



# Prevalence of Posttraumatic Stress Disorder in Schizophrenia Spectrum Disorders: A Systematic Review

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## ABSTRACT

**Background:** Posttraumatic stress disorder (PTSD) is a comorbidity often ignored and unexplored in patients with schizophrenia, despite a possible impact on its symptomology. Links and interactions between these disorders are still unknown. This article proposes a systematic review of the prevalence of PTSD in schizophrenia spectrum disorders (SSD).

**Methods and findings:** Thirty-eight studies were included.

**Results:** Results were heterogeneous with range of prevalence of PTSD varying between 0% and 55%. These wide ranges of prevalence were explained by the utilization of different assessment tools of trauma exposure, not all validated and heterogeneous population of SSD (schizoaffective disorders, comorbid addiction disorders mainly). Nevertheless, 78,9% of the studies found a prevalence of PTSD superior to 10 %.

**Conclusion:** Our review suggests a high rate of prevalence of PTSD in schizophrenia, which may be underestimated due to symptoms overlap. Moreover, the absence of difference in trauma exposure between SSD and the general population evokes an increased liability to trauma in patients with SSD.

## Keywords

PTSD, Trauma, Schizophrenia, Schizoaffective, Prevalence, Posttraumatic

## Introduction

Schizophrenia is a severe mental illness which has a considerable impact on quality of life. Its worldwide prevalence is estimated between 0,3 % and 0,7% [1]. The physio-pathology of schizophrenia is still unexplained. The first hypothesis was the dopaminergic hypothesis [2,3]. It suggests that there is a hyperactive dopamine transmission in the mesolimbic areas, responsible for positive symptoms in the disorder and a prefrontal dopaminergic hypoactive dopamine transmission in the prefrontal cortex responsible for negative symptoms and cognitive

alterations. But this hypothesis could not explain all by itself the emergence of schizophrenia in patients and other neurotransmitters are suspected to be involved such serotonin and glutamate [4]. The now most prevalent hypothesis is the stress-vulnerability model [5]. Schizophrenia would be the results of associations between genetic factor [6,7] and environmental risks such as stress, in particular childhood trauma [8]. It was shown that a history of childhood trauma in patients with schizophrenia is associated with increased stress reactivity later in life, with more severe symptoms as well as lower quality of life [9-11]. Nevertheless, the role

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of adulthood trauma in schizophrenia is not well known. Over the last 20 years, there has been a growing literature on the subject, especially on posttraumatic stress disorder (PTSD) and schizophrenia. PTSD is defined by experiencing a traumatic event and characterized by a group of 3 main symptoms: flashbacks, withdrawal and hyper vigilance [12]. People with PTSD can also experience hallucinations, social isolation and dissociative symptoms [13] which can overlap with schizophrenia symptoms. PTSD is often underdiagnosed in general population [14,15] and largely underdiagnosed in people with schizophrenia [16], even if anxiety disorders are among the most frequent comorbidities of this disorder [17]. A meta-analysis recensing this comorbidity [18] found that 38,3% of patients with schizophrenia had an anxiety disorder with 12,4% had a comorbid PTSD. However, this meta-analysis does not specifically address the comorbidity between schizophrenia and PTSD. Moreover, several studies since this work have questioned the links between these two disorders.

Our objective was to conduct a systematic review of studies having assessed the prevalence of PTSD in schizophrenia spectrum disorders (SSD), including studies published before and after Achim et al. metaanalysis.

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## Methods

### ■ Data search

A literature review was performed on MEDLINE. We included articles until 30 June 2017. Keywords were: PTSD or posttraumatic stress disorder and schizophrenia.

### ■ Inclusion criteria

Prevalence of PTSD was the main inclusion criteria. Only articles with adult patients were included. Main diagnosis needed to be a schizophrenia spectrum disorder (SSD: schizophrenia, schizoaffective disorder or schizophreniform disorder). Studies about severe mental illnesses (bipolar disorder, schizophrenia, depression, anxiety disorders, personality disorders and eating behavior disorder) were included only if data was available for SSD. Exclusion criteria were a main diagnosis of mood disorder (depression or bipolar disorder) and underage populations.

### ■ Selection

The selection of articles is detailed in **Figure 1**. We obtained 710 hits in PubMed, seven studies

were found through reference lists of the articles we included. On 717 articles, 621 were excluded from title or abstract because they did not mention schizophrenia spectrum disorder and/or trauma or PTSD or the population age was under 18 years old. From the 96 studies left for full text reading, 58 were excluded (38 did not mention a prevalence of PTSD, 16 were reviews and four used the same sample of patients as others included studies). 38 studies are included.

### ■ Data extraction

The following data were extracted: demographics characteristics, sample size, instruments used to assess SSD, instruments used to assess PTSD, instruments used to assess trauma exposure, prevalence of PTSD, prevalence of trauma exposure (when available).

If there was a lifetime and a current value for prevalence of PTSD, only current value was included.

Flow chart is **Figure 2**.

### ■ Data availability

All data analysed during this study are included in this published article.

