that of control subjects (p<0.001). In parallel, the number of individuals with schizophrenia with positive SCI–adult separation anxiety symptoms was significantly higher than that of control subjects (p<0.001). Individuals with schizophrenia scored significantly higher on the CTQ total (p<0.001), emotional abuse (p<0.01), physical abuse (p=0.014), physical neglect (p<0.01), and emotional neglect (p<0.01) subscales than controls. The mean WHOQoL-BREF-TR psychological health subscale score of control subjects was significantly higher than that of individuals with schizophrenia (p<0.001). Table 3 shows a comparison of the scale scores of the groups.

Table 1 Sociodemographic Features of the Participants

	Schizophrenia (n=111)	Controls (n=85)	p
Age[#]	34.2 ± 10.0	33.1 ± 8.5	0.527*
Age[§]	32.0 [18.0–63.0]	32.0 [18.0–58.0]	
Gender[‡]			
Female	33 (29.7)	28 (32.9)	0.745**
Male	78 (70.3)	57 (67.1)	
Education[‡]			
Primary School	24 (21.6)	22 (25.9)	0.783**
Secondary School	46 (41.4)	33 (38.8)	
University	41 (36.9)	30 (35.3)	
Marital Status[‡]			
Single	80 (72.1)	27 (31.8)	**<0.001****
Married	31 (27.9)	58 (68.2)	
Employment Status[‡]			
Employed	27 (24.3)	58 (68.2)	**<0.001****
Unemployed	84 (75.7)	27 (31.8)	
Residence[‡]			
Urban	71 (64.0)	61 (71.8)	0.317**
Rural	40 (36.0)	24 (28.2)	

Notes: [‡]n (%), [#]Mean ± standard deviation, [§]Median [min-max]. *Independent Samples *t* test. **Pearson Chi-Square test. The p values in bold are statistically significant (p<0.05).

Table 2 Clinical Characteristics of the Individuals with Schizophrenia

	ASAD(+) (n=64)	ASAD(-) (n=47)	p
Age of onset (year)[#]	25.09 ± 9.2	24.2 ± 11.2	0.658*
Number of hospitalizations[§]	3.3 ± 6.1	3 ± 5.3	0.793*
Family history of psychiatric disorder[‡]			
Presence	31 (48.4)	16 (34.04)	0.129**
Absence	33 (51.6)	31 (65.96)	
Adminstration of ECT[‡]			
Presence	18 (28.1)	19 (40.4)	0.174**
Absence	46 (35.9)	28 (59.6)	
History of suicide attempt[‡]			
Presence	22 (34.3)	6 (12.8)	0.018**
Absence	42 (29.7)	41 (34.2)	
Education[‡]			
Primary School	16 (25.0)	8 (17.0)	0.314**
Secondary School	28 (43.8)	18 (38.3)	
University	20 (31.2)	21 (44.7)	
Marital Status[‡]			
Single	47 (73.4)	33 (70.2)	0.873**
Married	17 (26.6)	14 (29.8)	
Employment Status[‡]			
Employed	14 (21.9)	13 (27.7)	0.633**
Unemployed	50 (78.1)	34 (72.3)	
Alcohol use, presence[‡]	5 (7.8)	4 (8.5)	0.999**
Substance use, presence[‡]	7 (10.9)	1 (2.1)	0.135**
Positive and Negative Syndrome Scale (PANSS), Total[§]	77.5 [30.0–157.0]	48.0 [30.0–106.0]	**0.002*** **
Positive	15.0 [7.0–47.0]	10.0 [7.0–30.0]	**0.003*** **
Negative	20.0 [2.0–42.0]	13.0 [7.0–34.0]	**0.010*** **
General Psychopathology	41.0 [16.0–83.0]	27.0 [16.0–67.0]	**0.001*** **
Childhood Trauma Questionnaire (CTQ)[§]	44.0 [32.0–80.0]	44.0 [34.0–90.0]	0.793***
Emotional Abuse	7.0 [5.0–25.0]	5.0 [5.0–20.0]	0.113***
Physical Abuse	5.0 [5.0–25.0]	5.0 [5.0–25.0]	0.228***
Sexual Abuse	5.0 [5.0–18.0]	5.0 [5.0–20.0]	0.235***
Physical Neglect	15.0 [11.0–20.0]	16.0 [11.0–22.0]	0.124***
Emotional Neglect	11.0 [5.0–25.0]	11.0 [5.0–22.0]	0.814***

Notes: [‡]n (%), [#]Mean ± standard deviation, [§]Median [min-max]. *Independent Samples *t* test. **Pearson Chi-Square test. ***Mann–Whitney *U*-test. The p values in bold are statistically significant (p<0.05).

Abbreviations: ECT, Electroconvulsive therapy; ASAD, Adult Separation Anxiety Disorder.

Table 3 The Scale Scores of the Participants

	Schizophrenia (n=111)	Controls (n=85)	p
Separation Anxiety Symptom Inventory (SASI)[§]	12.0 [0.0–44.0]	8.0 [0.0–28.0]	0.039*
SCI- Childhood Separation Anxiety Symptoms, positive[‡]	63 (56.8)	17 (20.0)	**<0.001****
Adult Separation Anxiety Questionnaire (ASAQ)[§]	27.0 [0.0–81.0]	9.0 [0.0–45.0]	**<0.001***

(*Continued*)

Table 3 (Continued).

	Schizophrenia (n=111)	Controls (n=85)	p
SCI- Adult Separation Anxiety Symptoms, positive‡	64 (57.7)	21 (24.7)	**<0.001****
Positive and Negative Symptom Scale (PANSS) Total§	64.0 [30.0–157.0]	-	-
Positive	12.0 [7.0–47.0]	-	-
Negative	17.0 [2.0–42.0]	-	-
General Psychopathology	34.0 [16.0–83.0]	-	-
Childhood Trauma Questionnaire (Total)§	44.0 [32.0–90.0]	29.0 [25.0–41.0]	**<0.001***
Emotional abuse	7.0 [5.0–25.0]	5.0 [5.0–10.0]	**<0.001***
Physical abuse	5.0 [5.0–25.0]	6.0 [5.0–9.0]	**0.014***
Sexual abuse	5.0 [5.0–20.0]	5.0 [5.0–9.0]	0.104*
Physical neglect	15.0 [11.0–22.0]	5.0 [5.0–9.0]	**<0.001***
Emotional neglect	11.0 [5.0–25.0]	5.0 [5.0–9.0]	**<0.001***
WHOQoL-BREF-TR§			
Psychological health	19.0 [6.0–30.0]	30.0 [24.0–30.0]	**<0.001***

Notes: ‡n (%), §Median [min-max]. *Mann–Whitney *U*-test, p < 0.05 statistically significant, Bonferroni-Holm correction was used for pairwise comparisons (Significance level p=0.025). **Pearson Chi-Square test. The p values in bold are statistically significant (p<0.05).
Abbreviations: WHOQoL-BREF-TR, World Health Organization Quality of Health Scale-Short Form; SCI, Structured Clinical Interview.