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## Results

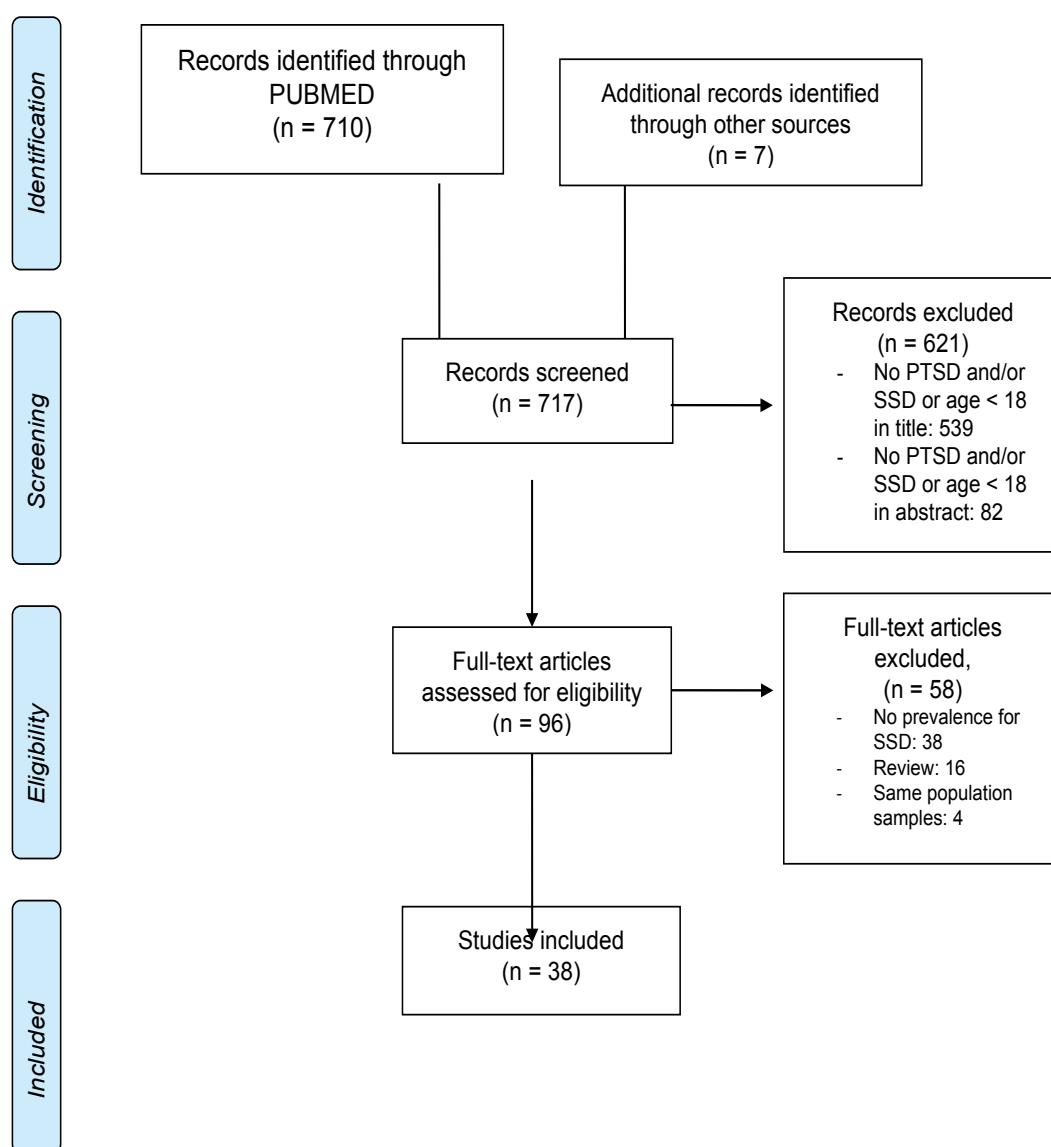
The contents of the articles are summed up in **Table 1**. Studies started from 1995 to 2016. Studies prior to 1995 didn't have homogeneous population in terms of diagnosis (schizophrenia, delusional mania, acute psychotic episode) or a formal indication of diagnosis (patients labelled with psychosis without any specification, no validation with International Classification of Diseases or Diagnostic and Statistical Manual of Mental Disorders; DSM).

### ■ Countries

On 38 studies, 55,2 % took place in America and 37% in Europe. Countries which most investigated PTSD in SSD were USA (n=19), Germany (n=4) and UK (n=3). Other studies were conducted in Asia (n=2) and Africa (n=1).

### ■ Sample characteristics

Twenty-one studies included outpatients, nine included inpatients and five included both inpatients and outpatients. One study used registries and two studies did not specify the kind of sample. Eleven studies included only patients with a schizophrenia diagnosis and excluded patients with schizoaffective disorder. Sample



**Figure 1:** Flow chart.

size varies from 18 to 87006 patients. Thirteen studies included more than 100 patients. Three studies included only SSD with substance use disorder. Two included only men and two only women. Mean age was between 29 years old (SD=5,9) and 55,3 years old (SD=9,9).

#### ■ Diagnostic tools for SSD

Most studies used DSM-IV for establishing SSD diagnosis, three used DSM-III and none used DSM5. 50 % used Structured Clinical Interview for DSM (SCID), three used charts to confirm SSD diagnosis.

#### ■ Assessment of trauma exposure

Not all studies investigate trauma exposure. Only 15 studies reported the prevalence of

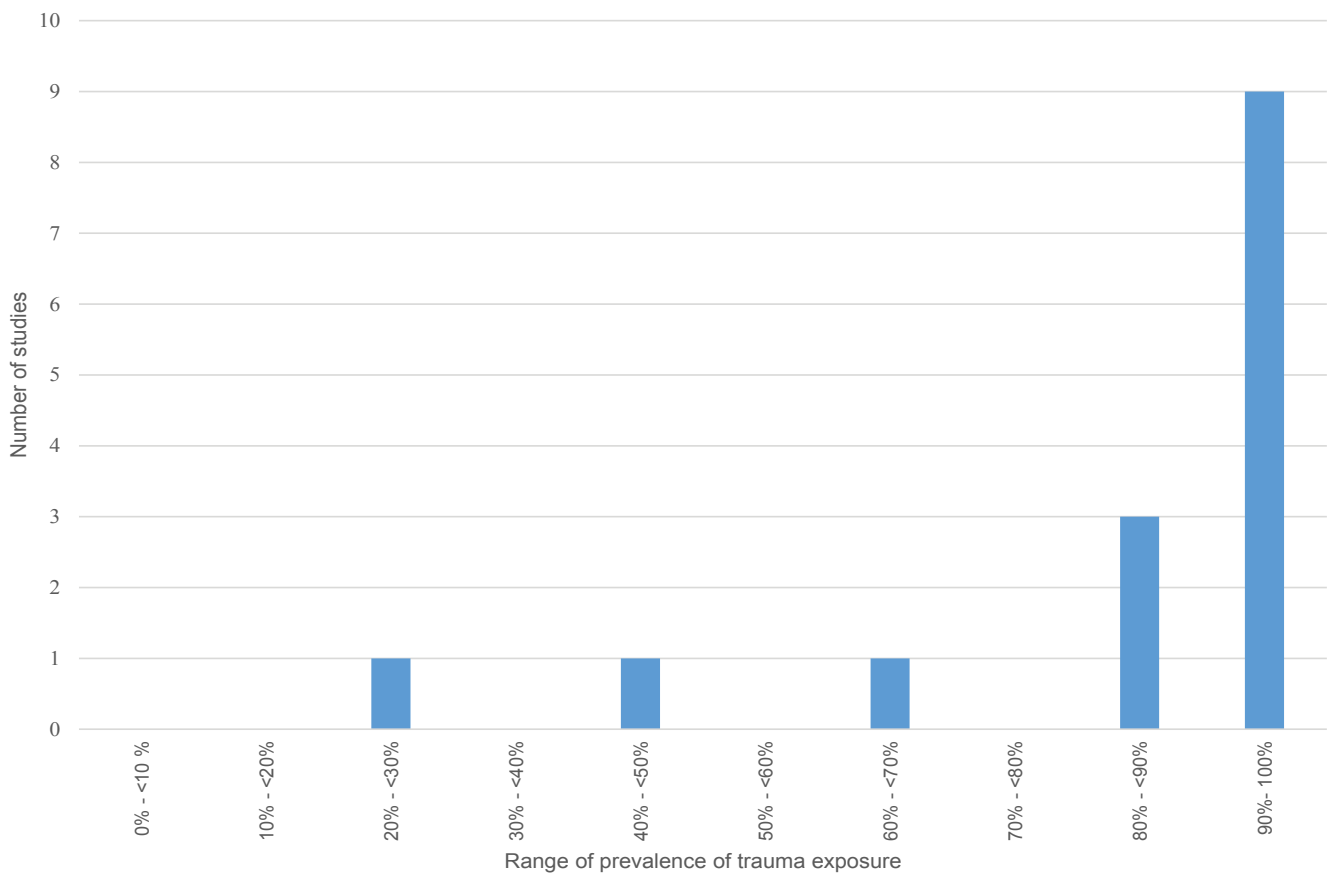
trauma exposure. The two most used tools for assessing trauma exposure were Trauma History Questionnaire (THQ; n=4) and Traumatic Life Events Questionnaire (TLEQ ; n=3).

#### ■ Prevalence of trauma exposure

Range of prevalence of trauma exposure starts from 25 to 100 % (Figure 3). Two studies were excluded because trauma exposure was one of the inclusion criteria [19,20]. 12 of the 15 studies find a trauma exposure superior to 80%.

#### ■ Assessment of PTSD

There is an important heterogeneity in assessment tools for prevalence of PTSD in the included studies (Table 2). Fifteen different methods were used. Twenty-three studies used



**Figure 2:** Distribution of reported prevalence of trauma exposure in SSD.

an interview tool, 11 used a self-report tool and three combined an interview tool and a self-report tool. One study was based on registries. The three most used assessment tools were the Clinician Administered PTSD Scale (CAPS ; n= 9 including CAPS-S n=3), the SCID (n=8) and the Posttraumatic Stress Disorder CheckList (PCL ; n=6). Among tools designed specifically for PTSD screening and diagnosis, only the CAPS-S and the PCL have a validity study in patients with SSD.