Correlation Analyses

The scores obtained from the ASAQ and SASI of individuals with schizophrenia, except those obtained from the negative syndrome subscale, revealed weak positive correlations in the r coefficient range between 0.234 and 0.291 (all p<0.05). SASI scores were found to be weakly correlated with the CTQ emotional abuse (r=0.336, p<0.001), physical abuse (r=0.363, p<0.001), and sexual abuse (r=0.195, p=0.04) subscales in the positive direction, and with the CTQ physical neglect subscale (r=−0.211, p=0.026) in the negative direction. ASAQ scores were found to be weakly correlated with total CTQ scores (r=0.331, p<0.001) and moderately correlated with the CTQ emotional (r=0.449, p<0.001) and physical abuse (r=0.393, p<0.001) subscales in the positive direction (Table 4 and Figure 1). Moderate correlations were found between the WHOQL-BREF-TR psychological

Table 4 Correlations Among PANSS, CTQ, WHOQoL-BREF-TR, SASI, and ASAQ

	Separation Anxiety Symptom Inventory (SASI)		Adult Separation Anxiety Questionnaire (ASAQ)		WHOQoL-BREF-TR Psychological Health	
	r	p	r	p	r	p
Positive and Negative Syndrome Scale (PANSS), Total	0.247	**0.009**	0.289	**0.002**	-	-
Positive	0.234	**0.014**	0.253	**0.007**	-	-
Negative	0.184	0.054	0.254	**0.007**	-	-
General Psychopathology	0.241	**0.011**	0.291	**0.002**	-	-
Childhood Trauma Questionnaire (CTQ)	0.184	0.053	0.331	**<0.001**	−0.410	**<0.001**
Emotional Abuse	0.336	**<0.001**	0.449	**<0.001**	−0.479	**<0.001**
Physical Abuse	0.363	**<0.001**	0.393	**<0.001**	−0.443	**<0.001**
Sexual Abuse	0.195	**0.040**	0.186	0.051	−0.178	0.062
Physical Neglect	−0.211	**0.026**	−0.174	0.068	0.285	**0.002**
Emotional Neglect	0.055	0.569	0.163	0.088	−0.299	**0.001**
WHOQoL-BREF-TR						
Psychological health	−0.460	<0.001	−0.561	<0.001	-	-
Adult Separation Anxiety Questionnaire (ASAQ)	0.707	<0.001	-	-	-	-

Notes: Spearman's rho correlation coefficient. The p values in bold are statistically significant (p<0.05).
Abbreviation: WHOQoL-BREF-TR, World Health Organization Quality of Health Scale-Short Form.

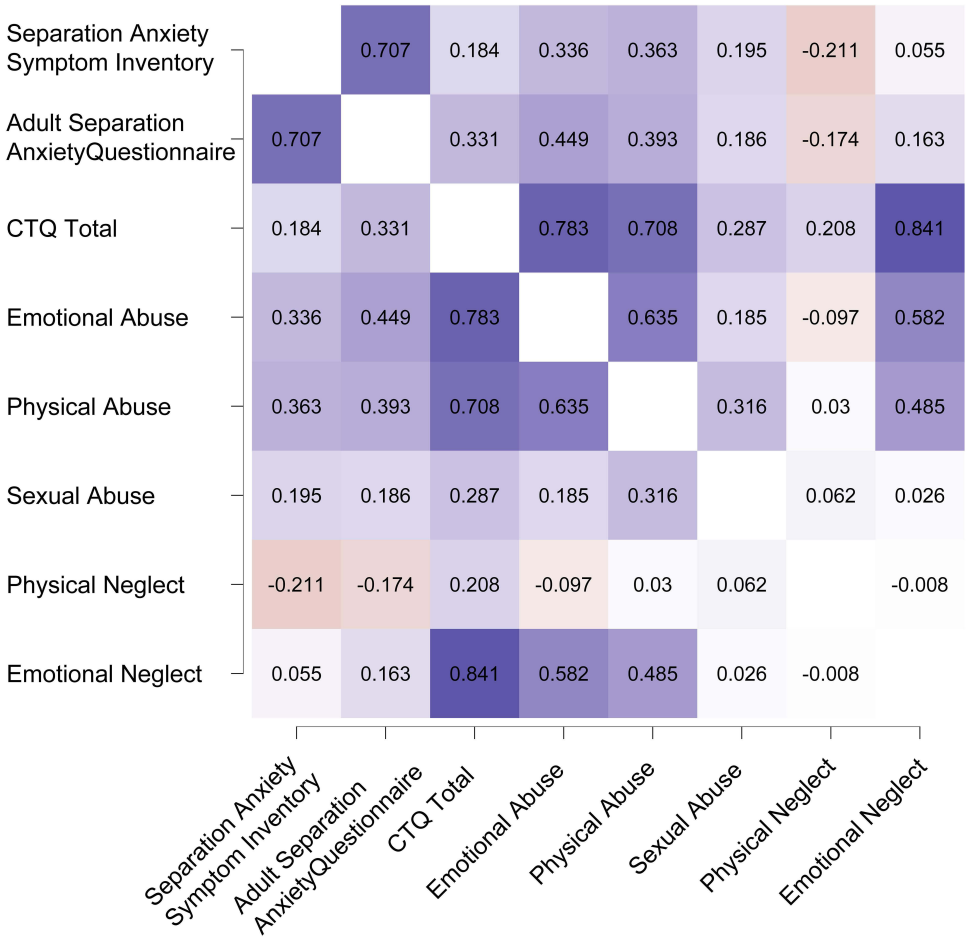

Figure 1 Correlations among CTQ, SASI and ASAQ scores.

health subscale scores and the SASI (r=−0.460, p<0.001) and ASAQ (r=−0.561, p<0.001) scores in the negative direction (Table 4 and Figure 2). The ASAQ scores were found to be strongly correlated with the SASI scores (r=0.707, p<0.001) in the positive direction. The psychological health subtype of the WHOQoL-BREF-TR in individuals with schizophrenia was correlated with the total CTQ (r=−0.410, p<0.001), emotional abuse (r=−0.479, p<0.01), physical abuse (r=−0.443, p<0.01), physical neglect (r=0.285, p=0.02), and emotional neglect (r=−0.299, p=0.01) (Table 4 and Figure 3).