■ **Prevalence of PTSD**

Range of prevalence of PTSD starts from 0% to 55 %. Thirty studies found prevalence superior to 10 % (Figure 4).

Among countries which published the more studies, there is a range between 10 % and 55% in USA, between 12% and 51% in Germany and between 9% and 53% in the United Kingdom .

Only two studies found a difference of prevalence between men and women, with a higher prevalence for women. Other studies did not found this difference or did not mention it.

**Discussion**

We found 38 studies which explored prevalence of PTSD in SSD, that is 18 more studies than Achim et al. [18]. Prevalence of trauma exposure in SSD was generally over 80%, a rate quite similar to that reported in the general population (89.7% [21]). This seems to refute the assumption that patients with SSD have a higher trauma exposure and, conversely, is in line with the hypothesis that these patients show increase vulnerability to traumatic events [16]. Range of prevalence of PTSD was extremely wide (over 50% between the lowest value and the highest), with 30 of the 38 studies (78.9%) finding prevalence over 10%, consistent with Achim et al. findings. Even if results are heterogeneous, when we compare to general population, prevalence of PTSD in SSD remains superior. For example, in USA, prevalence of PTSD in SSD is 1, 8 to 8 times higher than in general population (general population= 6,8% [22]; SSD = 10%-55%). Contrary to general population where women are more subject to PTSD [23], we did not found differences between genders in SSD.

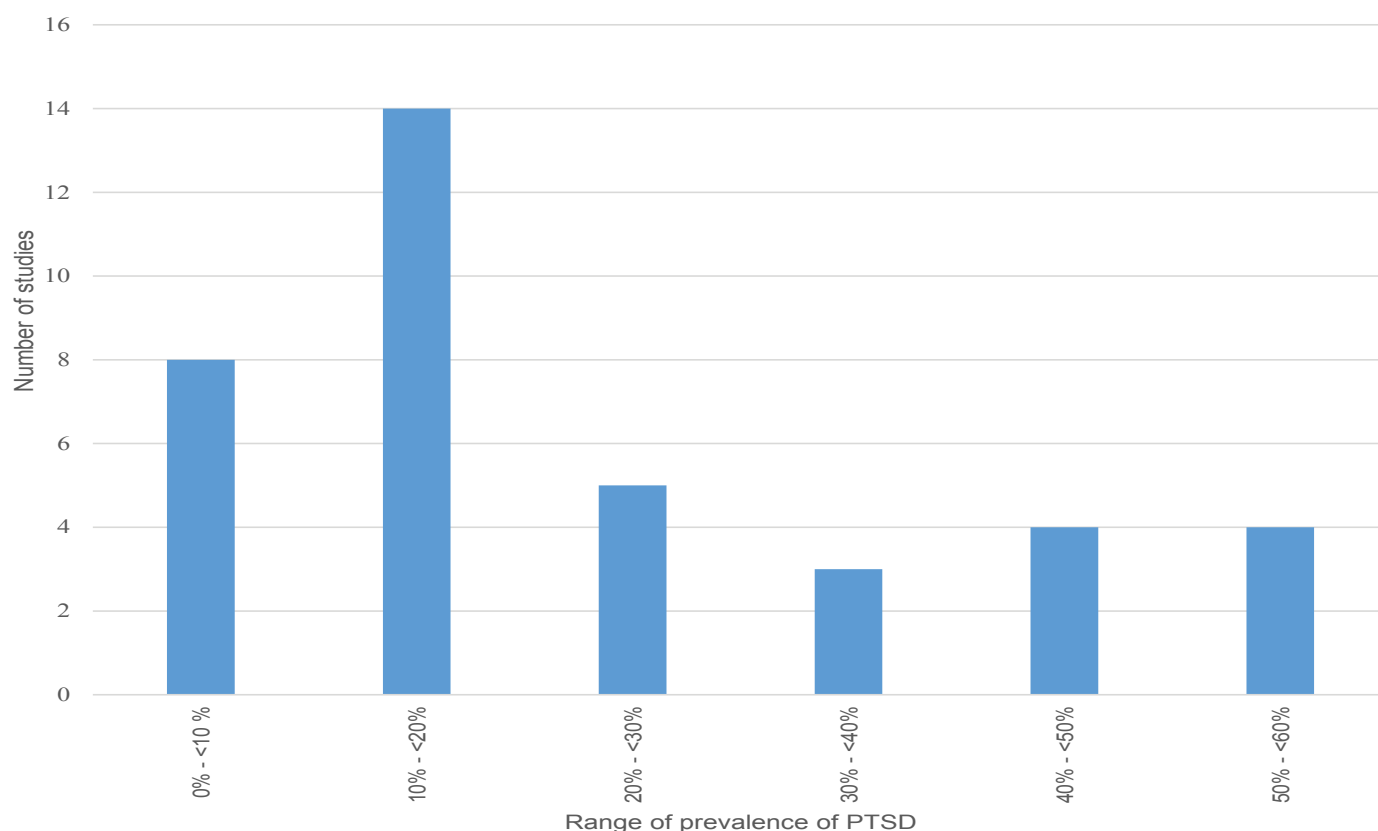
**Table 1: Studies results.**

Authors	Country	Population	Number of patients	Mean age (SD)	Assessment			Prevalence of trauma exposure	
			(% men)		SSD	Trauma exposure	PTSD		Prevalence of PTSD
Aakre et al. [1]	USA	Female drug addict outpatients	42 (0%)	41,0 (6,8)	SCID-4	TLEQ	CAPS-S	100%	48%
Alvarez et al. [2]	Spain	Outpatients	62 (64,5%)	39,4 (10,4)	DSM-IV	TLEQ	DEQ	88,2%	SCZ : 10,2% SZA : 22,2%
Birgenheir et al. [3]	USA	Outpatients	87006 (93,3%)	-	Charts	-	Charts	-	15,2 %
Braga et al. [4]	Brazil	Outpatients	53 (71,7%)	-	DSM-IV	-	SCID-4	-	3,8%
Calhoun et al. [5]	USA	Veteran inpatients	165 (100%)	48 (7,8)	SCID-4	SAEQ	PCL	96%	47%
						CTS			
						CES			
Chapleau et al. [6]	USA	Inpatients and outpatient	60 (93,3%)	50,3 (11,09)	SCID-3	-	PCL	-	55%
Fan et al. [7]	USA	Outpatients	87 (74,7%)	43,7 (8,9)	SCID-4	HTQ	HTQ	100%	17%
Frame and Morrison [8]	UK	Outpatients	60 (61,7%)	-	DSM-IV	-	DTS	-	50%
Gearon et al. [9]	USA	Female drug addict outpatients	54 (0%)	40,6 (6,8)	SCID-4	TLEQ	CAPS-S	96%	46%
Halasz et al. [10]	Hungary	Outpatients	125 (55,2%)	-	SCID-4	-	CAPS	-	17%
Harvey et al. [11]	USA	Outpatients	3445 (93%)	55,3 (9,9)	DSM-IV	-	MINI	-	22%
Kennedy et al. [12]	USA	Outpatients	30 (-)	-	DSM-IV	-	Penn PTSD	-	23,3%
Kilcommons and Morrison [13]	UK	Outpatients	32 (78,1%)	34,5 (9,96)	DSM-IV	THQ	PSS	94%	53,1%
Lommen and Restifo [14]	Netherlands	Outpatients	33 (69,7%)	42,3 (10,6)	Charts	THQ	PSS	97%	9,1%
Lyon et al. [15]	USA	Twin outpatients	24 (100%)	44,6	Charts	-	DIS-III-R	-	16,7%
Meyer et al. [16]	Finland	Inpatients and outpatients	46 (39%)	40,8 (12,1)	DSM-IV	-	CAPS	-	11%
Mueser et al. [17]	USA	Inpatients and outpatients	94	-	DSM-IV	THQ	PCL	98%	30,9%
					Charts				
					SCID-4				
Mueser et al. [18]	USA	Inpatients and outpatients	526	-	SCID-4	-	PCL	-	31,6%
Nebioglu and Altindag [19]	Turkey	Outpatients	82 (76,8%)	-	DSM-IV	-	SCID-4	-	7,3%
Authors	Country	Population	Number of patients	Mean age (SD)	Assessment			Prevalence of trauma exposure	
			(% men)		SSD	Trauma exposure	PTSD		Prevalence of PTSD
Neria et al. [20]	USA	Outpatients	165 (-)	-	DSM-IV	DIS-3-R	DIS-III-R	68,5%	10%
Newman et al. [21]	USA	Inpatients	70 (71,4%)	-	DSM-IV	SLESQ	SCID-4	12,8%	87%
Ng et al. [22]	USA	Outpatients	125 (75,2%)	44,05 (9,51)	DSM-IV	HTQ	HTQ	12%	82%
Pallanti et al. [23]	Italy	Outpatients	80 (48,8)	29 (5,9)	SCID-4	-	SCID4	-	1,3%