In the univariate regression analysis, scores obtained from CTQ subscales, except for the physical neglect subscale and PANSS, SASI, and ASAQ scales, showed negative correlations (with r values=0.14–0.55, p<0.05 for all), whereas the CTQ physical neglect subscale scores showed a strong positive correlation (r=0.77, p=0.03) with the WHOQoL-BREF-TR psychological health subscale scores. The adjustment of the beta values in the multiple linear regression model revealed a correlation between the CTQ physical neglect subscale scores and the WHOQoL-BREF-TR psychological health subscale scores as the only significant correlation (r=0.61, p=0.006) (Table 5).

Mediation Analysis

First, the basic model (Model I) was used to analyze the mediating role of SASI on the impact of CTQ and ASAQ on WHOQoL-BREF-TR. Accordingly, the impact of total CTQ scores on WHOQoL-BREF-TR psychological health scores was assessed without including the SASI or ASAQ scores. A significant negative effect was observed in Model 1 (beta= −0.341, p<0.001). Second, the impact of total CTQ scores on the SASI and ASAQ scores was investigated, and a significant effect was observed on the ASAQ scores (beta=0.263, p=0.005). The effects of both SASI and ASAQ scores were significantly negative on the WHOQoL-BREF-TR scores (beta=−0.401 and −0.436, respectively; p<0.001 for both). SASI

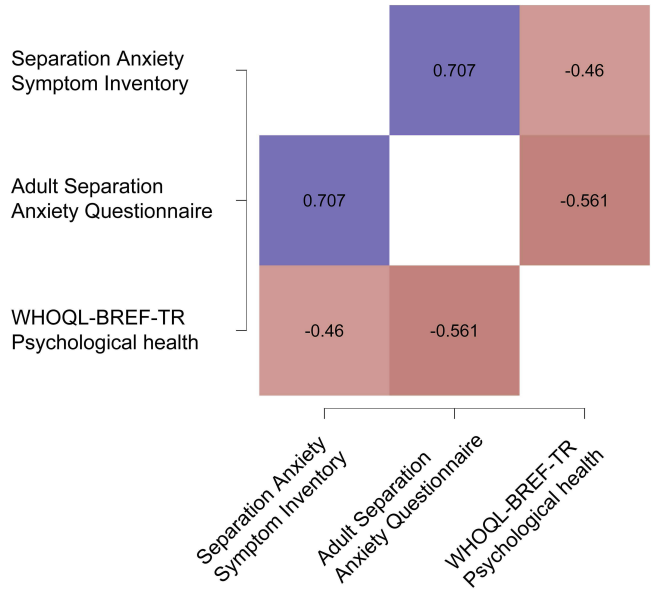

Figure 2 Correlations among SASI, ASAQ and WHOQoL-BREF-TR Psychological health scores.

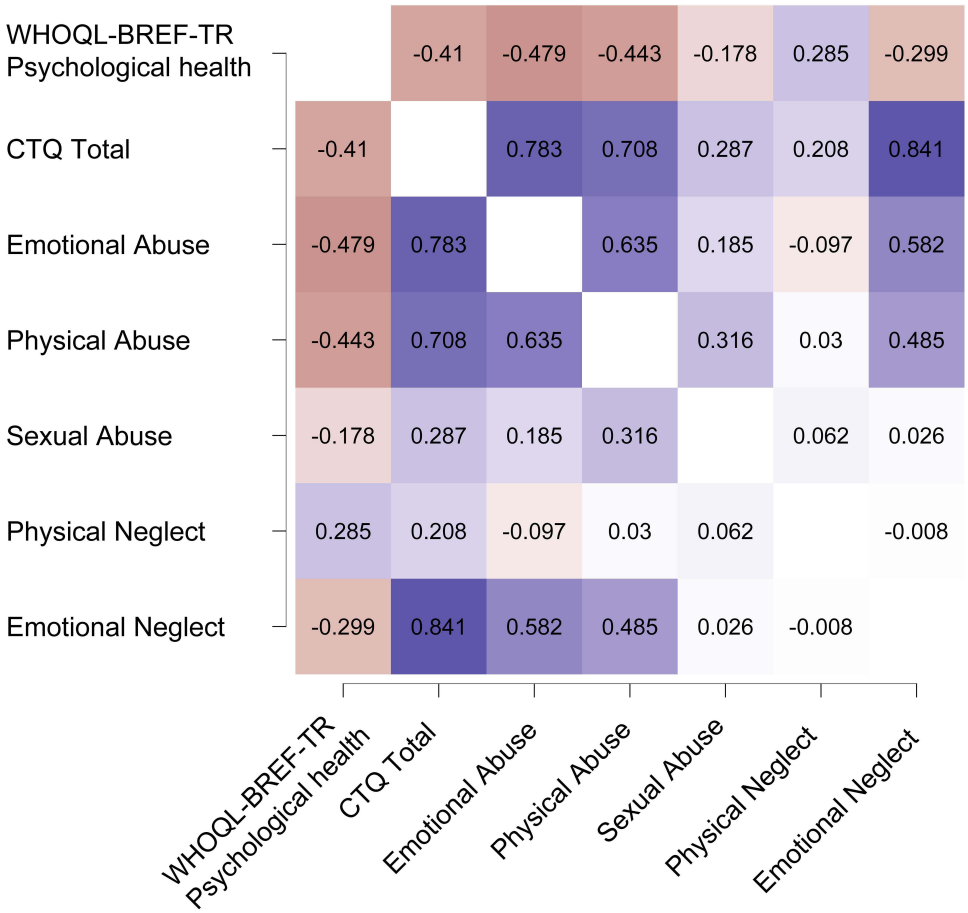

Figure 3 Correlations between CTQ and WHOQoL-BREF-TR Psychological health scores.