Peleikis et al. [24]	Norway	Inpatients and outpatients	292 (55,1%)	-	SCID-4	MINI	MINI	25%	7%
Picken and Tarrier [25]	UK	Drug addict outpatients	110 (90%)	37 (9,95)	SCID-4	PDS	PDS	91%	9%
							CAPS-S		
Pollice et al. [26]	Italy	Inpatients	54 (69,2%)	44,6 (14,1)	SCID-4	-	IES	100%	17%
							SCDI-4		
Priebe et al. [27]	Germany	Outpatients	105 (44,8%)	38,6 (9,4)	DSM-III	-	PTSD-I	-	51%
Renard et al. [28]	USA	Veteran outpatients	49 (91,8%)	51,8 (9,8)	SCID-4	-	PCL	-	43%
Resnick et al. [29]	USA	Outpatients	47 (36,2%)	44,1 (9,7)	SCID-4	THQ	CAPS	97,9%	12,8%
Rosenberg et al. [30]	USA	Outpatients	569 (67,8%)	42 (9)	SCID-4	-	PCL	-	34%
Schäfer et al. [31]	Germany	Inpatients	145 (66,9%)	34,1	SCID-4	STI	SCID4	-	12%
Seedat et al. [32]	South Africa	Inpatients	70 (54,3%)	35,8 (11,2)	Charts	-	MINI	-	4,3%
					MINI				
Sin et al. [33]	Singapore	Inpatients and outpatients	45 (-)		SCID-4	-	CAPS	-	15,5%
Steinert et al. [34]	Germany	Inpatients	118 (47,5%)	-	ICD-10	DSM-IV	SCID4	49,2%	28%
						A criteria	PDS		
Strakowski et al. [35]	USA	Outpatients	18 (50%)	37,2 (20,5)	SCID-3	-	SCID3	-	22%
Strauss et al. [36]	USA	Outpatients	70 (57,1%)	42,4 (-)	SCID-4	-	CAPS	-	21,4%
Tibbo et al. [37]	Canada	Outpatients	32 (78%)	-	MINI	-	MINI	-	0%
							CAPS		
Vogel et al. [38]	Germany	Inpatients	74 (66,2%)	39 (14)	DSM-IV	-	DSM-III	-	15,5%
CES: Combat Exposure Scale CTS: Conflict Tactics Scale DEQ: Distressing Events Questionnaire DIS-III-R: Diagnostic Interview Schedule DTS: Davidson Trauma Scale HTQ: Harvard Trauma Questionnaire IES: Impact of Event Scale MINI: Mini International Neuropsychiatric Interview					PDS: Posttraumatic Diagnostic Scale PSS-I: PTSD Symptom Scale - Interview PTSD-I: PTSD-Interview SAEQ: Sexual Abuse Exposure Questionnaire SCZ: schizophrenia SLESQ: Stressful Life Events Screening Questionnaire STI: Structured Trauma Interview SZA: schizoaffective disorder				

Many causes can explain the heterogeneity of the reported prevalence of PTSD in SSD. The first one is the heterogeneity of samples. Most studies included SSD, which mean schizophrenia, schizoaffective disorder and schizophreniform disorder. When we look at studies that separated data of schizophrenia and schizoaffective disorder, we observe that prevalence of PTSD is higher in schizoaffective disorder than it is in schizophrenia. Alvarez et al. found a prevalence of PTSD of 10.2% in schizophrenia while it was 22.2 % in schizoaffective disorder, a rate similar to bipolar disorders (21%; [24]). Other

causes of heterogeneity occurred when studies included only one gender or included SSD with other comorbidities such as drug abuse. In the general population, patients with substance use disorder have higher risk of comorbid PTSD (36,6%; [25]). The only 2 studies that included SSD with substance use disorder found a very high prevalence of PTSD [26,27]. Also, the assessment of the prevalence of PTSD was made in inpatients and outpatients which can cause large variations. Indeed, recent works show the traumatic impact of psychiatric disorder and, in some cases, of psychiatric care. Several



**Figure 3:** Range of reported prevalence of PTSD in SSD.

studies showed that hospitalization can cause trauma, especially seclusion and isolation [28,29]. Several authors modify criteria A of DSM definition for PTSD in order to include trauma linked to disease and to care [16,30]. When Lommen and modify the A criteria of DSM definition of PTSD and included trauma exposure linked to hospitalization and disorder, the prevalence of PTSD was estimated to 39 % while when they apply strictly DSM 4 criteria, the prevalence of PTSD dropped at 9% [16]. On the opposite, some authors deliberately excluded patients with trauma linked to care and disease [31,32]. Despite a growing literature on the traumatic impact of first psychotic episode and hospitalization, DSM5 did not include care and disorder trauma in criteria A of PTSD.

We also notice that 66 % of the studies had less than 100 patients, suggesting a majority of studies could be less representative of the SSD population, especially given the heterogeneity of this population.

Another factor of heterogeneity is the variety of tools used to assess prevalence of PTSD. Only 9 studies used the CAPS, considered as

the gold standard of PTSD diagnosis [33] and only 3 used the Clinician-Administered PTSD Scale for Schizophrenia (CAPS-S) which is a modified version of the CAPS for patients with schizophrenia [34]. Besides CAPS-S and general psychiatric assessment tools (SCID, MINI), none of the tools used to assess PTSD were validated for SSD. [35] did a validity study of the PCL-5 in patients with SSD. Results showed a very high number of false positive (70.3 %), which renders the PCL an inadequate screening tool with an overrating of PTSD diagnosis [35]. Even if some modifications were made between PCL-S and PCL-5, we can speculate that the prevalence of PTSD in studies using the PCL-S might be overrated. Few screening tools were validated for patients with SSD. Moreover, most of the scales used were self-report tools, which might weaken the reliability of PTSD diagnosis. We included every study that had reported prevalence of PTSD in SSD. This can create a bias as not all of these studies were designed for this epidemiologic purpose. Also, we excluded 38 studies which did not report a prevalence of PTSD in SSD. Some of these studies did assess the prevalence of PTSD but in the context of