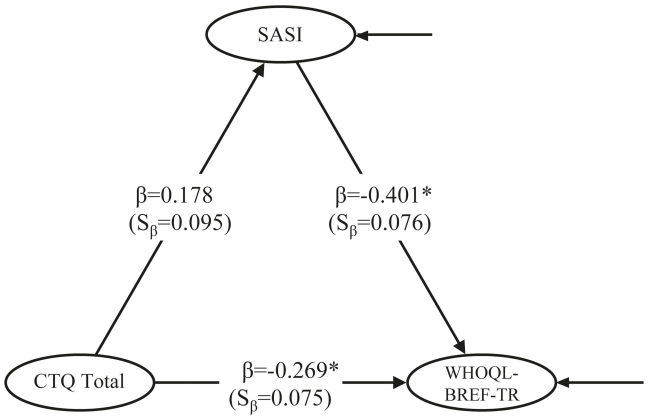

Figure 4 The role of SASI scores on the effect of CTQ scores on the WHOQoL-BREF-TR Psychological health scores.

scores did not have any significant indirect effect (beta=−0.071, p=0.089), whereas ASAQ scores had a significant negative indirect effect (beta=−0.115, p=0.024) on the relationship between total CTQ scores and the WHOQoL-BREF-TR psychological health subscale scores. A direct negative effect of ASAQ scores (beta=−0.026, p=0.006) on the pathway between total CTQ scores and WHOQoL-BREF-TR psychological health subscale scores was also observed. The mediation analysis did not reveal any significant effect of SASI scores on the effect of CTQ scores on WHOQoL-BREF-TR scores (Table 6 and Figure 4). Furthermore, a partial mediating role of ASAQ scores was observed over the effect of total CTQ scores on the WHOQoL-BREF-TR psychological health subscale scores (Table 7 and Figure 5). Additionally, marital, educational, and employment status did not mediate the relationship between the CTQ and WHOQoL-BREF (data not shown).

Discussion

This cross-sectional study revealed that a significantly higher number of individuals with schizophrenia had an adult separation anxiety disorder comorbidity than control subjects did. Additionally, we found that childhood trauma predicted adult separation anxiety disorder comorbidity and that adult separation anxiety disorder had a partial mediating role over the effect of childhood trauma on the quality of life of individuals with schizophrenia. We also determined that individuals with schizophrenia and adult separation anxiety disorder comorbidity experienced significantly more childhood trauma than control subjects. Furthermore, the quality of life of individuals with schizophrenia was significantly lower than that of control subjects. In a meta-analysis of 36 studies, experiencing social disadvantages in childhood was

Table 5 The Univariate and Multiple Linear Regression Models for Variables Related to WHOQoL-BREF-TR Psychological Health Subscale

	Beta [95% CI]	p-value	Adj. Beta [95% CI]	p-value
Emotional Abuse	−0.55 [−0.78–0.32]	**< 0.001**	−0.29 [−0.65–0.07]	0.118
Physical Abuse	−0.37 [−0.6--0.14]	**0.002**	0.07 [−0.25–0.40]	0.654
Sexual Abuse	−0.31 [−0.62–0.01]	**0.046**	−0.17 [−0.45–0.11]	0.228
Physical Neglect	0.77 [0.27–1.27]	**0.003**	0.61 [0.19–1.03]	**0.006**
Emotional Neglect	−0.33 [−0.54–0.13]	**0.002**	−0.10 [−0.31–0.1]	0.318
PANSS Positive	−0.22 [−0.33–0.11]	**< 0.001**	−0.07 [−0.19–0.06]	0.300
PANSS Negative	−0.21 [−0.32–0.11]	**< 0.001**	−0.11 [−0.24–0.01]	0.068
SASI	−0.23 [−0.32–0.14]	**< 0.001**	−0.06 [−0.19–0.06]	0.318
ASAQ	−0.14 [−0.19–0.10]	**< 0.001**	−0.05 [−0.13–0.02]	0.144

Notes: Dependent Variable: WhoQol-Bref-TR psychological health. The p values in bold are statistically significant (p<0.05).

Abbreviations: PANSS, Positive and Negative Syndrome Scale; SASI, Separation Anxiety Symptom Inventory; ASAQ, Adult Separation Anxiety Questionnaire; WHOQoL-BREF, World Health Organization Quality of Health Scale-Short Form; CI, Confidence Interval; Adj, Adjusted.

Table 6 The Mediation Analysis of SASI on the Effect of CTQ on WHOQoL-BREF-TR

Model	Pathway	Std. Path Coefficient (β)	Std Error (S_β)	p-value
Model I. Basic model (without SASI)	CTQ Total → WHOQoL-BREF-TR psychological health	−0.341	0.083	**<0.001**
Model II. Mediation Analysis	CTQ Total → SASI	0.178	0.095	0.060
Model II. Mediation Analysis	SASI→ WHOQoL-BREF-TR psychological health	−0.401	0.076	**<0.001**
Model II. Mediation Analysis (Direct effect)	CTQ total → WHOQoL-BREF-TR psychological health	−0.269	0.075	**<0.001**
Model II. Mediation Analysis (Indirect Effect)	CTQ total → SASI → WHOQoL-BREF-TR psychological health	−0.071	0.042	0.089

Note: The p values in bold are statistically significant (p<0.05).
Abbreviations: CTQ, Childhood Trauma Questionnaire; SASI, Separation Anxiety Symptom Inventory; WHOQoL-BREF, World Health Organization Quality of Health Scale-Short Form.

Table 7 The Mediation Analysis of ASAQ on the Effect of CTQ on WHOQoL-BREF-TR

Model	Pathway	Std. Path Coefficient (β)	Std Error (S_β)	p-value
Model I. Basic model (Without ASAQ)	CTQ total → WHOQoL-BREF-TR-psychological health	−0.341	0.083	**<0.001**
Model II. Mediation Analysis	CTQ total → ASAQ	0.263	0.094	**0.005**
Model II. Mediation Analysis	ASAQ→ WHOQoL-BREF-TR-psychological health	−0.436	0.087	**<0.001**
Model II. Mediation Analysis (Direct Effect)	CTQ total → WHOQoL-BREF-TR-psychological health	−0.226	0.081	**0.006**
Model II. Mediation Analysis (Indirect Effect)	CTQ total → ASAQ → WHOQoL-BREF-TR-psychological health	−0.115	0.051	**0.024**

Note: The p values in bold are statistically significant (p<0.05).
Abbreviations: CTQ, Childhood Trauma Questionnaire; ASAQ, Adult Separation Anxiety Questionnaire; WHOQoL-BREF, World Health Organization Quality of Health Scale-Short Form.

highly associated with an increased risk of psychosis.[39] Similarly, losing a parent during childhood was also associated with a two- to three-fold increase in the risk of psychosis.[40,41] Hence, it can be concluded that childhood trauma induces several neuropsychiatric changes, increasing the risk of both psychosis and adult separation anxiety disorder. Further studies are needed to identify the pathways between childhood trauma, psychosis, and adult separation anxiety disorders.

In our study, mediation analyses conducted using various model pathways revealed that ASAQ scores partially mediated the relationship between CTQ and WHOQoL-BREF-TR scores. To our knowledge, this is the first study in which the predictive power of childhood trauma on adult separation anxiety disorder and a mediator effect of adult separation anxiety disorder on the impact of childhood trauma on quality of life were shown in individuals with schizophrenia. Using the Brief Psychiatric Rating Scale, Lukoff et al demonstrated that anxiety disorder was the most crucial determinant of quality of life in individuals with schizophrenia.[42] Wang et al identified complex pathways between hope and quality of life in individuals with schizophrenia, including factors related to sex and depression.[43] Conversely, our mediation analyses revealed that treatment approaches that consider separation anxiety in addition to classical antipsychotic drugs might improve psychological quality of life in individuals with schizophrenia who

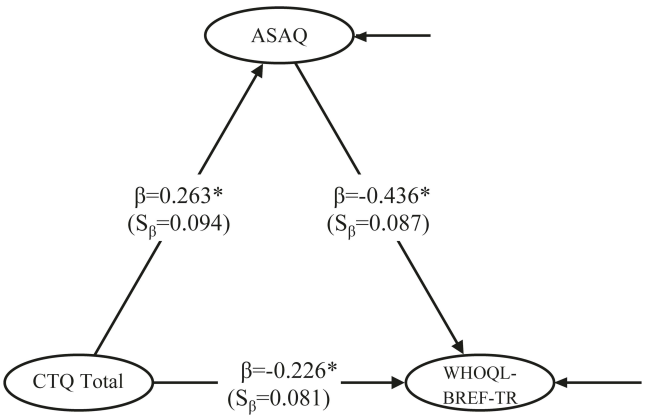

Figure 5 The role of ASAQ scores on the effect of CTQ scores on the WHOQoL-BREF-TR Psychological health scores.

experienced childhood trauma. Several psychotherapeutic methods, including attachment-oriented therapy, may help relieve separation anxiety symptoms in individuals with schizophrenia. "Attachment-oriented therapy" aims to improve individuals' capacity for reflection and enables them to identify and tolerate emotional responses and perceived dangers associated with attachment. Therapists may notice individuals' separation fears in transference or outside connections and can use dynamic or interpersonal approaches to help individuals understand them better, thereby decreasing their intensity.[44,45]

We determined that childhood trauma, except sexual abuse, was more common in individuals with schizophrenia than in control subjects. These results align with those of a review that found that sexual abuse was the least common type of childhood trauma in individuals with psychotic disorders.[46] Different types of childhood traumas may lead to different psychological problems, as demonstrated by the relationship between chronic fatigue syndrome in adulthood and childhood sexual harassment.[47] In addition, emotional and physical trauma experienced during childhood was associated with significant anxiety symptoms in late adulthood.[48] In another study conducted with individuals without a history of psychiatric disorders, positive correlations were observed between ASAQ and total CTQ scores and CTQ sexual abuse, emotional abuse, and emotional neglect subscale scores, and between SASI scores and total CTQ scores and CTQ emotional abuse, physical abuse, sexual abuse, and emotional neglect subscale scores. There was also a positive correlation between the SASI and ASAQ scores.[48] In comparison, we found that the total CTQ scores were significantly correlated with the ASAQ scores, but not the SASI scores. Analysis of the subscales of the CTQ revealed that sexual abuse and physical neglect subscale scores correlated with SASI scores, but not with ASAQ scores. The differences between ours and the aforementioned study in the relationships between the CTQ subscale scores and ASAQ and SASI scores may be attributed to the differences in the main characteristics of the study populations, that is, individuals with schizophrenia in our study and individuals without a history of psychiatric disorders in the earlier study. The positive and strong correlation between the ASAQ and SASI scores in this study conformed with the results of another study.[49] Gabinio et al identified a moderate correlation between anxious attachment and early life trauma in individuals with schizophrenia.[3] Although approximately half of the study population reported having experienced childhood sexual abuse, no correlations were found between the scores obtained from the CTQ subscales and anxious attachment patterns. Grummitt et al revealed that anxiety, depression, and distress were associated with multiple childhood neglects other than physical neglect.[50] In the present study, separation anxiety symptoms correlated with emotional and sexual childhood maltreatment in the same direction, but with physical neglect in the opposite direction. Our results reveal that individuals with schizophrenia react differently to various childhood traumas. In contrast, positive and moderate correlations were found between the ASAQ scores and the emotional or physical abuse subscale scores of the CTQ. Additionally, significant correlations were found between the SASI scores and the scores obtained from all subscales of the CTQ, except for the emotional neglect subscale. Our results suggest that separation anxiety symptoms in childhood or adulthood may be associated with different types of childhood trauma of varying severities. However, we did not classify trauma as single or chronic, which might have affected the relationship between childhood trauma and mental symptoms in individuals with schizophrenia. Future studies, especially those evaluating the effects of repetitive trauma, will help to shed light on this subject.

To our knowledge, this is the first study to investigate the relationship between childhood trauma subtypes and psychological health subtype of quality of life in individuals with schizophrenia. Our literature review revealed a limited number of studies on the relationship between childhood trauma and QoL in individuals with schizophrenia. Kilian et al revealed that higher exposure to traumatic events during childhood is associated with lower quality of life in adulthood.[51] Andrianarisoa et al determined that childhood trauma is independently associated with poor quality of life in individuals with schizophrenia.[16] We found that the psychological health subtype of quality of life in individuals with schizophrenia was associated with childhood traumas, such as emotional abuse, physical abuse, and emotional neglect. In addition, our results revealed that quality of life decreases as the severity of childhood trauma increases in individuals with schizophrenia, which is consistent with existing literature.