**Table 2: Assessment tools for PTSD.**

Screening tools	Interview or self-report	Validation study in general population	Validation study in SSD	Number of studies	Studies
CAPS	Interview	Blake et al. [39]	CAPS-S: Gearon et al. 2004 [40]	9 3 CAPS-S	CAPS: Halasz et al. [10] Meyer et al. [16] Resnick et al. [29] Sin et al. [33] Strauss et al. [36] Tibbo et al. [37]  CAPS-S: Aakre et al. [1] Gearon et al. [9] Picken and Tarrier [25]
DEQ	Self-report	Kubany et al. [41]	-	1	Alvarez et al. [2]
DIS-III-R	Interview	Robins et al. [42]	Robins et al. 1981[42]	2	Lyons et al. Neria et al. [20]
DTS	Self-report	Davidson et al. [43]	-	1	Frame and Morrison [8]
HTQ	Self-report	Mollica et al. [44]	-	2	Fan et al. [7] Ng et al. [22]
IES	Self-report	Zilberg et al. [45]	-	1	Pollice et al. [26]
SCID	Interview	DSM-III: Spitzer et al. [46] DSM-IV: First et al. [47]	DSM-III: Spitzer et al. 1992[46] DSM-IV: First et al. 1996[47]	8	Braga et al. [4] Nebioglu and Altindag [19] Newman et al. [21] Pallanti et al. [23] Pollice et al. [26] Schäfer et al. [31] Steinert et al. [34] Strakowski et al. [35]
MINI	Interview	Sheehan et al. [48]	Sheehan et al. 1998[48]	4	Harvey et al. [11] Peleikis et al. [24] Seedat et al. [32] Tibbo et al. [37]
PCL-S	Self-report	Weathers et al. [49]	PCL-5: Steel et al. 2017[50]	6	Calhoun et al. [5] Chapleau et al. [6] Mueser et al. [17] Mueser et al. [18] Renard et al. [28] Rosenberg et al. [30]
PDS	Self-report	Foa et al. [51]	-	2	Picken and Tarrier [25] Steinert et al. [34]
PENN-PTSD	Self-report	Hammarberg [52]	-	1	Kennedy et al. [12]
PSS-I	Interview	Foa et al. [53]	-	2	Kilcommons and Morrison [13] Lommen and Restifo [14]
PTSD-I	Interview	Watson et al. [54]	-	1	Priebe et al. [27]

2 studies used only DSM-III-R criteria and 1 study was based on charts.

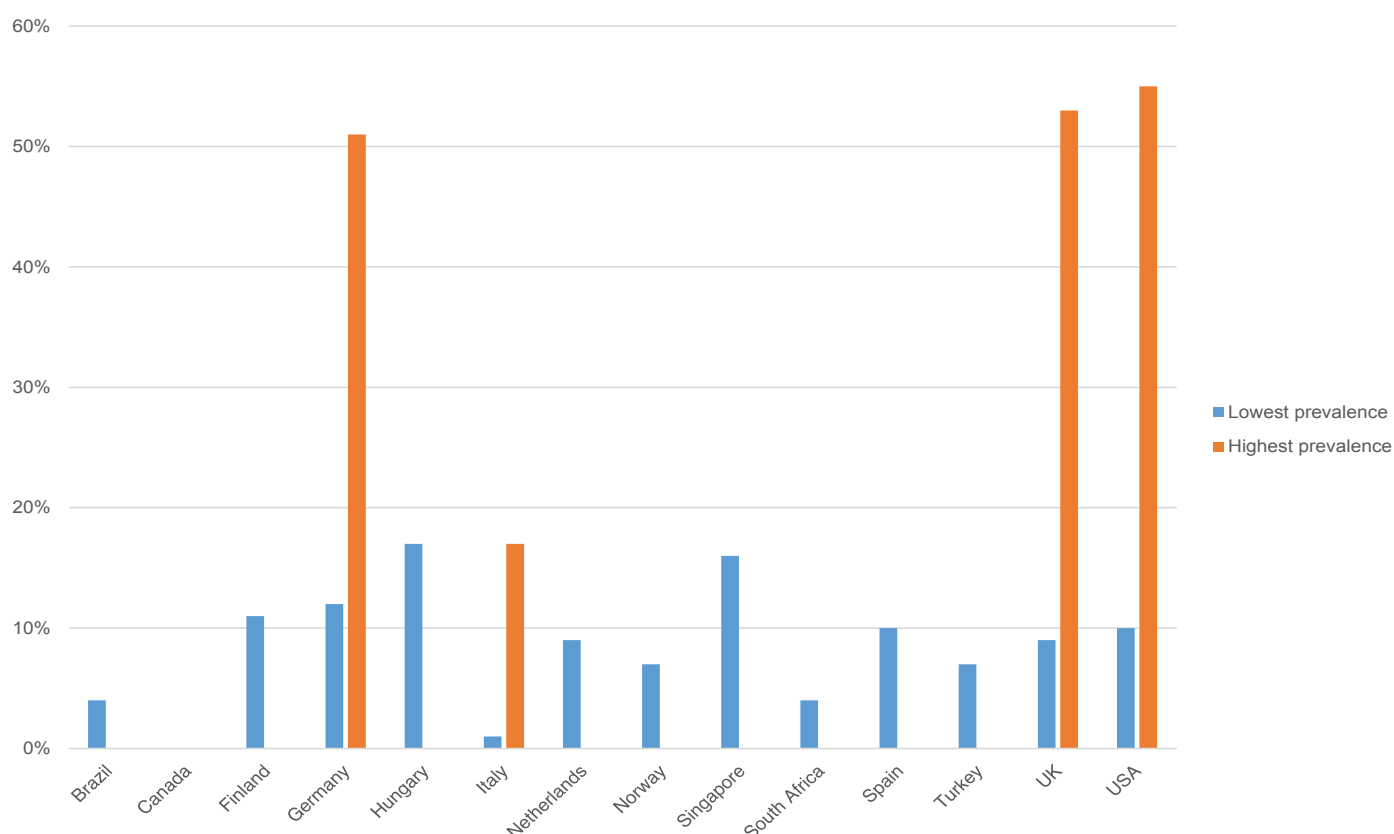
broad severe mental illness and they did not provide specific data about the prevalence of PTSD in SSD.