Anxiety, anxiety sensitivity,[52] and panic disorder[53] severity reportedly correlate with separation anxiety symptoms. The correlation between psychotic symptom severity and separation anxiety symptoms and the higher PANSS scores of individuals with schizophrenia and adult separation anxiety disorder in our study suggests that separation anxiety

symptoms may also be related to general psychopathology severity. Our results also suggest that some features of the clinical aspects of individuals with schizophrenia may be related to separation anxiety symptoms. Separation anxiety symptoms may increase in parallel with disease severity and should be differentiated from the positive and negative symptoms of schizophrenia.

The WHOQoL-BREF-TR psychological health subscale scores moderately negatively correlated with the SASI and ASAQ scores. A study that assessed the relationship between quality of life in individuals with schizophrenia and sociodemographic and clinical features, and satisfaction from social support demonstrated that unemployment and less satisfaction with intimate and friendly relations led to poorer quality of life.[54] In parallel, we found that unemployment and lack of intimacy were significantly more common among individuals with schizophrenia and comorbid adult separation anxiety disorder. Additionally, a moderate negative correlation was found between WHOQoL-BREF-TR psychological health subscale scores and separation anxiety disorder in individuals with schizophrenia. Furthermore, univariate analysis revealed that childhood trauma, positive and negative symptoms of schizophrenia, and separation anxiety disorder were significantly related to WHOQoL-BREF-TR scores. However, the multi-regression analysis revealed that only the physical neglect subscale of the CTQ significantly correlated with WHOQoL-BREF-TR scores. Recent reports have emphasized the importance of personalized treatment in individuals with schizophrenia and have suggested incorporating the assessment of childhood trauma in the initial evaluation of individuals with schizophrenia.[2,55]

Tasdemir et al determined that suicide rates were higher in individuals diagnosed with bipolar disorder with adult separation anxiety disorder comorbidity.[9] A study comparing a control subject and adult separation anxiety disorder in terms of suicide showed that approximately half of the individuals with adult separation anxiety disorder had a history of suicide attempts.[56] Another study showed that suicide is at a higher rate in individuals diagnosed with schizophrenia and comorbid anxiety disorder.[57] In the present study, the rate of suicide attempt history was significantly higher in the group with comorbid adult separation anxiety disorder. Our results are consistent with previously reported results. In future studies, it will be valuable to investigate the factors that influence the relationship between adult separation anxiety disorder and suicide.

Individuals with schizophrenia obtained the highest mean score on the general psychopathology subscale, followed by the PANSS negative symptoms subscale. Similarly, Wietkamper et al revealed that individuals with schizophrenia obtained the highest mean score on the general psychopathology subscale, followed by the negative symptoms subscale of PANSS.[46] The lack of social interactions due to adult separation anxiety disorder might have augmented the negative symptoms of schizophrenia, causing individuals with schizophrenia to obtain higher scores on the negative symptoms subscale of the PANSS. In one study, the sociodemographic characteristics that differed significantly between the study groups were employment and marital status, and the unemployed and single individuals with schizophrenia rates were significantly higher than those of control subjects.[39] The differences between the findings of our study and those of this study may be attributed to the fact that adult separation anxiety disorder was not included among the types of anxiety disorder investigated in the said study.[4] Priebe et al observed that working individuals with schizophrenia perceived their quality of life as better than that perceived by unemployed individuals.[58] Pinho et al determined that working and getting married are associated with a high quality of life.[59] In our study, the proportion of single and unemployed individuals with schizophrenia was significantly higher in the schizophrenia group than in the control subjects. Based on the results of previous studies, the low psychological health quality of individuals with schizophrenia may also be related to their negative perceptions of life due to their economic and marital status.

Limitations

The limitations of this study include the recall bias inherent to self-report scales, especially considering the retrospective nature of the responses provided in the CTQ. As time passes, trauma increases, and the effect of trauma on the individual may change. Therefore, using a wide age range, such as 18–65 years, can be considered a limitation. The study's cross-sectional design did not permit the assessment of a causal link among variables or the quality of life changes over time. Selecting a control group from a narrow sample may affect the study's results, as it may not represent the general healthy population. Another limitation of our study was that the MMSE is a non-sensitive scale and the internal consistency

coefficient in the validity study of SCI–separation anxiety symptoms was low. The lack of other information on the demographic and clinical conditions of individuals with schizophrenia and the difficulty of differentiating adult separation anxiety disorder from other symptoms of schizophrenia using questionnaires alone could be considered other limitations. The strengths of this study are that the employed assessment tools included reliable and valid Turkish versions of the original scales used as standardized diagnostic measurements for the respective conditions. The exclusion criteria were sufficiently strict to control for the inclusion of individuals with acute psychotic episodes and comorbid mental disorders in the study to minimize the risk of the related confounding effects.

Conclusion

More than half of the individuals diagnosed with schizophrenia in this study exhibited concurrent adult separation anxiety disorder, the symptoms of which were associated with increased disease severity, history of childhood trauma, and decreased quality of life. Moreover, this study revealed two significant outcomes for individuals with schizophrenia. First, childhood trauma was a predictor of adult separation anxiety disorder. Second, adult separation anxiety disorder partially mediated the relationship between childhood trauma and quality of life. Considering the comorbidity of adult separation anxiety disorder in individuals with schizophrenia, particularly in those with a history of childhood trauma, treating it with appropriate, individualized interventions may increase the quality of life.

Disclosure

The authors report no conflicts of interest in this work.

References

1. World Health Organization. Schizophrenia [homepage on the Internet]. Available from: https://www.who.int/news-room/fact-sheets/detail/schizophrenia. Accessed January 10, 2022.
2. Inyang B, Gondal FJ, Abah GA, et al. The role of childhood trauma in psychosis and schizophrenia: a systematic review. *Cureus*. 2022;14(1):21466.
3. Gabínio T, Ricci T, Kahn JP, Malaspina D, Moreira H, Veras AB. Early trauma, attachment experiences and comorbidities in schizophrenia. *Trends Psychiatry Psychother*. 2018;40(3):179–184. doi:10.1590/2237-6089-2017-0005
4. Kiran C, Chaudhury S. Correlates and management of comorbid anxiety disorders in schizophrenia. *Ind Psychiatry J*. 2018;27(2):271–278. doi:10.4103/ipj.ipj_66_17
5. Misiak B, Krefft M, Bielawski T, Moustafa AA, Sąsiadek MM, Frydecka D. Toward a unified theory of childhood trauma and psychosis: a comprehensive review of epidemiological, clinical, neuropsychological and biological findings. *Neurosci Biobehav Rev*. 2017;75:393–406. doi:10.1016/j.neubiorev.2017.02.015
6. Bowlby J. Separation anxiety: a critical review of the literature. *J Child Psychol Psychiatry*. 1961;1:251–269. doi:10.1111/j.1469-7610.1960.tb01999.x
7. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th. Washington (DC): American Psychiatric Association Publishing; 2013.
8. Elbay RY, Görmez A, Kılıç A, Avcı SH. Separation anxiety disorder among outpatients with major depressive disorder: prevalence and clinical correlates. *Compr Psychiatry*. 2021;105:152219. doi:10.1016/j.comppsych.2020.152219
9. Tasdemir A, Tamam L, Keskin N, Evlice YE. Assessment of co-morbidity of adult separation anxiety in patients with bipolar disorder. *Nord J Psychiatry*. 2016;70(2):93–102. doi:10.3109/08039488.2015.1053098
10. Ozten E, Tufan A, Eryilmaz G, Sayar G, Bulut H. The prevalence of adult separation anxiety disorder in a clinical sample of patients with ADHD. *Anatol J Psychiatry*. 2016;17(6):459–465. doi:10.5455/apd.205976
11. Fisher HL, Schreier A, Zammit S, et al. Pathways between childhood victimization and psychosis-like symptoms in the ALSPAC birth cohort. *Schizophr Bull*. 2013;39(5):1045–1055. doi:10.1093/schbul/sbs088
12. Deveci Şirin H. Parental acceptance–rejection and adult separation anxiety: the mediation of adult attachment insecurity. *SAGE Open*. 2019;9(4):1–9. doi:10.1177/2158244019885138
13. Achim AM, Maziade M, Raymond É, Olivier D, Mérette C, Roy MA. How prevalent are anxiety disorders in schizophrenia? A meta-analysis and critical review on a significant association. *Schizophr Bull*. 2011;37(4):811–821. doi:10.1093/schbul/sbp148
14. Feola B, Armstrong K, Woodward ND, Heckers S, Blackford JU. Childhood temperament is associated with distress, anxiety and reduced quality of life in schizophrenia spectrum disorders. *Psychiatry Res*. 2019;275:196–203. doi:10.1016/j.psychres.2019.03.016
15. World Health Organization. Official records of the World Health Organization No. 2. Available from: https://apps.who.int/iris/bitstream/handle/10665/85573/Official_record2_eng.pdf;jsessionid. Accessed January 10, 2022.
16. Andrianarisoa M, Boyer L, Godin O, et al. Childhood trauma, depression and negative symptoms are independently associated with impaired quality of life in schizophrenia. Results from the national FACE-SZ cohort. *Schizophr Res*. 2017;185:173–181. doi:10.1016/j.schres.2016.12.021
17. Naidu K, Van Staden W, Fletcher L. Discerning undifferentiated anxiety from syndromal anxiety in acute-phase schizophrenia. *Ann Gen Psychiatry*. 2020;19:26. doi:10.1186/s12991-020-00277-4
18. Buonocore M, Bosia M, Baraldi MA, et al. Exploring anxiety in schizophrenia: new light on a hidden figure. *Psychiatry Res*. 2018;268:312–316. doi:10.1016/j.psychres.2018.07.039