Our review suggests that the prevalence of PTSD tends to be higher in patients with SSD than in the general population. Links between trauma and schizophrenia are still unexplained. Mueser et al elaborated an interactive model in which each group of symptoms of PTSD influences the evolution of schizophrenia, which lead to more frequent relapses and more severe symptoms [36]. Avoidance syndrome worsens schizophrenia

symptoms and impairs areas of functioning, re-experience syndrome acts as stressors, over arousal syndrome increases negative symptoms and the vulnerability to retraumatization.

This review suggests that assessment of PTSD in SSD should be an important matter in everyday clinic. Impact of PTSD on SSD is not negligible, as SSD patients with comorbid PTSD tend to have more severe psychotic symptoms and are more subject to depressive and anxious symptoms [19,37–39]. Suicidal risk is increased in patients with SSD, as well as suicide attempts





**Figure 4:** Range of prevalence of PTSD by country.

and substance use disorders all of which worsen the prognosis [31,40,41]. Comorbid PTSD decreases quality of life, self-worth and increases the use of medical and psychiatric care [19,42-45]. In line with this, it should be emphasize that the association between psychiatric disorders and obesity and/or diabetes constitutes a major public health concern and needs to be specifically addressed in the management of these disorders and of this comorbidity [46,47].

Despite all these clinical implications, PTSD in SSD remains under diagnosed [16,40,48-0]. One explanation could be the similarities of symptoms between PTSD and schizophrenic disorders [39,51]. Indeed, there is a certain amount of overlap between symptoms in both disorders: for instance, hallucinations are present in schizophrenia but also in some cases of PTSD, or avoidance in PTSD which can be confused with negative symptoms in schizophrenia. Also, clinicians may believe that patients with SSD cannot deliver a reliable or precise story of their trauma history, which may contribute to underdiagnose PTSD in this population. Literature suggests that patients with SSD tend

to under report their traumatic experiences but are as reliable as general population [52]. Finally, Resnick et al suggests that clinicians are less willing to diagnose PTSD in SSD because there are no official therapeutic recommendations [39]. Salyers et al. tried to identify barriers in diagnosis and treatment of PTSD in patient with SSD [53]. They found that physician's competence/confidence and his belief that an intervention would be useful is positively correlated with the percentage of patients in which PTSD has been discussed or documented. It implies that clinicians need to be trained to improve their skills and knowledge in order to detect and treat PTSD in patients with SSD. Use of diagnosis and screening tools can help clinicians in detecting PTSD. Many studies validate PTSD assessment tools in patients with SSD. Psychometric properties of THQ, CAPS and Trauma Screening Questionnaire (TSQ) were first validate for general population but also for SSD [39,52,54-57]. Moreover, Gearon et al. (2004) validated the CAPS-S, CAPS for schizophrenia with some linguistic simplifications [34]. At last, there is promising results in treatment of PTSD in patients with SSD. Many studies confirmed

efficiency of Cognitive Behavioural Therapy (CBT) to treat PTSD in SSD such as cognitive restructuring [58-60] and prolonged exposure therapy [61]. Eye Movement Desensitization and Reprocessing (EMDR) showed also good results in SSD by significantly decreasing prevalence of PTSD in SSD population and by improving PTSD symptoms, verbal auditory hallucinations, anxiety and depression without secondary effects or symptomatology exacerbation [61,62].

that patients with SSD might not be overexposed but might show an increased vulnerability to trauma. A specific meta-analysis should be done in order to incorporate the new studies and mechanisms between trauma and schizophrenia needs to be explored. The underdiagnosis of PTSD in SSD could be improved by using validated assessment tools. Improving clinician's knowledge and skills in PTSD in SSD could decrease patients' distress and highly improve their quality of life.

### Conclusion

Prevalence of PTSD in patients with SSD seems to be higher than in general population. However, prevalence of trauma exposure seems similar to the general population. This suggests

### Additional Information

Competing financial interests

The authors declare no competing financial interests.

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