19. Albert U, Tomassi S, Maina G, Tosato S. Prevalence of non-psychotic disorders in ultra-high risk individuals and transition to psychosis: a systematic review. *Psychiatry Res*. 2018;270:1–12. doi:10.1016/j.psychres.2018.09.028
20. Kiran C, Chaudhury S. Prevalence of comorbid anxiety disorders in schizophrenia. *Ind Psychiatry J*. 2016;25(1):35–40. doi:10.4103/0972-6748.196045
21. Veras AB, Cougo S, Meira F, et al. Schizophrenia dissection by five anxiety and depressive subtype comorbidities: clinical implications and evolutionary perspective. *Psychiatry Res*. 2017;257:172–178. doi:10.1016/j.psychres.2017.07.048
22. William WHI, Berg A, Malhotra S. An examination of separation anxiety disorder symptoms in adults from a clinical population. *J Syst Integr Neurosci*. 2018;4(2):1–5.
23. Andreasen NC, Carpenter WT, Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. *Am J Psychiatry*. 2005;162(3):441–449. doi:10.1176/appi.ajp.162.3.441
24. Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. *J Clin Psychiatry*. 2003;64(6):663–667. doi:10.4088/JCP.v64n0607
25. Wright P, Stern J, Phelan M. *Core Psychiatry*. 3rd ed. Edinburgh: Saunders Elsevier; 2012.
26. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189–198. doi:10.1016/0022-3956(75)90026-6
27. Maltais JR, Gagnon G, Garant MP, Trudel JF. Correlation between age and MMSE in schizophrenia. *Int Psychogeriatr*. 2015;27(11):1769–1775. doi:10.1017/S1041610215000459
28. Qiu W, Qiu MW Package 'powerMediation'. R Foundation for Statistical Computing; 2018. Avaliable from: https://cran.r-project.org/web/packages/powerMediation/. Accessed September 14, 2021.
29. Manicavasagar V, Silove D, Wagner R, Drobny J. A self-report questionnaire for measuring separation anxiety in adulthood. *Compr Psychiatry*. 2003;44(2):146–153. doi:10.1053/comp.2003.50024
30. Diriöz M, Alkın T, Yemez B, Onur E, Eminağaoğlu N. Ayrılma anksiyetesi belirti envanteri ile yetişkin ayrılma anksiyetesi anketinin Türkçe versiyonunun geçerlik ve güvenirliği. *Türk Psikiyatr Derg*. 2011;22(2):108–116.
31. Silove D, Manicavasagar V, O'Connell D, Blaszczynski A, Wagner R, Henry J. The development of the Separation Anxiety Symptom Inventory (SASI). *Aust NZ J Psychiatry*. 1993;273:477–488. doi:10.3109/00048679309075806
32. Cyranowski JM, Shear MK, Rucci P, Fagiolini A. Adult separation anxiety: psychometric properties of a new structured clinical interview. *J Psychiatr Res*. 2002;36:77–86. doi:10.1016/S0022-3956(01)00051-6
33. Dirioz M, Alkın T, Yemez B, Eminagaoglu N, Onur E. Psychometric properties of the Turkish version of the Structured Clinical Interview for Separation Anxiety Symptoms. *Arch Neuropsychiatry*. 2012;49:6–13.
34. Eser E, Fidaner H, Fidaner C, Eser SY, Elbi H, Göker E. WHOQOL-100 ve WHOQOL-BREF'in psikometrik özellikleri. *Psikiyatr Psikol Psikofarmakol Derg*. 1999;7(2):23–40.
35. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261–276. doi:10.1093/schbul/13.2.261
36. Kostakoğlu E, Batur S, Tiryaki A, Göğüş A. Pozitif ve Negatif Sendrom Ölçeğinin (PANSS) Türkçe uyarlamasının geçerlilik ve güvenilirliği. *Türk Psikol Derg*. 1999;14(44):23–32.
37. Bernstein DP, Stein JA, Newcomb MD, et al. Development and validation of a brief screening version of the childhood trauma questionnaire. *Child Abus Negl*. 2003;27(2):169–190. doi:10.1016/S0145-2134(02)00541-0
38. Sar B, Ozturk E, Ikikardes E. Çocukluk çağı ruhsal travma ölçeğinin Türkçe uyarlamasının geçerlik ve güvenilirliği. *Turkiye Klin J Med Sci*. 2012;32(4):1054–1063.
39. Varese F, Smeets F, Drukker M, et al. Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective-and cross-sectional cohort studies. *Schizophr Bull*. 2012;38(4):661–671. doi:10.1093/schbul/sbs050
40. Agid O, Shapira B, Zislin J, et al. Environment and vulnerability to major psychiatric illness: a case control study of early parental loss in major depression, bipolar disorder and schizophrenia. *Mol Psychiatry*. 1999;4(2):163–172. doi:10.1038/sj.mp.4000473
41. Morgan C, Kirkbridge J, Leff J, et al. Parental separation, loss and psychosis in different ethnic groups: a case-control study. *Psychol Med*. 2007;37(4):495–503. doi:10.1017/S0033291706009330
42. Lukoff D, Liberman RP, Nuechterlein KH. Symptom monitoring in the rehabilitation of schizophrenic patients. *Schizophr Bull*. 1986;12(4):578–602. doi:10.1093/schbul/12.4.578
43. Wang WL, Zhou YQ, Chai NN, Li GH, Liu DW. Mediation and moderation analyses: exploring the complex pathways between hope and quality of life among patients with schizophrenia. *BMC Psychiatry*. 2021;21:565. doi:10.1186/s12888-021-03517-3
44. Milrod B, Altemus M, Gross C, et al. Adult separation anxiety in treatment nonresponders with anxiety disorders: delineation of the syndrome and exploration of attachment-based psychotherapy and biomarkers. *Compr Psychiatry*. 2016;66:139–145. doi:10.1016/j.comppsych.2016.01.004
45. Gelso CJ, Palma B, Bhatia A. Attachment theory as a guide to understanding and working with transference and the real relationship in psychotherapy. *J Clin Psychol*. 2013;69(11):1160–1171. doi:10.1002/jclp.22043
46. Weitkämper A, Kellner M, Iffland JR, et al. Childhood maltreatment in individuals with schizophrenia spectrum disorders: the impact of cut-off scores on prevalence rates. *Front Psychiatry*. 2021;12:675749. doi:10.3389/fpsyt.2021.692492
47. De Venter M, Illegems J, Van Royen R, Moorkens G, Sabbe BGC, Van Den Eede F. Corrigendum to "Differential effects of childhood trauma subtypes on fatigue and physical functioning in chronic fatigue syndrome". *Compr Psychiatry*. 2019;89:78–79. doi:10.1016/j.comppsych.2018.12.011
48. Lähdepuro A, Savolainen K, Lahti-Pulkkinen M, et al. The impact of early life stress on anxiety symptoms in late adulthood. *Sci Rep*. 2019;9:4395. doi:10.1038/s41598-019-40698-0
49. Cakmak B, Hızlı Sayar G, Unubol H, Bulut H, Ozten E. Çocukluk çağı travmaları ile yetişkin ayrılma anksiyetesi arasındaki ilişki. *J Neurobehav Sci*. 2018;5(3):150–155.
50. Grummitt LR, Kelly EV, Barrett EL, et al. Associations of childhood emotional and physical neglect with mental health and substance use in young adults. *Aust N Z J Psychiatry*. 2022;56(4):365–375. doi:10.1177/00048674211025691
51. Kilian S, Asmal L, Phahladira L, et al. The association between childhood trauma and treatment outcomes in schizophrenia spectrum disorders. *Psychiatry Res*. 2020;289:113004. doi:10.1016/j.psychres.2020.113004

52. Wheaton MG, Kaiser N. Anxiety sensitivity and intolerance of uncertainty as factors related to adult separation anxiety disorder symptoms. *Int J Cogn Ther*. 2021;14(3):473–484. doi:10.1007/s41811-021-00114-w
53. Dogan B, Kocabas O, Sevincok D, Baygin C, Memis CO, Sevincok L. Separation anxiety disorder in panic disorder patients with and without comorbid agoraphobia. *Psychiatry*. 2021;84(1):68–80. doi:10.1080/00332747.2021.1875730
54. Guedes de Pinho LM, Pereira AM. Quality of life in schizophrenic patients: the influence of sociodemographic and clinical characteristics and satisfaction with social support. *Trends Psychiatry Psychother*. 2018;40(3):202–209. doi:10.1590/2237-6089-2017-0002
55. Tortorella A. We should improve personalization of management in patients with a diagnosis of schizophrenia. *J Clin Med*. 2022;11(1):184. doi:10.3390/jcm11010184
56. Karaytuğ MO, Tamam L, Demirkol ME, Namlı Z, Gürbüz M. The related factors with functionality and the comorbidity in the patients with adult separation anxiety disorder. *J Clin Psychiatry*. 2020;24(4):481–490. doi:10.5505/kpd.2021.82957
57. Fuller-Thomson E, Hollister B. Schizophrenia and suicide attempts: findings from a representative community-based Canadian sample. *Schizophr Res Treatment*. 2016;2016:3165243. doi:10.1155/2016/3165243
58. Priebe S, Warner R, Hubschmio T, Eckle I. Employment. attitudes toward work, and quality of life among people with schizophrenia in three countries. *Schizophr Bull*. 1998;24:469–477. doi:10.1093/oxfordjournals.schbul.a033341
59. Pinho LGD, Pereira A, Chaves C. Influence of sociodemographic and clinical characteristics on the quality of life of patients with schizophrenia. *Rev Esc Enferm USP*. 2017;51:e03244. doi:10.1590/s1980-220x2016031903244